Bleeding complications after hospital discharge following acute coronary syndrome: an electronic health records database study

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Declaration

This project was supported by the North Staffordshire Medical Institute 50th Anniversary Award (Grant No: B890). The sponsor had no role in the design, data collection, analysis or interpretation of findings, or writing of the thesis. The initial idea for the research in this thesis was first conceived by my supervisors: prof Kelvin P. Jordan, Mamas A. Mamas, and Umesh T. Kadam. But over the course of the program, I have refined the focus of the research with their guidance and assistance. This led to the development of an analytic framework that was used to secure a UK national primary care consultation data (CPRD) with linkage to secondary care data (HES) and mortality data (ONS).

The studies presented in this thesis are therefore based in part on the data from the Clinical Practice Research Datalink obtained under licence from the UK Medicines and Healthcare products Regulatory Agency (Independent Scientific Advisory Committee approval number 17_181). The data is provided by patients and collected by the National Health Service (NHS) as part of their care and support. The Office for National Statistics is the provider of the ONS data contained within the linked CPRD data used in this thesis. The interpretation and conclusions contained in this thesis are those of the author alone.

Prof Kelvin P. Jordan, Mamas A. Mamas, Umesh T. Kadam and Dr John J. Edwards gave constructive feedback and comments on data analyses, writing and presentations of chapters. All analyses, writing and presentations in this thesis have been carried out by the author.

Abstract

The management of acute coronary syndrome (ACS) with antithrombotic medication achieves the desired goal of reducing the risk of future ischaemic events. However, these reductions are accompanied by increased risk of bleeding complications. A systematic review of the literature highlighted that there was a paucity of evidence on the incidence, timing, types, and predictors of these bleeding events, and their prognostic impact on mortality following hospital discharge after ACS. Using a UK national primary care consultation database with linkage to secondary care data and mortality data, the incidence, timing, types, and predictors of these bleeding events, and their association with all-cause mortality following hospital discharge post ACS were determined.

Among the 27,660 patients that fulfilled the inclusion/exclusion criteria for the study, 3,620 (13%) experienced first bleeding events at a median time of 123 days (IQR: 45 to 223) post-hospital discharge. The incidence of bleeding was 162/1000 person-years (95% CI: 157 to 167) within the first 12 months after discharge. Bleeding occurred more frequently in the first 30 days after discharge, with bruising (949 bleeds (26%)) and gastrointestinal bleed (705 bleeds, (20%)) the most common type of first bleeding events, while intracranial bleed was relatively rare (81 bleeds (2%)). Significant predictors of any post-discharge bleeding included prior history of bleeding complication, oral anticoagulant prescription, history of peripheral vascular disease, chronic obstructive pulmonary disease, and advanced age >80 years. Predictors for post-discharge bleeding varied depending on the severity and anatomic site of the bleeding event. Patients that experienced bleeding complications following hospital discharge for ACS had higher risk of mortality than those who did not (HR 1.70, 95% CI: 1.50, 1.92). This increased risk of

mortality also varied by severity and anatomic site of the bleeding event, with intracranial bleed having the worst prognostic impact. This increased risk of mortality was more pronounced within the first 30 days following the bleeding event.

Patients who experienced bleeding complications following hospital discharge after ACS have distinct baseline characteristics. These characteristics can inform risk-benefit considerations in deciding on favourable combination and duration of secondary antithrombotic therapy. Further work is now required to combine these characteristics to develop and validate a risk score for bleeding complications following hospital discharge for use in the primary care setting.

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Presentations

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Chapter 1.0: **Introduction**

This study examines bleeding complications after hospital discharge following acute coronary syndrome (ACS) within an English primary care setting. In this chapter, the rationale, aims, objectives, and outline of the study are summarised.

1.1 Bleeding – An important complication of ACS management

ACS encompass a group of clinical presentations that include unstable angina (UA), ST-elevation myocardial infarction (STEMI), and non ST-elevation myocardial infarction (NSTEMI) (Kumar and Cannon, 2009). The management of ACS depends on the clinical presentation with an overall aim of reducing myocardial ischaemia and adverse cardiac events (O'Connor et al., 2010). In the acute setting (in-hospital), the management of UA/NSTEMI is guided by risk stratification, and depending on individual patient risk profile, management may involve a combination of antiplatelets and anticoagulant, or an invasive strategy, most notably percutaneous coronary intervention (PCI) (Roffi et al., 2016). In the case of STEMI, the preferred management strategy is PCI (Ibanez et al., 2017). Following hospital discharge, and regardless of the in-hospital management strategy, aspirin therapy is continued indefinitely, and adjunctively with a P2Y12 receptor inhibitor for up to 12 months (Ibanez et al., 2017; Roffi et al., 2016). The addition of an oral anticoagulant to both aspirin and a P2Y12 receptor inhibitor for shorter period is advocated for patients with comorbidities such as atrial fibrillation (Roffi et al., 2016).

These management strategies, whilst achieving the desired goal of reducing the risk of future ischaemic events, also increases the risk of bleeding complications (Cayla et al., 2013; Jolly et al., 2008; Yeh et al., 2015). There are several definitions for bleeding for use in research, but the majority of these definitions were conceived in the clinical (in-hospital) settings and incorporate both clinical parameters (such as recorded

gastrointestinal bleed), laboratory parameters (such as recorded drops in haemoglobin), and/or receipt of blood transfusion data (Chesebro et al., 1987; Feit et al., 2007; Moscucci et al., 2003; Stone et al., 2008; The GUSTO Investigators, 1993; Wallentin et al., 2009; Yusuf et al., 2001). These definitions typically classified bleeding based on severity into: major, minor, and nuisance bleeding events. In primary care, bleeding tends to be recorded based only on clinical parameters. Therefore, the applicability of these definitions in primary care research using electronic healthcare record (EHR) is uncertain, and there remains a lack of a standardised definition for use in this setting. Previous studies of bleeding complications in the primary care setting have developed their own definitions (Buresly et al., 2005; Raposeiras-Roubín, Faxén, et al., 2018; Valle et al., 2016). But these definitions are conservative in that they do not capture minor/nuisance bleeding events (such as nose bleed and bruising) which patients may be concerned about.

The incidence of major bleeding following ACS has been estimated to be between 1% - 10% in clinical trials (Rao et al., 2007; Stone et al., 2006; The PURSUIT Trial Investigators, 1998; Yusuf et al., 2006), with observational studies reporting incidences of between 2.8% (Spencer et al., 2007) and 11% (Amlani et al., 2010). However, the emphasis in the majority of these studies has been on major in-hospital or bleeding events within the first 30-days of ACS (a composite of in-hospital and post-discharge events) with little consideration for events in the longer-term after hospital discharge. Following hospital discharge, ACS patients may remain on dual antiplatelet therapy for up to a year or longer, and aspirin indefinitely, so their risk of bleeding complications may persist in the longer-term. A recent study has indicated that while ACS patients do sustain bleeding complications in the in-hospital setting, these bleeding events continued to transpire

even after hospital discharge into the primary care setting (Khan et al., 2015). Presently, it is unclear how common these bleeding events are within the primary care setting or their types and timing post-hospital discharge.

Further to this, major in-hospital bleeding has been associated with socio-demographic, cardiovascular and non-cardiovascular comorbidities, pharmacological, and procedural characteristics, leading to the development of risk scoring algorithms for these bleeding events in the in-hospital setting (Mathews et al., 2011; Mehran et al., 2011; Subherwal et al., 2009). However, it is unclear whether these characteristics are also predictive of longer-term bleeding events post-hospital discharge. For example, procedural characteristics may become less important in predicting the risk of post-discharge bleeding events, whereas patient characteristics and pharmacological choice may become more important post-discharge. The few studies (Alfredsson et al., 2017; Costa et al., 2017; Yeh et al., 2016) that have associated some characteristics with bleeding post-hospital discharge have mostly been carried out in the PCI setting within randomised controlled trials (RCTs), where minor bleeding events have been ignored, and high-risk elderly patients or those on chronic oral anticoagulants (a potential risk factor for bleeding) have been excluded. Minor bleeding may be common in primary care and may lead to discontinuation of guideline-recommended therapy, which is known to worsen prognosis (Armero et al., 2011; Jura-Szołtys and Chudek, 2011; Roy et al., 2008). Also, only a small proportion of the cohorts in these studies are high-risk ACS patients, with the majority being patients with stable coronary artery and other unspecified cardiovascular diseases (Baber et al., 2016; Costa et al., 2017; Yeh et al., 2016). Therefore, the generalisability of these studies to the wider ACS population in primary care is unclear. Identifying the baseline characteristics which may increase the risk of bleeding

complications within the primary care setting can support clinicians in deciding on the most favourable longer-term antiplatelets and/or anticoagulant for individual patients.

Previous studies have associated major in-hospital bleeding with increased risk of adverse outcomes, including but not limited to mortality (Eikelboom et al., 2006; Kinnaird et al., 2003; Manoukian et al., 2007; Rao et al., 2005, 2006). The increased risk of mortality (after an in-hospital bleed) appeared to be maintained regardless of the bleeding definition used (Kwok et al., 2014; Rao et al., 2006), in both the short-term (in-hospital) and longer-term (post-hospital discharge) (Eikelboom et al., 2006; Kwok et al., 2014; Rao et al., 2005), with risk increasing as the severity of bleeding increases (Rao et al., 2005, 2006). This adverse effect of in-hospital bleeding depends on the anatomic site of the bleed (Kwok et al., 2015), and the site of bleeding may vary between the in-hospital and post-discharge settings. Whilst the adverse effect of major in-hospital bleeding event on mortality has been well described mostly within the clinical trial setting, there is limited evidence regarding the association of bleeding events that occur after hospital discharge with clinical outcomes such as mortality.

This dearth in knowledge evidently underscores the need for more research in order to further our understanding of the nature and prognostic impact of these late bleeding events within the primary care setting, which also form the basis for the aim and objectives below. It is anticipated that outputs from this research may inform clinical practice, which may translate to better management for individual patients.

1.2 Aim and objectives of the thesis

This section outlines the overall aim of this thesis and the specific objectives that have been formulated to address this overall aim.

1.2.1 **Aim**

The aim of this thesis is to provide evidence on the frequency, timing, and types/sites of bleeding events following hospital discharge for ACS, the characteristics associated with these events, and whether these bleeding events are associated with longer-term outcomes. This overall aim is anticipated to be achieved via the following objectives:

1.2.2 **Objective 1 (*Chapter 3*): Conduct a systematic review of the incidence, types, timing, and prognostic impact of bleeding complications after hospital discharge following ACS.**

The primary objectives were to:

- Determine the incidence of bleeding after hospital discharge following ACS.
- Determine the incidence of bleeding by time following hospital discharge for ACS.
- Determine the incidence of site-specific bleeding events (such as gastrointestinal, intracranial) after hospital discharge following ACS.

The secondary objectives were to:

Determine the association between bleeding following hospital discharge for ACS and subsequent risk of

- Mortality.
- MACE (as defined in individual studies).

- Re-infarction.
- Rehospitalisation.

1.2.3 **Objective 2 (*Chapter 4*): By means of consensus, define bleeding complications following ACS in primary care.**

The main focus of this objective will be to define bleeding complications in primary care through consensus of General Practitioners (GPs) and an Interventional Cardiologist. This will mainly be a pilot study, using routinely coded consultation information stored in primary care EHR. The definition generated will primarily be used to inform the main studies of the thesis (objectives 3, 4, and 5).

1.2.4 **Objective 3 (*Chapter 7*): Determine the incidence, timing, and types/sites of bleeding events after hospital discharge following ACS**

Specific objectives:

- To determine the incidence of bleeding events in the first 12 months after hospital discharge following ACS.
- To determine the incidence of bleeding events by time within the first 12 months after hospital discharge following ACS.
- To determine the types/sites of bleeding events in the first 12 months after hospital discharge following ACS.

A descriptive cohort study set within a national primary care EHR database (the Clinical Practice Research Datalink (CPRD)) with linkage to secondary care records (Hospital Episode Statistics (HES)) and mortality records (Office for National Statistics (ONS) mortality data) will be used to address this objective. Patients with a discharge diagnosis

for ACS will be followed longitudinally from date of hospital discharge (for a maximum of 12 months) for recorded bleeding consultation in the patient's primary care record or a death record in the ONS mortality data with bleeding as the primary underlying cause (Chapter 7). The CPRD, HES, and ONS mortality data are described in chapter 5 of this thesis.

1.2.5 **Objective 4 (*Chapter 8*): Determine independent risk factors for bleeding after hospital discharge following ACS.**

The main focus of this objective will be to determine the baseline characteristics most likely to increase an individual patient's risk of bleeding in the longer-term following hospital discharge for ACS. To address this objective, two linked sub-objectives were formulated.

Primary objective:

- To determine independent associations between the outcome of any bleeding in the first 12 months after hospital discharge for ACS and baseline socio-demographic, pharmacological, comorbidity and in-hospital procedural characteristics.

Secondary objectives:

To determine independent associations between baseline socio-demographic, pharmacological, comorbidity and in-hospital procedural characteristics with the outcomes of:

- Early bleeding events (defined as any bleed within the first 30 days after hospital discharge for ACS).

- Serious and non-serious bleeding events within the first 12 months after hospital discharge for ACS.
- Site-specific bleeding events (such as intracranial bleed) within the first 12 months after hospital discharge for ACS.

A cohort study set within CPRD with linkage to HES and ONS mortality data will be carried out to address these objectives. The outcome of interest will be first bleeding events that occur following hospital discharge for ACS, and the potential risk factors will be baseline patient characteristics.

1.2.6 **Objective 5 (*Chapter 9*): Determine the prognostic impact of bleeding on all-cause mortality after hospital discharge following ACS.**

The emphasis here will be to examine whether bleeding complications which occur after hospital discharge following ACS increases a patient's risk of mortality or not. To address this objective, two linked sub-objectives were devised.

Primary objective:

- To determine the independent association between any bleeding and all-cause mortality within the first 12 months following hospital discharge for ACS.

Secondary objectives:

To determine the independent associations between:

- Serious and non-serious bleeding events with all-cause mortality within the first 12 months after hospital discharge for ACS.
- Site-specific bleeding event with all-cause mortality within the first 12 months after hospital discharge for ACS.

- Whether patients who sustain early bleeding events (defined as any bleed within the first 30 days following hospital discharge for ACS) have a higher short-term risk of mortality (within the first 30 days following the bleeding event) than those who sustained late bleeding events (defined as any bleed occurring between 31 – 335 days post-hospital discharge).
- Whether the risk factors identified for bleeding are also associated with mortality in patients that experienced bleeding complications in the first 12 months after hospital discharge.

To address these objectives, a cohort study set within CPRD with linkage to HES and ONS mortality data will be carried out. Patients with recorded bleeding events post-hospital discharge will be compared to those without recorded bleeding events in relation to the outcome of all-cause mortality. Association between the outcome of all-cause mortality and bleeding will then be determined. When determining the risk factors for mortality in patients that sustained bleeding complications, the outcome of interest will also be all-cause mortality, and the potential risk factors will be baseline patient characteristics.

1.3 Outline of the thesis

Chapter 2 will give the clinical description of ACS, its epidemiology, management strategies, and the bleeding complications associated with these management strategies. This will be followed by a systematic review of the current evidence on the incidence, timing, types, and prognostic impact of bleeding complications within the primary care setting in **Chapter 3**. Bleeding complications following ACS will be defined in primary care through consensus of GPs and an Interventional Cardiologist in **Chapter 4**, which will then inform subsequent studies that will be carried out in the thesis. **Chapter 5** will describe the datasets that will be used to address objectives 3, 4, and 5 (the main studies in this thesis). In this chapter (Chapter 5), the inclusion and exclusion criteria for the study population, study design, key variable definitions, and the approaches to handling missing data and analyses for the main studies in this thesis (objectives 3, 4, and 5) will be outlined. Following on from this, the baseline characteristics of those who fulfilled the inclusion/exclusion criteria for the study population will be descriptively summarised and compared to those of patients with ACS who did not fulfil these criteria (referred to as the sensitivity cohort in this thesis) in **Chapter 6**. The incidence, timing, and types/sites of bleeding events within the primary care setting will be examined in **Chapter 7**, followed by descriptive comparisons between those who experienced bleeding and those who did not post-hospital discharge. In this chapter (Chapter 7), mortality rates following hospital discharge for ACS will also be determined. In **Chapter 8**, independent associations between baseline patient characteristics (including: socio-demographic, comorbidity, pharmacological, and in-hospital procedural characteristics) and the outcome of bleeding will be explored. **Chapter 9** will examine the independent associations between bleeding following hospital discharge and all-cause mortality within the primary care setting,

before finally summarising the overall findings of the thesis, and their implications in **Chapter 10**.

Chapter 2.0: **Background**

This section of the thesis gives the clinical description of acute coronary syndrome (ACS), its epidemiology, management strategies, and the bleeding complications associated with these management strategies.

2.1 ACS

ACS is an umbrella term that describes a group of clinical presentations that include UA and myocardial infarction (MI). Clinically, MI is subdivided into STEMI and NSTEMI (Kumar and Cannon, 2009). More recently, MI has been further sub-classified into five categories, ranging from type 1 (spontaneous MI) to type 5 (MI related to coronary artery bypass graft) (Thygesen et al., 2018). The majority of MI events are spontaneous (type 1 MI), triggered by atherosclerotic plaque rupture and erosion (Timmis, 2015). For detailed description of the different types of MI, the reader is referred to the fourth universal definition of MI (Thygesen et al., 2018). The emphasis of this thesis will be on MI (STEMI and NSTEMI) and UA events will be excluded.

2.1.1 The epidemiology of ACS

Over 87,000 confirmed episodes of MI were reported from hospitals in England, Wales, Northern Ireland and Isle of Man between April 2016 and March 2017 (MINAP, 2017). The majority (61%) of these cases were for NSTEMI, with the remaining 39% attributed to STEMI (MINAP, 2017). The ratio of NSTEMI to STEMI is approximately the same in those under the age of 60 years, but in those between the age of 70 and 79 years, the ratio is 2:1, and almost 3:1 in those aged 80 years and over (MINAP, 2017). Before the age of 60 years, men more often present with ACS than women, but after the age of 75 years,

women represent the majority of cases (Regitz-Zagrosek et al., 2016). In men diagnosed with MI, 43% of all diagnoses tend to be for STEMI, with the remaining 57% attributed to NSTEMI. While in women, 35% of all diagnoses are for STEMI, and the remaining 65% attributed to NSTEMI (MINAP, 2014). The overall age-standardised incidence of MI is reported to be 174/100,000 persons in men and 73.7/100,000 persons in women in England (as at 2010) (Smolina et al., 2012). The incidence of MI has gradually declined over the past decade in England (Smolina et al., 2012). Yet, despite the decline, ACS remains a major cause of premature death in adults (Bhatnagar et al., 2015) and a major public health burden (BHF, 2017).

2.1.2 Management of ACS

The fundamental goal in ACS management is to prevent/reduce the amount of myocardial cell necrosis and the risk of adverse events by restoring coronary patency to the occluded artery (O'Connor et al., 2010). This goal is achieved via management with antiplatelets, anticoagulants and invasive strategies. In the emergency setting, initial anti-ischaemic therapy with oxygen, beta-blockers, nitrates, and calcium channel blockers have shown effectiveness in reducing acute ischaemic episodes by either reducing myocardial oxygen demand or increasing myocardial oxygen supply (Hamm et al., 2011; Steg et al., 2012). But overall, the management strategy wholly depends on the underlying ACS diagnosis, i.e. whether NSTEMI or STEMI (Hamm et al., 2011; Steg et al., 2012).

In the acute setting, and for patients diagnosed with STEMI, revascularisation, most commonly with PCI, is the mainstay therapy. PCI is a non-surgical procedure that

introduces a catheter via the radial or femoral artery to the heart. Through the catheter, a stent is inserted to open up the occluded coronary artery in order to restore coronary blood flow. Although effective in restoring perfusion, PCI increases the risk of bleeding complications (Jolly et al., 2011; Moscucci et al., 2003). These bleeding complications range from superficial (such as bruising, hematoma) to more severe systemic bleeds (such as gastrointestinal or intracranial bleeds (Jolly et al., 2011; Kwok et al., 2015)). For patients presenting with NSTEMI, management in the acute setting is initially guided by risk stratification. Risk stratification uses an algorithm to stratify individual patients into different risk profiles for death or MI based on baseline characteristics. The [1]TIMI and [2]GRACE risks scores are the most widely used tools in guiding treatment in this setting (Antman et al., 2000; Granger et al., 2003). Depending on a patient's risk profile, management can be medical with antiplatelets and anticoagulants or invasively with angiography, PCI or coronary artery bypass graft (CABG).

2.1.3 Antiplatelets and anticoagulants in the acute and longer-term prevention of ACS and risk of bleeding complications

2.1.3.1 Antiplatelets

The fundamental goal of management with antiplatelets is to inhibit platelet activation and aggregation pathways, integral steps in the formation of thrombus after plaque rupture or erosion. Four antiplatelets, namely; aspirin, clopidogrel, prasugrel, and

[1] Thrombolysis in myocardial infarction

[2] Global registry of acute coronary events

ticagrelor have been advocated by the European Society of Cardiology (ESC) for the acute and longer-term management of ACS (Ibanez et al., 2017; Roffi et al., 2016).

2.1.3.1.1 Aspirin

Aspirin inhibit platelet activation and aggregation via irreversible inactivation of cyclooxygenase (COX-1), thereby completely suppressing the production of thromboxane A_2 (Patrono et al., 2011). Aspirin remains the cornerstone antiplatelet in the management of ACS (Braunwald, 2003). It is advocated as first-line therapy as soon as ACS is suspected, unless contraindicated, in which case aspirin is substituted by clopidogrel (Ibanez et al., 2017; Roffi et al., 2016). Aspirin is administered at a loading dose of 300mg in the acute setting, followed by a daily maintenance dose of 75mg post-hospital discharge (Ibanez et al., 2017; Roffi et al., 2016). Management with aspirin has been shown to reduce the risk of 30-day mortality by 25 percent and those of non-fatal reinfarction, and stroke by 50 percent (Baigent et al., 2009; ISIS-2, 1988), albeit at the expense of increased risk of bleeding complications (Berger et al., 2012; Serebruany et al., 2004). Higher doses of aspirin have not shown improved efficacy but rather exacerbated the risk of bleeding complications (Berger et al., 2012; Serebruany et al., 2005; Xian et al., 2015). Aspirin therapy is continued indefinitely in the absence of complications such as bleeding events.

Although the cornerstone antiplatelet in the management of ACS, platelet activation and aggregation is only partially inhibited by aspirin. Other pathways, namely; the adenosine diphosphate (ADP), and the thrombin-protease-activated receptor pathways, are largely unaffected (Patrono et al., 2011). The addition of an ADP (P2Y12) receptor inhibitor (clopidogrel, prasugrel, and ticagrelor) to aspirin in both the acute and longer-term management of ACS has been shown to be more effective in platelet inhibition and

reduction of adverse ischaemic events (Wallentin et al., 2009; Wiviott et al., 2007; Yusuf et al., 2001). This additive benefit has been the basis for recommending aspirin plus a P2Y12 receptor inhibitor for the management of ACS (Ibanez et al., 2017; Roffi et al., 2016).

2.1.3.1.2 Clopidogrel

Clopidogrel is an inactive prodrug, metabolised by hepatic cytochrome p450 enzymes in two steps. The first step converts clopidogrel to an inactive metabolite by de-esterification (Herbert et al., 1993). The second step converts clopidogrel into its active metabolite (Caplain et al., 1999) which then inhibit platelet activation by irreversibly binding to P2Y12 receptors (the main platelet receptor responsible for ADP-induced platelet aggregation) to inactivate the aggregation response initiated by P2Y1 receptors (Herbert and Savi, 2003; Savi and Herbert, 2005). The additive benefit of inactivating COX-1 with aspirin and the blockage of P2Y12 receptors with clopidogrel is evident in the [3]CURE trial (Yusuf et al., 2001), where dual antiplatelet therapy (DAPT) with aspirin and clopidogrel reduced the composite endpoint of death, non-fatal MI and stroke by 20 percent (over aspirin plus placebo) in patients with NSTEMI (Yusuf et al., 2001). However, this additive benefit was accompanied by an increased number of bleeding events (Yusuf et al., 2001).

Due to substantial interindividual variability in response to clopidogrel (Matetzky et al., 2004), there remains the risk of recurrent ischaemic events, with hyporesponsiveness to clopidogrel resulting in increased risk of non-fatal MI, stent thrombosis and death (Aradi

[3] Clopidogrel in unstable angina to prevent recurrent events

et al., 2010; Brar et al., 2011; Sofi et al., 2010), and hyperresponsiveness leading to increased risk of bleeding (Sibbing et al., 2010).

2.1.3.1.3 Prasugrel

Prasugrel is an inactive prodrug converted in a single step to an active metabolite which inhibit platelet activation by irreversibly binding to P2Y12 receptors on platelets (Jakubowski et al., 2007; Patrono et al., 2011). Prasugrel metabolism is less dependent on cytochrome p450 enzymes, resulting in less interindividual variability, and faster and more profound inhibition of platelets than clopidogrel (Jakubowski et al., 2007). The [4]TRITON-TIMI 38 trial demonstrated the superiority of prasugrel over clopidogrel, where prasugrel reduced the composite endpoint of death, non-fatal MI, and stroke by 19% over a follow-up period of 15 months post ACS (Wiviott et al., 2007). For this reason, preference is now given to prasugrel over clopidogrel for the management of ACS in the setting of PCI, unless prasugrel is contraindicated (such as history of stroke/transient ischaemic attacks, low body weight (<60kg) and age greater than 75 years) (Ibanez et al., 2017; Roffi et al., 2016). However, the reduction in adverse events was accompanied by increased number of bleeding events which were more pronounced in the prasugrel arm than the clopidogrel arm of the trial (Wiviott et al., 2007).

2.1.3.1.4 Ticagrelor

Unlike clopidogrel and prasugrel, ticagrelor is a direct-acting platelet inhibitor that does not require metabolic activation by hepatic enzymes (Patrono et al., 2011). Ticagrelor

[4] Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction

inhibit platelet activation by directly and reversibly binding to P2Y12 receptors. Maximal platelet inhibition is achieved within 1 – 3 hours of treatment (Wallentin, 2009). Like prasugrel, management with ticagrelor provides faster, consistent, and more profound platelet inhibition than clopidogrel (Husted et al., 2006; Storey et al., 2007). In a head to head comparison, the [5]PLATO trial demonstrated the superiority of ticagrelor over clopidogrel, where ticagrelor reduced the composite endpoint of death, MI and stroke by 16% over a follow-up period of 12 months post ACS (Wallentin et al., 2009). This additive benefit has been the basis for recommending ticagrelor for ACS patients treated either invasively or conservatively, including those pretreated with clopidogrel. However, this reduction in adverse events by ticagrelor was also accompanied by increased number of bleeding complications (Wallentin et al., 2009).

2.1.3.2 Anticoagulants

Anticoagulants act on the coagulation pathway of thrombus formation to inhibit thrombin generation/activities and blood clotting. Inhibition of thrombin blocks the remaining platelet activation pathway (namely the thrombin-protease-activated receptor pathway) which is not addressed by antiplatelets. In the acute setting, parenteral unfractionated heparin (UFH), low molecular weight heparin (LMWH), bivalirudin, and fondaparinux, all acting at different levels of the coagulation cascade are advocated for the management of ACS by the ESC guidelines (guidelines for the management of patients with ACS) (Roffi et al., 2016). UFH, LMWH and fondaparinux exert their anticoagulant effects by binding to, and activating antithrombin, which inhibits factor Xa and thrombin

[5] platelet inhibition and patient outcome

(De Caterina et al., 2013). Bivalirudin, on the other hand, is a direct thrombin inhibitor that binds directly to thrombin and prevents thrombin mediated activities (De Caterina et al., 2013). There is evidence that parenteral anticoagulation in the acute management of ACS reduces adverse ischaemic events, albeit at the expense of increased risk of bleeding complications (Eikelboom et al., 2000; Silvain et al., 2012; Yusuf et al., 2006).

Factor Xa and thrombin play a key role in the formation of thrombus after an atherosclerotic plaque rupture/erosion. There are indications that inhibitors of both factor Xa (such as apixaban) and thrombin (such as dabigatran and rivaroxaban) may play a role in the prevention of adverse ischaemic events in the longer-term after hospital discharge post ACS. But these evidences are presently ambiguous.

Apixaban in addition to standard therapy with aspirin and clopidogrel increased the risk of bleeding complications without a net reduction in adverse ischaemic events (the composite endpoint of death, MI and stroke) (Alexander et al., 2011). Dabigatran (in addition to standard therapy with aspirin and clopidogrel) on the other hand, results in significant reduction in coagulation activities. But this reduction was offset by a dose-dependent increase in the number of bleeding complications (Oldgren et al., 2011). Rivaroxaban, the only oral anticoagulant that reduced the composite endpoint of cardiovascular death, MI, and stroke (Mega et al., 2012) has now been recommended for the longer-term prevention of ischaemic events in patients at high risk of ischaemic and low risk of bleeding complications (Ibanez et al., 2017; Roffi et al., 2016). However, Just like apixaban and dabigatran, the reduction in ischaemic events by rivaroxaban was also accompanied by increased number of bleeding complications (Mega et al., 2012).

Approximately 6% to 8% of ACS patients on dual antiplatelet therapy also have an indication for long-term oral anticoagulation due to the presence of co-morbidities such

as atrial fibrillation (Hamm et al., 2011). Triple therapy with aspirin, a P2Y12 receptor inhibitor (mostly clopidogrel) and an oral anticoagulant increase the number of administered antithrombotic agents. As the number of administered antithrombotic agent's increases, the risk of bleeding is even more amplified in this subgroup of patients (DeEugenio et al., 2007; Khurram et al., 2006).

2.2 What is bleeding?

Bleeding is an important complication of ACS management. As outlined above, the management of ACS achieves the desired goal of reducing adverse ischaemic events. But these reductions are at the expense of increased risk of bleeding complications. There are several definitions for bleeding for use within the research setting, with the majority developed using composites of laboratory parameters (such as recorded drops in haemoglobin), clinical parameters (such as recorded gastrointestinal bleed), and/or receipt of blood transfusion data. The initial TIMI criteria for bleeding defined major bleeding as intracranial bleed or bleeding associated with a decrease in haemoglobin of greater than 5.0 g/dL or haematocrit of greater than 15% (Chesebro et al., 1987). The TIMI criterion defined minor bleeding as any bleed associated with a decrease in haemoglobin of greater than 3.0 but less than 5.0 g/dL or a drop in haematocrit of less than 10% (Chesebro et al., 1987). However, the TIMI criterion was developed in the fibrinolytic era to measure short term bleeding associated with fibrinolytic therapy and predominantly relies on laboratory parameters (Chesebro et al., 1987) (see **table 2.1** for definition). Over the years, the TIMI criterion has been modified to reflect new developments in this arena. To address the shortcomings of the TIMI criterion, investigators from the global use of strategies to open occluded arteries study developed a new definition "referred to as the GUSTO criterion". The GUSTO criterion stratified bleeding into severe/life threatening, moderate, and mild bleeding events (**table 2.1**) (The GUSTO Investigators, 1993). However, just like the TIMI criterion, the GUSTO definition was also conceived in the fibrinolytic era and relies heavily on clinical parameters,

thereby making classification of bleeding by severity highly challenging (Mehran et al., 2011).

Recently, several criteria including CURE (Yusuf et al., 2001), PLATO (Wallentin et al., 2009), GRACE (Moscucci et al., 2003), [6]ACUITY (Stone et al., 2006), [7]OASIS (Yusuf et al., 2006), [8]STEEPLE (Montalescot et al., 2006), [9]HORIZON-AMI (Stone et al., 2008), [10]REPLACE (Feit et al., 2007), and [11]ISTH (Schulman and Kearon, 2005), which include both clinical and laboratory parameters with the sole aim of addressing the drawbacks of the TIMI and GUSTO definitions, have been used in research (in trials and studies using in-hospital registries). However, the multiple criteria used for bleeding introduces heterogeneity in terms of outcome reporting, and comparing outcomes such as the efficacy and safety of antithrombotic drugs across studies is often challenging (Steg et al., 2011). As an example, in the [12]SYNERGY trial, the rate of major bleeding defined by the TIMI criterion was 9.1% in the enoxaparin arm, whereas the rate using the GUSTO definition was 2.7% (Ferguson et al., 2004). Another pitfall of using multiple criteria for bleeding is variation in defining bleeding severity, that is to say, a major bleeding by one definition is regarded as a minor bleeding event by another. For example, the PLATO criterion considered bleeding that is associated with a drop in haemoglobin level of greater than 3 g/dL but less than 5

[6] Acute catheterisation and urgent intervention triage strategy

[7] Organisation for the assessment of strategies for ischaemic syndromes

[8] Safety and efficacy of enoxaparin in PCI patients, an international randomised evaluation

[9] Harmonizing outcomes with revascularisation and stents in acute myocardial infarction

[10] Randomised evaluation of PCI linking angiomax to reduce clinical events

[11] International society on thrombosis and haemostasis

[12] Superior yield of the new strategy of enoxaparin revascularisation and glycoprotein IIb/IIIa Inhibitors

g/dL as a major bleed, whereas the TIMI criteria considered this as a minor bleeding event.

For these reasons, the bleeding academic research consortium (BARC) convened a group of independent experts and proposed (by consensus) a standardised definition for bleeding in order to eliminate the deficiencies of the aforementioned definitions. This standardised definition referred to as the "BARC criterion" stratifies bleeding into five categories, ranging from type 1 (bleeding that is not actionable and does not cause the patient to seek medical attention) to type 5 (fatal bleeding) (**table 2.1**) (Mehran et al., 2011). The BARC definition has been validated against other definitions (such as TIMI, GUSTO, and REPLACE) in previous research in trials and studies using in-hospital registries where clinical parameters, laboratory parameters and receipt of blood transfusion data are readily available (Kikkert et al., 2014; Ndrepepa et al., 2012; Vranckx et al., 2014; Yoon et al., 2015). But the applicability of the BARC definition in primary care research, using EHR, where bleeding is mostly recorded using clinical parameters (such as gastrointestinal bleed) is unclear.

Table 2.1: The BARC, TIMI and GUSTO bleeding definitions

Criteria	Severity	Definition
BARC (Mehran et al., 2011)	**Type 0**	No bleeding
	Type 1	Bleeding that is not actionable (Nuisance bleeds)
	Type 2	Actionable bleeding requiring hospitalisation, diagnostic studies and treatment by healthcare professionals, but does not fit criteria for 3, 4 & 5.
	Type 3	
	A	Overt bleeding + haemoglobin drop of 3 to < 5 g/dL Any transfusion with overt bleeding
	B	Overt bleeding + haemoglobin drop ≥ 5 g/dL Cardiac tamponade Bleeding requiring surgical intervention Bleeding requiring intravenous vasoactive agents
	C	Intracranial bleed Intraocular bleed
	Type 4	CABG related bleeds
	Type 5	
	A	Probable fatal bleeding: no autopsy or imaging confirmation but clinically suspicious
	B	Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation
TIMI (Bovill et al., 1991)	**Major**	Intracranial or a ≥ 5 g/dL decrease in haemoglobin or Bleeding resulting in death within 7 days
	Minor	Overt blood loss or ≥ 3 to ≤ 5 g/dL decrease in haemoglobin or requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding including temporarily or permanently stopping or changing the dose of a medication or study drug) or leading to or prolonging hospitalisation or prompting evaluation (leading to unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)

Criteria	Severity	Definition
TIMI	**Minimal**	Any overt bleeding that does not meet major or minor bleeding criteria above.
GUSTO (The GUSTO Investigators, 1993)	**Severe or life-threatening**	Intracerebral or resulting in substantial hemodynamic compromise requiring treatment
	Moderate	bleeding requiring blood transfusion or bleeding that does not cause hemodynamic compromise
	Mild	bleeding that does not meet criteria for severe or moderate bleeding

***BARC**: Bleeding academic research consortium, **GUSTO**: Global use of strategies to open occluded arteries**, TIMI**: Thrombolysis in myocardial infarction, **CABG**: Coronary artery bypass graft.*

2.2.1 How common is bleeding in the acute (in-hospital) setting?

Establishing the overall incidence of bleeding post-ACS within the in-hospital setting is problematic due to wide variations across studies. These variations are largely attributed to differences in patient characteristics (such as age, gender and presence of comorbidities), management strategy (whether medically managed or invasively), the definition of bleeding used, the timing of event reporting, and the study design employed (whether RCT or registry). In trials such as [13]PURSUIT, which compared eptifibatide to placebo in a cohort of NSTEMI patients, the reported incidence of bleeding in the eptifibatide arm was 10.6% for TIMI major bleeding and 12.9% for TIMI minor bleeding events. However, when GUSTO criterion was applied, the authors reported an incidence of 1.5% for GUSTO severe, 11.3% for GUSTO moderate and up to 26.1% for GUSTO mild bleeding events (The PURSUIT Trial Investigators, 1998). The OASIS-5 trial, on the other hand, compared enoxaparin to fondaparinux and reported an incidence of 4.1% for major bleeding in the Enoxaparin arm and 2.2% in the Fondaparinux arm of the trial (Yusuf et al., 2006). The ACUITY trial, reported incidences of 0.9% and 3.7% for TIMI major and minor bleeding events in the Bivalirudin arm respectively, and 1.9% and 6.4% in the unfractionated heparin plus GP IIb/IIIa inhibitor arm of the trial (Stone et al., 2006). The overall incidence of major or severe (in-hospital) bleeding events in the clinical trial setting is estimated to be between 1% and 10% (Rao et al., 2007; Stone et al., 2006; The PURSUIT Trial Investigators, 1998; Yusuf et al., 2006). Although, it must be borne in mind that patients often recruited in RCTs tend to be highly selected and younger than patients typically encountered in clinical practice (Steg et al., 2007).

[13] Platelet glycoprotein IIb/IIIa in unstable angina: receptor suppression using integrilin therapy

Registries, on the other hand, have the tendency to provide estimates of the real-world incidence of bleeding than RCTs (Steg et al., 2011). In the GRACE registry of 24,045 ACS patients, the incidence of [14]major (in-hospital) bleeding was found to be 4.8% in those with STEMI, 4.7% in those with NSTEMI, and 3.9% overall (Moscucci et al., 2003). In the [15]ACTION registry, the incidence of [16]major bleeding among patients with STEMI was estimated at 11%, and 9% in those with NSTEMI (Kadakia et al., 2010). In line with the ACTION registry, the [17]CRUSADE registry, which used blood transfusion as a proxy for bleeding reported an incidence of 10.3% (Yang et al., 2005). However, this must be interpreted with caution given the variability in transfusion practices across centres that participated in the study (Yang et al., 2005).

One trial (the [18]APPRAISE-2 trial) has indicated that whilst ACS patients do sustain bleeding events in the in-hospital setting, nearly 60% of the bleeding events that transpire following ACS, may occur after hospital discharge (Khan et al., 2015).

[14] Defined as life threatening bleeding requiring transfusion of more than 2 units of packed red blood cells, or resulting in an absolute decrease in haematocrit of greater than 10% or death or haemorrhagic/subdural haematoma

[15] National cardiovascular data registry of acute coronary treatment and intervention outcome network registry get with the guidelines

[16] Defined as intracranial or retroperitoneal bleed or red cell transfusion when baseline haematocrit is greater than 28% or less than 28% with overt bleeding or absolute haematocrit drop of greater than 12%

[17] Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines

[18] Apixaban for prevention of acute ischaemic events

2.2.2 Specific population at risk of bleeding complications in the acute setting

Major in-hospital bleeding has been associated with socio-demographic, cardiovascular and non-cardiovascular comorbidities, pharmacological, and in-hospital procedural characteristics (Mathews et al., 2011; Mehran et al., 2010; Moscucci et al., 2003; Nikolsky et al., 2007; Subherwal et al., 2009). Characteristics such as advanced age, female gender, renal insufficiency, anaemia, and invasive procedures have shown consistency in predicting major in-hospital bleeding complications despite the variability across studies (in relation to patient characteristics, management strategies, definition of bleeding used, and the study design employed) (Mathews et al., 2011; Mehran et al., 2010; Moscucci et al., 2003; Nikolsky et al., 2007; Subherwal et al., 2009). In the GRACE registry of 24, 045 ACS patients, women had a 43% higher likelihood of major in-hospital bleeding complication relative to men. The same study showed that a decade increase in age was associated with almost 30% increased risk of major in-hospital bleeding complications (Moscucci et al., 2003). In the ACTION registry, the estimated risk of major in-hospital bleeding complications increased by 17% in patients with renal insufficiency, and more than twofold in patients with baseline anaemia (Mathews et al., 2011). Other characteristics such as antithrombotic medication, lower body weight, diabetes, hypertension, congestive heart failure, peripheral vascular disease and type of ACS indication have also been associated with higher risk of major in-hospital bleeding events (Mathews et al., 2011; Moscucci et al., 2003; Nikolsky et al., 2007; Subherwal et al., 2009). Risk factors for major in-hospital bleeding have been well described and risk scoring algorithms (ACTION, CRUSADE, ACUITY/HORIZON and REPLACE) have been developed which stratify ACS patients into risk profiles for these bleeding complications

within the in-hospital setting (Mathews et al., 2011; Mehran et al., 2010; Nikolsky et al., 2007; Subherwal et al., 2009). These risk scores and identified risk factors are summarised in **table 2.2**.

While the risk factors for major in-hospital bleeding have been well defined, those of bleeding events that occur in the longer-term after hospital discharge are unclear. Some studies (Alfredsson et al., 2017; Baber et al., 2016; Barra et al., 2013; Chen et al., 2019; Costa et al., 2017; Raposeiras-Roubín, Faxén, et al., 2018; Yeh et al., 2016) have reported on characteristics which may be associated with post-discharge bleeding, but the majority were either carried out in the PCI setting in clinical trials, or only considered major bleeding events, or were underpowered, or the majority of patients enrolled in the study were low-risk patients with stable coronary artery disease or other unspecified cardiovascular diseases (**table 2.2**).

Table 2.2: Bleeding risk assessment tools alongside characteristics identified to be associated with bleeding

Study	Country of origin	Setting	Presentation	ACS management strategy	Bleeding definition	Derivation cohort			Risk factors of bleeding
						N	Age	% of patients with ACS	
In-hospital setting									
REPLACE	US	Trial	ACS, Angina	PCI via the femoral artery	Major in-hospital bleeding	6,002	62.6 years (Mean)	Not available	Female gender, eGFR < 60, anaemia, age > 55 years, use of Intra aortic balloon pump, low molecular weight heparin and GP IIb/IIIa.
CRUSADE	US	Registry	NSTEMI	Not available	Major in-hospital bleeding	71,277	67 years (Median)	NSTEMI (100%)	Female gender, history of peripheral artery disease, diabetes mellitus, congestive heart failure, systolic blood pressure ≤ 110 vs 110-180mmhg, systolic blood pressure ≥ 180 vs 110-180mmhg, baseline haematocrit < 36%, creatinine clearance per 10 ml/min decrease and heart rate per 10bpm increase
ACUITY/HORIZON	Multi-centre	Trial	ACS	Medically, PCI and CABG	Major in-hospital bleeding	17,421	62.1 years (Mean)	ACS (100%)	Advanced age, female gender, anaemia, elevated serum creatinine, white blood cell count, NSTEMI and STEMI
ACTION	US	Registry	STEMI & NSTEMI	Not available	Major in-hospital bleeding	72,313	64.0 years (Median)	ACS (100%)	Female gender, age per 5-year increase, baseline serum creatinine per 1 mg/dl increase, St segment changes, St segment elevation, heart failure and/or shock on admission, diabetes, peripheral artery disease, bodyweight per 5 kg decrease, systolic blood pressure ≤ 130 vs 130-160mmhg, systolic blood pressure ≥ 160 vs 130-160mmhg, home warfarin use, heart rate on admission and baseline haemoglobin < 12g/dl

Study	Country of origin	Setting	Presentation	ACS management strategy	Bleeding definition	Derivation cohort			Risk factors for bleeding
						N	Age	% of patients with ACS	
GRACE	Multi-centre	Registry	ACS	Unclear	Major in-hospital bleeding	24,045	66.2 years (Median)	ACS (100%)	Age (per 10-year increase), female gender, history of renal insufficiency, history of bleeding mean arterial pressure (per 20 mmHg decrease), diuretics, low molecular weight heparin, thrombolytics, GP IIb/IIIa blockers, intravenous inotropes, other vasodilators, right heart catheterisation and PCI
Post-discharge setting									
DAPT	Multi-centre	Trial	ACS, SA, other	PCI	GUSTO moderate/severe bleeding at 12-30 months	11,648	61.3 years (Mean)	ACS (46%)	Age (per 10-year increase), peripheral arterial disease, hypertension, renal insufficiency or failure and thienopyridine
precise-DAPT	Multi-centre	Trial	ACS, SCAD	PCI	TIMI major/minor bleeding at 12 months	14,963	65 years (Median)	ACS (55.6%)	Age (per 10-year increase), previous bleeding, white cell count (for each increase of 1000 cells per microlitre), baseline haemoglobin (for each increase of 1g/dl), and creatinine clearance (for each increase of 10 mL/min)
TRILOGY-ACS	Multi-centre	Trial	NSTEMI & UA	Medically	GUSTO moderate/severe/life-threatening bleeding at 30 months	9,240	66 years (Median)	NSTEMI/UA (100%)	Age (per 5-year increase), female gender, creatinine (per 1 mg/dl increase), weight (per 5kg decrease), angiography at index hospitalisation, history of peptic ulcer disease, haemoglobin (per 1 g/dl decrease), beta-blocker at randomization, NSTEMI (vs UA), and systolic blood pressure per 10 mmHg

Study	Country of origin	Setting	Presentation	ACS management strategy	Bleeding definition	Derivation cohort			Risk factors of bleeding
						N	Age	% of patients with ACS	
BLEED-MI	Portugal	Hospital registry	STEMI & NSTEMI	Not available	Clinically significant bleeding at a median of 19.9 months	1,050	67.9 years (Mean)	MI (100%)	Advanced age, eGFR at admission, history of stroke/TIA, heart failure during hospitalisation, history of hypertension, diabetes, bleeding during hospitalisation, smoking until hospitalisation, haemoglobin at admission, blood urea nitrogen at admission and discharge antithrombotic therapy (whether 1 agent, 2 agents, 3 agents)
BleeMACS	Multi-centre	Registry	ACS	PCI	Serious spontaneous bleeding at 1 year	10,750	Unclear	ACS (100%)	Age, hypertension, vascular disease, history of bleeding, malignancy, creatinine and haemoglobin
PARIS	Multi-centre	Registry	ACS, SCAD	PCI	BARC 3-5 major bleeding at 2 years	4,190	63.6 years (Mean)	ACS (37.8%)	Age (per year increase), body mass index, triple therapy at discharge, anaemia, current smoking, and creatinine clearance < 60 ml/min.
BRIC-ACS	China	Registry	ACS	PCI	BARC ≥ 2	2,381	61 Years (Median)	ACS (100%)	Female gender, history of peptic ulcer disease, hypertension, multivessel lesion, dual therapy with aspirin and ticagrelor, body mass index, baseline haemoglobin, triglycerides, low-density lipoprotein-c

REPLACE: *Randomized evaluation of PCI linking angiomax to reduce clinical events,* ***CRUSADE:*** *Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines,* ***ACUITY****; acute catheterisation and urgent intervention triage strategy,* ***HORIZON-AMI****; Harmonizing outcomes with revascularisation and stents in acute myocardial infarction,* ***ACTION:*** *National cardiovascular data registry of acute coronary treatment and intervention outcome network registry get with the guidelines,* ***GRACE:*** *Global registry of acute coronary events,* ***DAPT;*** *Dual antiplatelet therapy study,* ***Precise-DAPT****: Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy,* ***TRILOGY-ACS:*** *Targeted platelet inhibition to clarify the optimal strategy to medically manage acute coronary syndromes,* ***BLEED-MI:*** *Bleed myocardial infarction,* ***BleeMACS:*** *Bleeding complications in a multicentre registry of patients discharged after an acute coronary syndrome,* ***PARIS:*** *Patterns of non-adherence to anti-platelet regimen in stented patients,* ***BRIC-ACS;*** *bleeding risk in real world Chinese acute coronary syndrome patients,* ***STEMI****: ST-Elevation myocardial infarction,* ***NSTEMI****: Non ST-Elevation myocardial infarction,* ***UA****:*

*Unstable angina, **SA:** Stable angina, **SCAD:** Stable coronary artery disease, **ACS**: Acute coronary syndrome, **PCI**: Percutaneous coronary intervention, **CABG**: Coronary artery bypass graft, **MI**: Myocardial Infarction, **BARC**: Bleeding academic research consortium, **GUSTO**: Global use of strategies to open occluded arteries**, TIMI**: Thrombolysis in myocardial infarction.*

2.2.3 Prognostic importance of bleeding

Bleeding was initially thought to be a benign and acceptable hazard due to the relative availability of blood products for transfusion. However, a growing body of evidence has shown that bleeding is an independent predictor of adverse outcomes including mortality (Eikelboom et al., 2006; Kinnaird et al., 2003; Manoukian et al., 2007; Rao et al., 2005, 2006). The risk of mortality with major in-hospital bleeding seems to be maintained regardless of the bleeding definition used (Kwok et al., 2014; Rao et al., 2006), with bleeding defined by REPLACE-2, STEEPLE and BARC criteria having the worst prognosis on mortality (Kwok et al., 2014). Compared with patients who did not sustain bleeding complications, patients who sustained in-hospital bleeding events are at increased risk of mortality in the early (within 30 days), and later stages (within 6 or 12 months) after hospital discharge for ACS (Eikelboom et al., 2006; Kwok et al., 2014; Rao et al., 2005). This increased risk of mortality, however, tends to be more pronounced within the first 30 days following hospital discharge (Eikelboom et al., 2006; Rao et al., 2005). Previous studies have shown that the risk of mortality from in-hospital bleeding may be dose-dependent, with risk of mortality increasing as the severity of bleeding increases (Rao et al., 2005, 2006). A previous study has also highlighted that the risk of mortality may depend on the site of the bleeding event, with events such as intracranial bleeds having the worst prognosis (Kwok et al., 2015).

While the prognostic impact of in-hospital bleeding events on mortality has been described, the indication that bleeding may continue to transpire even after hospital discharge (Khan et al., 2015), may mean that the risk of mortality after a bleed is likely to be maintained in the post-discharge setting.

2.3 Summary

This chapter has presented the clinical description of ACS, its epidemiology, management strategies, and the bleeding complications associated with these management strategies. The incidence, risk factors, and association of these bleeding events with mortality in the in-hospital setting were also described.

Whilst this chapter has shown that there was some evidence on the incidence and prognostic impact of bleeding events on mortality within the in-hospital setting, the next chapter (Chapter 3) will systematically review the current evidence on the incidence, and association of these bleeding events with outcomes such as mortality in the post-discharge setting.

Chapter 3.0: **Systematic review of the incidence, timing, and types/sites of bleeding after hospital discharge following ACS, and their prognostic impact on mortality, MACE, re-infarction, and rehospitalisation.**

3.1 Introduction

As highlighted in the preceding chapters, several studies have examined the incidence and association of major in-hospital bleeding events with outcomes such as mortality. However, following hospital discharge, patients with ACS may remain on dual antiplatelet therapy for up to 12 months, and aspirin indefinitely, so their risk of bleeding may persist in the longer-term after discharge. The study reported in this chapter will, therefore, examine the existing literature to collate current evidence on the incidence and prognostic impact of bleeding events on outcomes after hospital discharge for ACS using the methodology for systematic reviews.

A systematic review collates as much evidence as possible on a research question in a systematic, robust and replicable manner, such that conclusions derived from these evidences are relevant, up to date and useful. It involves first deconstructing the research question using a set of parameters, typically: the population, intervention, comparison, and outcome to be examined (Khan et al., 2003). These form the basis for a search strategy used in the literature search. A protocol is drafted, reviewed and piloted. Databases and institutional websites are searched, and relevant literature retrieved (Uman, 2011). Retrieved articles are screened by title, abstract, and full text following a predefined set of inclusion and exclusion criteria (Uman, 2011). Included studies are then characterised by quality, intervention, outcomes, research design, and type of analysis. Relevant outcomes are extracted from these studies and synthesised qualitatively or quantitatively to derive conclusions (Uman, 2011).

Accordingly, a systematic review of the incidence, timing, and types/sites of bleeding events following hospital discharge for ACS was carried out. The prognostic impact of these bleeding events on mortality, MACE, re-infarction, and rehospitalisation were

likewise explored in this systematic review. A paper arising from this systematic review has been published and is attached in **Appendix 3.1**.

3.2 Aims and objectives

3.2.1 Aims

The aims of the systematic review were twofold:

- The primary aim was to determine the incidence, timing, and types/sites of bleeding complications after hospital discharge following ACS.
- The secondary aim was to determine the prognostic impact of bleeding on mortality, MACE (as defined in individual studies), re-infarction, and rehospitalisation after hospital discharge following ACS.

3.2.2 Specific objectives

The primary objectives were to:

- Determine the incidence of bleeding after hospital discharge following ACS.
- Determine the incidence of bleeding by time following hospital discharge for ACS.
- Determine the incidence of site-specific bleeding events (such as gastrointestinal, intracranial) after hospital discharge following ACS.

The secondary objectives were to:

Determine the association between bleeding following hospital discharge for ACS and subsequent risk of

- Mortality.
- MACE (as defined in individual studies).
- Re-infarction.
- Rehospitalisation.

3.3 Methods

3.3.1 Eligibility criteria

For the primary objectives, studies that reported on the incidence, timing, and site-specific bleeding events after ACS following hospital discharge were included. For the secondary objectives, studies that compared patients with bleeding versus those without bleeding in relation to the outcomes of all-cause mortality, MACE, myocardial re-infarction, and rehospitalisation after hospital discharge following ACS were included in the review. RCTs where bleeding events were reported as primary or secondary or safety outcomes, and observational studies which were published in English were included. Studies, where the intervention was CABG or elective PCI, were excluded. Studies in which the cohort comprised patients with stable angina or other coronary artery disease were likewise excluded. **Table 3.1** gives the detailed inclusion and exclusion criteria for the review. For studies using the same data source, only one was included in the review, based on (in order of): (1) quality, (2) sample size, (3) length of follow-up, unless the studies reported on different outcomes.

Table 3.1: Inclusion and exclusion criteria specific to primary and secondary objectives

Inclusion criteria	Exclusion criteria
Primary objective	
• Participants aged 18 years and over	× Cannot be ascertained whether bleed occurred in-hospital or post-discharge
• Participants discharged with an ACS diagnosis at index hospitalisation	× In-hospital bleeds only
• Randomised controlled trial or Observational study	× Incidence and 95% CI or number of bleeding events cannot be extracted or calculated
• Bleeding measured after hospital discharge	× Study population combined patients with ACS and other coronary diseases such as stable angina
• Any type of bleeding examined (such as gastrointestinal bleed) post-hospital discharge for ACS.	× Post-discharge bleeding after PCI, without specifying the clinical presentation for the PCI or whether the PCI was elective.
• Incidence and associated 95% confidence interval can be extracted or calculated	× Only reporting CABG related bleeds
	× Conference/study abstracts, editorials and reviews
Secondary objective	
• Participants aged 18 years and over	× Cannot be ascertained whether bleed occurred in-hospital or post-discharge
• Participants discharged with an ACS diagnosis at index hospitalisation	× In-hospital bleeds only
• Randomised controlled trial or Observational study	× Study population combined patients with ACS and other coronary diseases such as stable angina
• Bleeding measured after hospital discharge	× Post-discharge bleeding after PCI, without specifying the clinical presentation for the PCI or whether the PCI was elective.
• Evaluated outcome of, or a composite of, mortality, MI, rehospitalisation, and MACE in bleed Vs no bleed cohorts	× Only reporting CABG related bleeds
	× Conference/study abstracts, editorials and reviews

***ACS**: Acute Coronary Syndrome, **PCI**: Percutaneous Coronary Intervention, **CI**: Confidence Interval, **CABG**: Coronary Artery Bypass Graft, **MI**: Myocardial Infarction*

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3.3.2 Literature search

3.3.2.1 Search terms

Supported by the systematic review team within the Research Institute for Primary Care and Health Sciences, a comprehensive search strategy combining keywords and related database-specific subject headings for both the primary and secondary objectives were developed. Specific to the primary objectives, the search strategy combined terms related to incidence (incidence, prevalence), ACS (acute coronary syndrome, myocardial infarction, NSTEMI/UA, STEMI), and bleeding (haemorrhage, hemorrhage, bleed, bleeding), with terms related to post-discharge (post, late-onset, discharge, home, hospital discharge) using the Boolean connectors "OR" and "AND" as appropriate (see **appendix table 3.1** for search terms). For the secondary objectives, the primary search terms were used except terms related to incidence were replaced by terms related to prognostic impact (mortality, death, MACE, re-infarction, hospital readmission, heart re-infarction, cardiovascular/hospital mortality). Due to the overlap of the articles for the primary and secondary objectives, the systematic review team recommended combining the two search strategies (for the primary and secondary objectives) with the Boolean operator "OR", such that the search strategy was able to pick up articles relevant to either the primary or secondary objective. Keywords and related database-specific subject headings were selected in collaboration with a GP (UTK) and an Interventional Cardiologist (MAM) with a keen interest in the field of bleeding complications. The selection process was based upon search terms used in previously published systematic reviews of in-hospital bleeding events (Kwok et al., 2014, 2015). The final search strategy was pre-piloted on Medline (HDAS), Embase (Ovid SP), Amed (Ovid SP) and Central (Cochrane central register of controlled trials) for sensitivity and specificity (see **appendix**

table 3.1 for the final search strategy). For each of these databases, the final search strategy was re-formatted to conform to their search criteria.

3.3.2.2 Databases searched

Medline (HDAS; 1946 – August 2018), Embase (Ovid SP; 1974 – August 2018), Amed (Ovid SP; 1985 – August 2018) and Central were searched up to August 2018 using the final search strategy (in **appendix table 3.1**). The search was re-run in July 2019 to identify recent publications. The *Journal of the American College of Cardiology (JACC), European Heart Journal (EHJ), Heart*, and *Circulation* were electronically searched for relevant articles and grey literature. The bibliographies of included studies and relevant review articles identified from each database were scrutinised for additional relevant articles. Citation tracking of included studies via Web of Science was carried out to retrieve additional relevant articles.

3.3.3 Study selection

The titles of all identified articles were screened by NI, and those which were obviously irrelevant were eliminated at this stage. The abstracts of the remaining articles were screened independently by NI and a statistician with experience in cardiovascular research (JP). Articles which clearly did not fulfil the study inclusion/exclusion criteria based on the abstract were eliminated and the remainder retrieved for further screening. Discordances were resolved by consensus between NI, JP and MAM. The full texts of the remaining articles were then screened by NI, with JP also screening 1 in 10. Overall, there was substantial agreement between NI and JP (kappa = 0.783, p = 0.000336). At this

stage, only articles fulfilling the inclusion/exclusion criteria were retrieved for inclusion in the review.

3.3.4 Data extraction

Characteristics, including study design, setting, length of follow-up, in-hospital interventions, participant characteristics, and discharged antithrombotic therapy, were extracted from individual studies. The outcomes of incidence of post-discharge bleeding and associated 95% confidence intervals, time of bleed, site/type of bleed, and the adjusted and unadjusted associations of bleeding with mortality, MACE, re-infarction and rehospitalisation were also extracted from individual studies onto a pre-piloted and formatted spreadsheet. In studies where incidence and associated 95% confidence intervals were not reported, but relevant data were available, incidence per 100 persons at risk were calculated (i.e. essentially derived as a proportion). For studies that combined in-hospital and post-discharge bleeds, and episodes of bleeds were stratified by time (for instance at 30 days, 6 months, 12 months after ACS), bleeds that occurred within the initial 30 days were considered to be in-hospital bleeds (decided by consensus of NI, KPJ, MAM, and UTK) and therefore removed from the numerator and denominator. In studies where bleeding was measured by multiple criteria (definitions), preference was given to BARC criteria since it is the preferred definition for reporting bleeding events (Mehran et al., 2011).

Authors of original studies were contacted where necessary data were missing or to confirm methodological aspects or other characteristics of the study. Overall, ten authors were contacted, and four responded to the requests. Based on these responses, two studies did not meet the review inclusion criteria and were therefore excluded, and the

remaining two were included in the review. Data extractions were carried out by NI, but the extraction process was repeated twice, and results compared for consistency.

3.3.5 Quality assessment

Quality assessment is a methodical inspection of a study's design and conduct such that inferences drawn from such a study are reliable and free from bias (Lohr and Carey, 1999; Zaccai, 2004). Quality assessment is partitioned into internal validity and external validity. Internal validity is the extent to which the results of a study are reflective of the participants, that is to say, the results were not influenced or cannot be explained by systemic bias emanating from (dependent on study design) confounding, blinding, attrition, allocation bias, analysis or data collection. While external validity is the extent to which the results of a study can be extrapolated beyond the study population onto the general population from which the study sample was drawn. In systematic reviews, assessing the quality of studies is simplified by the use of quality assessment tools. Applicability of these tools depend upon the type/design of the studies included in each review (whether interventional or observational design).

Supported by the systematic review team within the Research Institute, the Newcastle Ottawa Scale (NOS) for assessing the risk of bias in non-randomised observational studies (Wells et al., 2011) and the Scottish Intercollegiate Guideline Network (SIGN) (SIGN, 2017) quality assessment tools were selected and used to appraise the quality of included studies in the present review. Observational cohort studies and post hoc observational analyses of RCTs were appraised by the NOS quality assessment scale, whereas RCTs were evaluated using the SIGN quality assessment tool. The NOS quality assessment scale contains eight numbered items (but only seven used in this review) partitioned into three

categories of selection, comparability and outcome. A maximum of one star is allocated to a high quality study for each numbered item under selection and outcome and a maximum of two stars for comparability. A high quality study can be awarded a maximum of nine stars.

In this review, quality assessment was carried out simultaneously for both primary and secondary objectives, because the majority of the studies that reported on the secondary objectives also reported on the primary objectives (or data were extracted to calculate the primary objectives). Also, these studies were not designed using the conventional methodology employed for incidence studies, but incidence/episodes of bleeding were typically reported as safety or secondary outcome measures. Therefore, the quality assessment was based on each study primary objective (that is to say how each study was designed and conducted in attempting to answer its own primary objective). Quality assessments with NOS in this review were as follows:

Selection

1. *Representativeness of the exposed cohort*: In this review, a star was allocated if a study recruited participants from hospital in-patient setting or the cohort were patients enrolled in medical/hospital registries.
2. *Selection of the non-exposed cohort*: In this review, if a study had a non-exposed group and both exposed and unexposed groups were drawn from the same registry, or both were participants recruited from the same hospital or community, a maximum of one star was allocated.
3. *Ascertainment of exposure*: In this review, a star was awarded to each study, if the exposure under investigation was ascertained in hospital in-patients, or from medical records, or registries, or structured interviews.

Comparability

1. *Comparability of cohorts on the basis of the design or analysis*: In this review, a star was awarded to a study if the study controlled for confounding factors in the analysis or participants were matched on confounding factors.

Outcome

1. *Assessment of outcome*: In this review, a star was allocated if the outcome of a study was assessed by an independent panel blinded to the intervention received or outcomes were extracted from medical records/registries or outcomes were self-reported but confirmed by examining medical records.
2. *Was follow-up long enough for outcomes to occur*: In this review, a star was allocated if the length of follow-up for the primary objective of the study was more than 30 days (based on consensus of MAM and KPJ).
3. *Adequacy of follow-up of cohorts*: In this review, a star was awarded if a study specified that all participants were accounted for at the end of the study or the study reported the number of participants lost to follow-up and the attrition rate was less than 20%.

Studies with an overall number of stars less than or equal to five were categorised as low quality studies, while those with greater than or equal to six stars were categorised as high quality studies. These cut-offs were based on a comprehensive search of the literature which indicated that a study with NOS score greater than or equal to six can be considered a good study (Zhu et al., 2016); thus this criterion was applied as the cut off for good quality.

The SIGN quality assessment tool for RCTs contains ten numbered questions (SIGN, 2017). Each question is assessed by three response categories: yes, no, can't say. Based on these responses, a study is awarded either two plus signs (denoting high quality) or one (denoting acceptable quality) or a minus sign (denoting low quality). RCTs included in the review were assessed by these questions and based on the responses, each study was categorised as high quality, acceptable quality or low quality study; again based on that RCT's primary objective. For a detailed description of the SIGN quality assessment tool, the reader is referred to https://www.sign.ac.uk/checklists-and-notes.html.

3.3.6 Data synthesis

Narrative synthesis involves the use of words and textual data as opposed to statistical pooling to combine results from individual studies in order to derive a single conclusion (Rodgers et al., 2009). Narrative synthesis is mostly applied when individual studies are too heterogeneous to combine statistically by meta-analysis, but may also be used alongside meta-analysis and other numerical analysis (Rodgers et al., 2009).

For both the primary and secondary objectives of this review, a narrative synthesis approach was applied due to heterogeneity in relation to length of follow-up, type of ACS presentation, the definition of bleeding used, type of bleeding examined, severity of bleeding examined and discharge therapy across studies. For the primary objective, the narrative synthesis was carried out in stages. Initially, the incidence of bleeding overall was summarised separately for observational studies and RCTs. To assess the risk of bias on reported incidence, the incidence of bleeding was then stratified by quality of included studies, dichotomised as low and high quality. The incidence of bleeding was then stratified by type of ACS presentation (STEMI, NSTEMI/UA) and discharge antithrombotic

drug combinations and duration (single antiplatelet (SAPT), dual antiplatelet (DAPT) and receipt of oral anticoagulant) in studies that reported these. To assess the incidence of bleeding by time from hospital discharge, the incidence of bleeding was stratified by follow-up time within studies that looked at multiple time-points. Where studies allowed, the incidence of major, minor, and nuisance bleeds, and the incidence of different types of bleeding events were examined.

The strength of the evidence (SOE) for the association of bleeding with mortality, MACE, re-infarction, and rehospitalisation was assessed following the Agency for Healthcare Research and Quality guideline (AHRQ) (Owens et al., 2010). For each of these associations, the assessment was carried out by:

a) Evaluating the aggregate quality of individual studies that reported on that objective, and scored as low, medium or high risk of bias (risk of bias).
b) Whether the effect estimates in studies that reported on that objective are in agreement in regards to the direction of the effect (consistency).
c) Whether the studies that reported on that objective showed a direct link (association) between the exposure and the outcome of interest (directness).
d) Whether there is a high degree of certainty surrounding the effect estimates in studies that reported on that objective (precision).

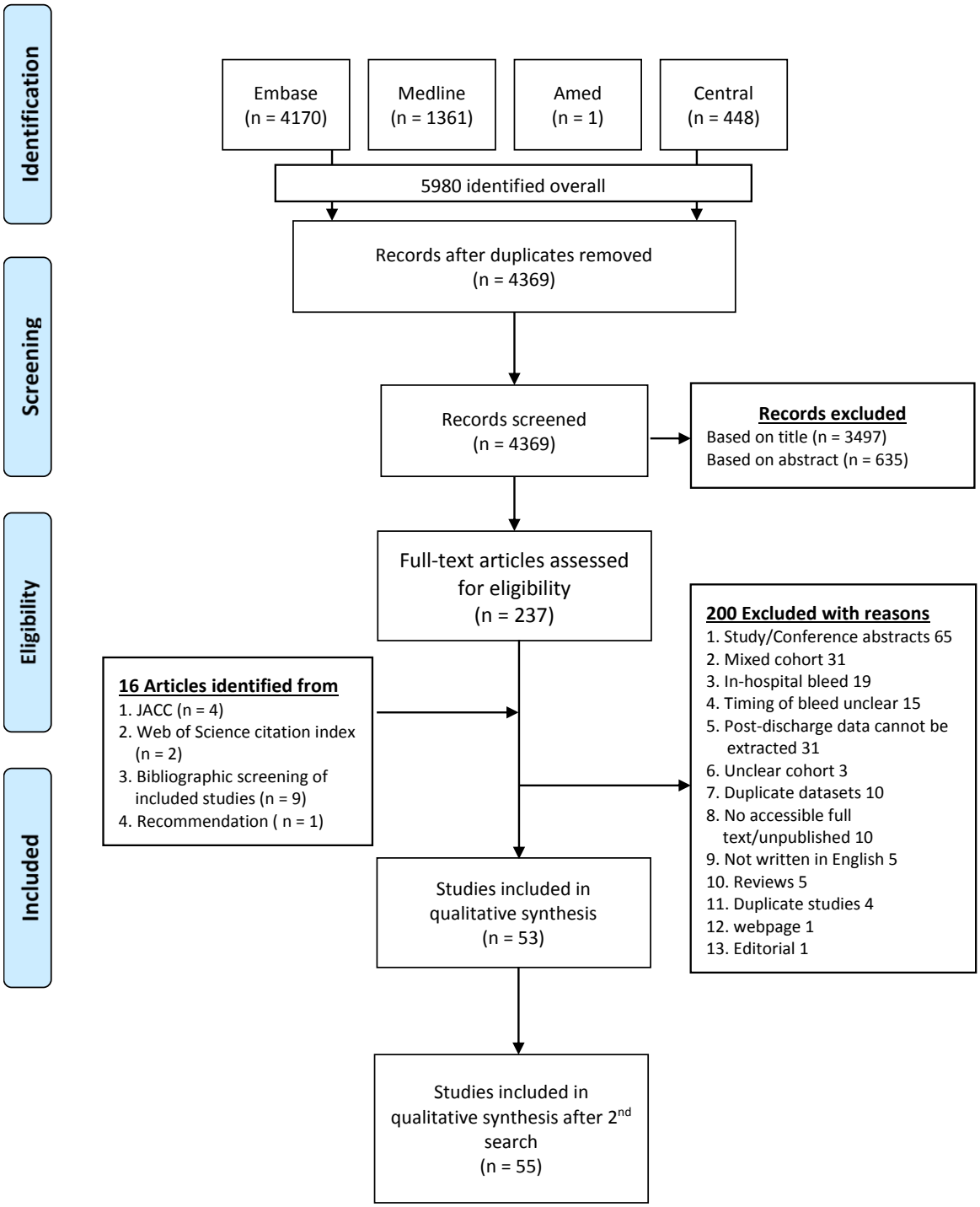
Based on these overall assessments, a grade was assigned to each of the secondary objectives examining the association between bleeding and mortality, MACE, re-infarction, and rehospitalisation, indicating the strength of the evidence for these associations. A grade assigned as high indicates that the evidence reflects a true association and further research is unlikely to change the effect estimate. A moderate grade indicates that the evidence shows a true association, but further research may

change the effect estimate. A low grade indicates that the evidence reflects a true association, but further research may change confidence in the evidence and the effect estimate. An insufficient grade indicates that evidence is unavailable or does not permit a conclusion (Owens et al., 2010). For a detailed description of the assessment and grading procedure, the reader is referred to Owens et al (Owens et al., 2010).

3.4 Results

The initial search of Medline, Embase, Amed and Central (Cochrane) identified 37 studies (Amin et al., 2013, 2016; Bacquelin et al., 2016; Barra et al., 2013; Bergen et al., 1994; Blin et al., 2017; Boggon et al., 2011; Braun et al., 2015; Brinkert et al., 2017; Caneiro-Queija et al., 2018; Carrero et al., 2017; Chamberlain et al., 2015; Cuisset et al., 2009, 2017; Effron et al., 2018; Ertaş and Tokgozoglu, 2018; Fosbol et al., 2012; Garay et al., 2018; Graipe et al., 2015; Han et al., 2015; Kassaian et al., 2015; Khan et al., 2015; Kohli et al., 2014; Lattuca et al., 2016; Mahaffey et al., 2014; Mrdovic et al., 2013; Raposeiras-Roubín, Caneiro Queija, et al., 2018; Savonitto et al., 2012; Schjerning Olsen et al., 2015; Sørensen et al., 2009; Sra et al., 2016; Valgimigli et al., 2016; Voss et al., 2016; Wang et al., 2015; Wong et al., 2006; Yetgin et al., 2018; Yusuf et al., 2006), 4 studies were further identified from the electronic search of JACC database (Brener et al., 2016; Nikolsky et al., 2015; Palmerini et al., 2014; Yeh et al., 2015), 2 from Web of Science citation index (Atar et al., 2006; Cuschieri et al., 2014), 9 from bibliographic screening of included studies (Bonaca et al., 2015; Buresly et al., 2005; Carrabba et al., 2016; Costa et al., 2015; Jolly et al., 2008; Kazi et al., 2015; Ko et al., 2010; Lamberts et al., 2013; Tsai et al., 2011), and finally, 1 from recommendation by an expert within the field (Garay et al., 2016). Fifty-three studies (36 observational studies and 17 RCTs) were identified after the initial search (**figure 3.1**). Two further studies were identified following the second update search in July 2019 (Chen et al., 2019; Sorrentino et al., 2018) (see **appendix figure 3.1**). Overall, fifty-five studies were included in the review (38 observational studies and 17 RCTs) with a combined cohort of 721,342 participants for the primary objectives, and 189,698 for the secondary objectives.

Figure 3.1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart depicting steps involved in selecting or rejecting studies for inclusion in the review



3.4.1 Characteristics of excluded studies

Figure 3.1 describes the number of excluded studies alongside reasons for exclusions based on the initial literature search. Eighty-four percent of the studies (n = 200) did not fulfil the review inclusion/exclusion criteria and were therefore excluded after full text review. The most common reasons for exclusion were; abstracts (32.5%) such as paper and conference abstracts where the full text articles were not published, mixed cohort studies (15.5%) where the population were a mixture of patients with ACS and those with stable coronary artery diseases or other unspecified cardiovascular diseases, studies where post-discharge data on bleeding could not be extracted (15.5%), studies examining in-hospital bleeds (9.5%) only, studies where it was unclear when bleeding occurred (7.5%), and studies where the full text article could not be retrieved/unpublished (5.0%). These reasons were also the cause for excluding studies after the second literature search (see **appendix figure 3.1**).

3.4.2 Characteristics of included studies

The characteristics of included studies (for the primary objectives) are summarised in **table 3.2** for observational studies and **table 3.3** for RCTs. Overall, fifty-two studies reported on the primary objectives, of which 69% (n = 36) were cohort studies and 31% (n = 16) were RCTs. The characteristics of included studies for the secondary objectives are summarised in **table 3.4**. Overall, nine studies reported on the secondary objectives, of which 8 were cohort studies and one was an RCT.

Length of follow up varied from 1 month (Cuisset et al., 2009) to just over 4 years (Kazi et al., 2015) post-hospital discharge. The number of participants ranged from 193 to 187,386. The definitions for bleeding used by each study in the review are provided in

appendix table 3.2. Some studies (n = 25) did not report bleeding events based on recognised definitions (such as BARC). Of the included studies, 29 had specified the in-hospital ACS management strategy. In 28 of these studies, PCI was the baseline management strategy, and in one study, the management strategy was a combination of PCI, angiography and medical therapy.

3.4.3 Risk of bias assessment

Summaries of risk of bias of individual studies are provided in **tables 3.2**, **3.3**, and **3.4**. Justification for each score/rating is provided in **appendix table 3.3** for observational studies, and studies which were post hoc observational analysis of RCTs, and **appendix table 3.4** for RCTs. Overall, seventy-six percent (n = 29) of the observational studies were at high risk of bias (for addressing their primary objective) due to lack of reporting on attrition rate and comparability of cohorts based on analysis (whether study adjusted for confounders or not). Twenty-four percent (n = 9) were at low risk of bias. Two RCTs were high risk, four were at an acceptable risk of bias, and two were low risk. The main reasons for low quality in RCTs were inadequate reporting on randomisation, concealment, blinding, adequacy and reliability of outcome measurements. For studies that were post hoc observational analysis of RCTs, five were at high risk, and four were at low risk of bias.

Table 3.2: Summary of observational studies included in the review by length of follow-up, bleeding definition used and in-hospital management strategy

Author/year	Location	Setting	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed (n)	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Cuisset et al 2009	France	In-patient	Prospective cohort	1 month	TIMI major/minor	PCI	597	16	2.68 (1.66, 4.31) *	2
Braun et al 2014	Sweden	Registry	Retrospective cohort	3 months	BARC 2-5	PCI	263	26	9.89 (6.84, 14.1) *	5
Amin et al 2016	US	Registry	Retrospective cohort	6 months	BARC 1-5	PCI	9290	2246	24.2 (23.3, 25.1) *	5
Amin et al 2013	US	Registry	Retrospective cohort	12 months	BARC 1	PCI	3560	1335	37.5 (35.9, 39.1) *	4
Lattuca et al 2016	France	In-patient	Prospective cohort	12 months	BARC 1-3	PCI	369	132	35.8 (31.1, 40.8) *	5
Bacquelin et al 2015	France	Registry	Prospective cohort	12 months	BARC 2-5	PCI	1006	79	7.85 (6.35, 9.68) *	5
Chen et al 2019	China	Registry	Cohort	12 months	BARC ≥ 2	PCI	2381	117	4.91 (4.12, 5.86) *	5
Palmerini et al 2014	Multi-centre	Unclear	Prospective cohort	12 months	BARC (any)	PCI	1053	41	3.91 (2.89, 5.26) *	5
Kassaian et al 2015	Iran	Registry	Prospective cohort	12 months	GUSTO mild, moderate, severe.	NR	1640	23	1.40 (0.94, 2.10) *	4
Yetgin et al 2018	The Netherland	Registry	Cohort	12 months	TIMI major	PCI	2443	23	0.94 (0.63, 1.41) *	5

Author/year	Location	Setting	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed (n)	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Fosbol et al 2012	US	Registry	Prospective cohort	12 months	Bleed leading to hospitalisation	NR	7619	928	12.2 (11.5, 12.9) *	7
Tsai et al 2011	Taiwan	Registry	Retrospective cohort	12 months	Gastrointestinal bleed	NR	3580	273	7.63 (6.80, 8.54) *	5
Garay et al 2016	Spain	Registry	Retrospective cohort	12 months	Bleed leading to hospitalisation, transfusion, or suspension of antithrombotics	NR	1375	69	5.02 (3.98, 6.30) *	3
Garay et al 2018	Multi-centre	Registry	Cohort	12 months	Intracranial bleeding or bleed leading to hospitalisation or transfusion	PCI	15401	489	3.18 (2.91, 3.46) *	5
Effron et al 2018	US	Registry	Retrospective cohort	12 months	Bleed leading to hospitalisation or transfusion	PCI	15788	492	3.12 (2.86, 3.40) *	4
Brinkert et al 2017	Canada	Registry	Cohort	12 months	Hospitalisation with major bleeding	PCI, angiography, medically	22312	588	2.72 (2.51, 2.94) *	5
Ko et al 2010	Canada	Registry	Cohort	12 months	Bleed leading to hospitalisation	PCI	8672	230	2.65 (2.33, 3.01) *	6
Sorrentino et al 2018	US	In-patient	Retrospective cohort	12 months	Bleed leading to hospitalisation or transfusion	PCI	4503	83	1.84 (1.49, 2.28) *	5
Boggon et al 2011	UK	Registry	Retrospective cohort	12 months	Any bleeding in patient GPRD or HES record	NR	7543	NR	11.4 (10.4, 12.6) †	5

Author/year	Location	Setting	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed (n)	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Carrero et al 2016	Sweden	Registry	Prospective cohort	12 months	Major bleed	NR	36001	333	0.92 (0.83, 1.03) *	6
Graipe et al 2015	Sweden	Registry	Prospective cohort	12 months	Intracranial bleed	NR	187386	590	0.32 (0.30, 0.34)	6
Wang et al 2015	US	Registry	cohort	12 months	Haemorrhagic stroke	NR	169863	335	0.20 (0.18, 0.22)	5
Barra et al 2013	Portugal	In-patient	Prospective cohort	13.4 months (mean)	TIMI/GUSTO major criteria	NR	852	60	7.04 (5.51, 8.96) *	3
Sra et al 2016	Canada	In-patient	Prospective cohort	15 months	BARC 1-5	PCI	2034	440	21.6 (19.9, 23.5) *	5
Caneiro-Queija et al 2018	Spain	Registry	Cohort	455 days (median)	BARC 2 - 3	PCI	4229	500	11.8 (10.9, 12.8) *	6
Sorensen et al 2009	Denmark	Registry	Prospective cohort	476.5 days (mean)	Fatal and non-fatal bleed	PCI	40812	1967	4.82 (4.62, 5.03) *	5
Raposeiras-Roubin et al 2018	Multi-centre	Registry	Cohort	17.2 months (mean)	BARC 3 or 5	PCI	4310	66	1.53 (1.21, 1.94) *	6
Cuschieri et al 2014	US	Registry	Retrospective cohort	1.7 years (mean)	Gastrointestinal bleed	NR	3218	107	3.33 (2.76, 4.00) *	4
Wong et al 2006	UK	In-patient	Retrospective cohort	21 months	CURE major/life threatening	NR	224	15	6.70 (4.10, 10.8) *	4

Author/year	Location	Setting	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed (n)	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Buresly et al 2005	Canada	Registry	Cohort	654 days (mean)	Bleed leading to hospitalisation	NR	21443	1428	6.66 (6.33, 7.00) *	4
Voss et al 2016	New Zealand	Registry	cohort	1.94 years (mean)	Other	NR	3666	206	5.88 (5.15, 6.71) *	4
Brener et al 2016	US and Germany	Registry	Prospective cohort	24 months	TIMI, GUSTO and ACUITY Major bleed	PCI	8582	430	5.17 (4.71, 5.66) *	4
Ertas et al 2018	Turkey	Registry	Cohort	24 months	Physician-confirmed bleeding event	NR	1010	21	2.08 (1.36, 3.16) *	4
Blin et al 2017	France	Registry	Cohort	3 years	Hospitalisation with bleeding	NR	1585	49	3.09 (2.35, 4.06) *	5
Chamberlain et al 2016	US	Registry	Cohort	4.3 years	Other	NR	1159	312	26.9 (24.5, 29.6) *	6
Kazi et al 2015	US	Registry	Retrospective cohort	4.42 years (mean)	Major spontaneous bleeding	PCI	22527	368	1.63 (1.48, 1.81) *	5

Incidence and associated 95% CI calculated from data within study, †Incidence and associated 95% CI reported within study per 100 person-years,* ***CI**: Confidence Interval,* ***NR****; not reported,* ***BARC****; bleeding academic research consortium,* ***GUSTO****; global use of strategies to open occluded arteries,* ***TIMI****; thrombolysis in myocardial infarction,* ***ACUITY****; acute catheterisation and urgent intervention triage strategy,* ***CURE****; clopidogrel in unstable angina to prevent recurrent events,* ***GPRD****; general practice research database,* ***HES****; hospital episodes statistics,* ***AMI****; acute myocardial infarction,* ***PCI****; percutaneous coronary intervention.*

Table 3.3: Summary of RCTs included in the review by length of follow-up, bleeding definition used and in-hospital management strategy

Author/year	Location	Trial	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Yusuf et al 2006	Multi-centre	OASIS - 5	RCT	6 months	OASIS-5 major	NR	20078	357	1.84 (1.66, 2.03) *	High
Jolly et al 2009	Multi-centre	CURE	Post hoc analysis of RCT	8 months	CURE major	PCI	2658	28	1.07 (0.74, 1.54) *	6†
Khan et al 2015	Multi-centre	APPRAISE-2	Post hoc analysis of RCT	240 days (median)	Any bleeding event	NR	7392	506	7.32 (6.73, 7.96) *	6†
Carraba et al 2016	Italy	BLESS	RCT	12 months	BARC 1-3	PCI	193	76	39.4 (32.8, 46.4) *	Acceptable
Cuisset et al 2017	France	TOPIC	RCT	12 months	BARC ≥ 2	PCI	634	106	16.7 (14.0, 19.8) *	low
Han et al 2015	China	BRIGHT	RCT	12 months	BARC 1-5	PCI	2194	47	2.33 (1.76, 3.08) *	Acceptable
Savonitto et al 2012	Italy	Italian Elderly ACS	RCT	12 months	BARC 2, 3a & 3b	NR	313	3	0.96 (0.33, 2.78) *	Acceptable
Mrdovic et al 2013	Serbia	RISK-PCI	Post hoc analysis of RCT	12 months	TIMI major/minor	PCI	2045	25	1.29 (0.87, 1.89) *	5†

Author/year	Location	Trial	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Atar et al 2006	Multi-centre	OPUS-TIMI 16	Post hoc analysis of RCT	12 months	Gastrointestinal bleed	NR	10288	104	1.02 (0.84, 1.24) *	4†
Kohli et al 2014	Multi-centre	TRITON-TIMI 38	Post hoc analysis of RCT	15 months	TIMI major/minor	PCI	12674	407	3.23 (2.94, 3.56) *	6†
Mahaffey et al 2014	Multi-centre	TRACER	Post hoc analysis of RCT	502 days (median)	TIMI major/minor	NR	11368	236	2.12 (1.87, 2.41) *	6†
Yeh et al 2015	US	DAPT	RCT	18 months	BARC 2-5	PCI	3576	111	3.10 (2.58, 3.72) *	Acceptable
Costa et al 2015	Italy	PRODIGY	Post hoc analysis of RCT	24 months	BARC 2-5	PCI	1465	82	5.60 (4.53, 6.89) *	5†
Bonaca et al 2015	Multi-centre	PEGASUS-TIMI 54	RCT	33 months	TIMI major	NR	21162	435	2.08 (1.89, 2.28) *	High
Nikolsky et al 2015	Multi-centre	HORIZON-AMI	Post hoc analysis of RCT	3 years	HORIZON major	PCI	3602	63	2.15 (1.68, 2.74) *	4†
Bergen et al 1994	The Netherland	ASPECT	RCT	37 months	Major bleed	NR	3404	99	2.91 (2.39, 3.53) *	Low

Incidence and associated 95% CI calculated from data within study, † Quality assessed by Newcastle Ottawa Scale, **CI: Confidence Interval, **NR**; not reported, **BARC**; bleeding academic research consortium, **TIMI**; thrombolysis in myocardial infarction, **CURE**; clopidogrel in unstable angina to prevent recurrent events, **HORIZON**; harmonizing outcomes with revascularisation*

*and stents**, RCT**; randomised controlled trial**, OASIS-5**; the fifth organization to assess strategies in acute ischemic syndromes, **APPRAISE-2**; Apixaban for prevention of acute ischemic events, **BLESS;** Bleeding events and maintenance dose of prasugrel, **TOPIC;** Timing of platelet inhibition after acute coronary syndrome, **BRIGHT;** Bivalirudin in acute myocardial infarction vs heparin and glycoprotein inhibitor plus heparin, **RISK-PCI;** Risk scoring model to predict net adverse cardiovascular outcomes after primary percutaneous coronary intervention, **TRACER**; Thrombin receptor antagonist for clinical event reduction in acute coronary syndrome, **OPUS-TIMI 16;** Orbofiban in patients with unstable coronary syndrome-thrombolysis in myocardial infarction 16, **TRITON-TIMI 38;** Trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38, **DAPT;** Dual antiplatelet therapy study, **PRODIGY;** Prolonging dual antiplatelet treatment after grading stent induced intimal hyperplasia, **PEGASUS-TIMI 54**; Prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared to placebo on a background of aspirin thrombolysis in myocardial infarction 54, **HORIZON-AMI**; Harmonizing outcomes with revascularisation and stents in acute myocardial infarction, **ASPECT;** Anticoagulants in the secondary prevention of events in coronary thrombosis, PCI; Percutaneous coronary intervention*.

3.4.4 Primary objectives

This section reports and summarises the incidence, timing, and types of post-discharge bleeding events as reported in included studies. It should be noted that in the majority of studies, it was unclear whether patients were included in the numerator more than once if they had multiple episodes of bleeding events.

3.4.4.1 Incidence of bleeding

In a cohort of 618,296 participants, 14,417 (2.3%) episodes of bleeds were reported in thirty-six observational studies and 2,685 (2.6%) episodes in a cohort of 103,046 participants in sixteen RCTs (721,342 participants overall). A summary of the incidence from each study is presented by length of follow-up, bleeding definition used, and in-hospital management strategy in **table 3.2** for observational studies and **table 3.3** for RCTs. The overall incidence of bleeding within the first 12 months following hospital discharge for ACS varied from 0.2 (Wang et al., 2015) to 37.5 (Amin et al., 2013) percent in observational studies, and between 0.96 (Savonitto et al., 2012) and 39.4 (Carrabba et al., 2016) percent in RCTs. But, overall, the length of follow up varied from 1 month to just over 4 years in observational studies, and between 6 months and 3 years in RCTs.

The incidence of bleeding stratified by type of ACS presentation (STEMI, NSTEMI/UA) and discharge antithrombotic drug combinations and duration (SAPT, DAPT and receipt of oral anticoagulant) are summarised by length of follow-up and the bleeding definition used in **appendix tables 3.5**, **3.6**, and **3.7**. In observational studies, the incidence of bleeding based on BARC criteria in those with STEMI ranged from 4.71 to 39.8 percent in the first 12 months following hospital discharge, and from 3.91 to 35.7 percent in those with NSTEMI/UA (**appendix table 3.5**). Among those discharged on DAPT with aspirin and a

P2Y12 inhibitor, the incidence of bleeding within the first 12 months based on BARC criteria ranged from 3.91 to 38.8 (**appendix table 3.6**) in observational studies, and between 0.96 to 47.4 percent in RCTs (**appendix table 3.7**). In both observational studies and RCTs, incidence of bleeding was generally higher in low quality studies.

3.4.4.2 Timing of bleeding

There were only nine observational studies (Barra et al., 2013; Brinkert et al., 2017; Chen et al., 2019; Ertaş and Tokgozoglu, 2018; Garay et al., 2016; Lattuca et al., 2016; Palmerini et al., 2014; Wong et al., 2006; Yetgin et al., 2018) and two RCTs (Nikolsky et al., 2015; Yusuf et al., 2006) comprising 55,699 participants that reported bleeding episodes at different time points during follow-up. In these studies, around one-half of bleeds that occurred in the first year following hospital discharge for ACS happened in the initial 1 – 3 months (**figure 3.2** and **3.3**).

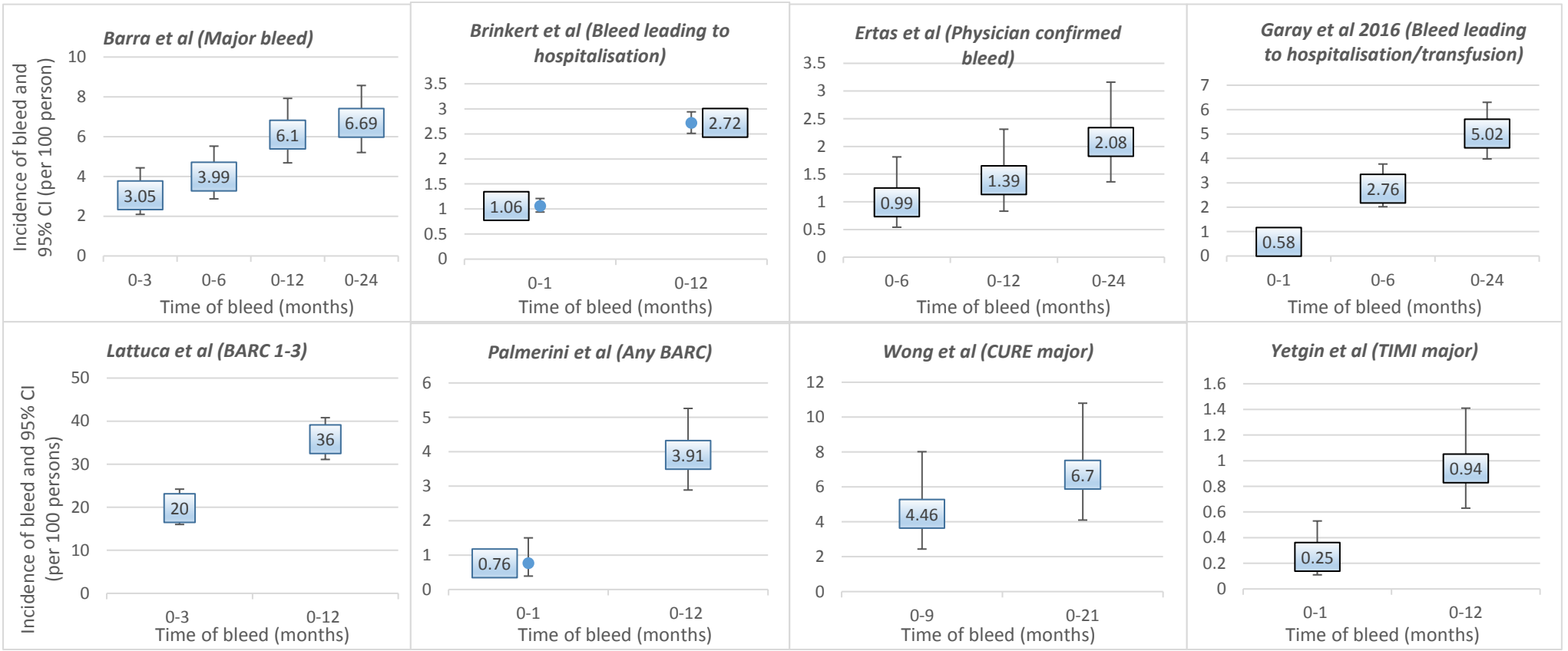
3.4.4.3 Bleeding by severity

The incidence of bleeding by severity is summarised in detail in **appendix table 3.8**. In observational studies, the incidence of major bleeding events (based on BARC 3 – 5) within the first 12 months following hospital discharge was around 1.29 – 3.25 percent. The incidence of minor bleeding events (based on BARC 2) and nuisance bleeds (based on BARC 1) within the same period were around 6.56 – 10.6, and 21.9 – 37.5 percent respectively (**figure 3.4**).

3.4.4.4 Types/site-specific bleeding events

The summary of the incidence of different types of bleeding events post-hospital discharge is presented in **appendix table 3.9**. Generally, bruising (defined as skin haematoma, ecchymosis, petechiae) were the most commonly reported types of bleeding events after hospital discharge (range: 0.84 to 22.5 percent within 12 months) followed by gastrointestinal bleeds (range: 0.25 to 7.63 percent within 12 months; **figure 3.5**), while intracranial bleeds were relatively rare (range 0.20 to 0.40 percent within 12 months; **figure 3.5**).

Figure 3.2: Cumulative incidence of bleeding as reported within observational studies at different time points (incidence expressed as proportion per 100 persons)



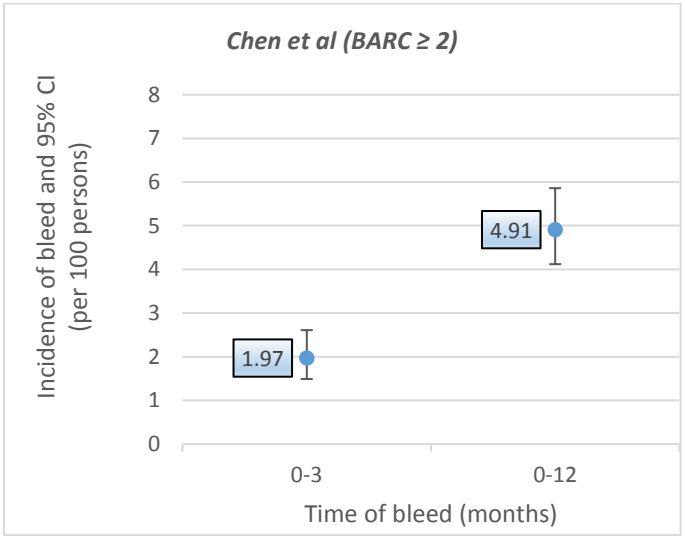

Chen et al (BARC ≥ 2)
Incidence of bleed and 95% CI (per 100 persons)
8
7
6
5
4
3
2
1
0
4.91
1.97
0-3
0-12
Time of bleed (months)

Figure 3.3: Cumulative incidence of bleeding as reported within individual RCTs at different time points (incidence expressed as proportion per 100 persons)

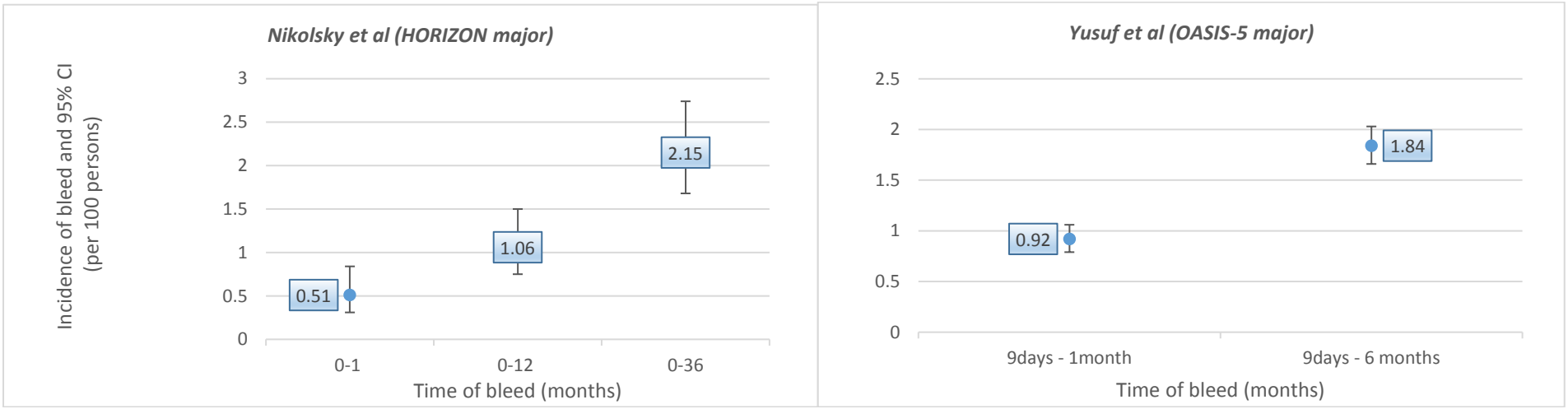


Figure 3.4: Incidence of bleeding stratified by severity in observational studies that reported bleeding by BARC criteria within the first 12 months after hospital discharge

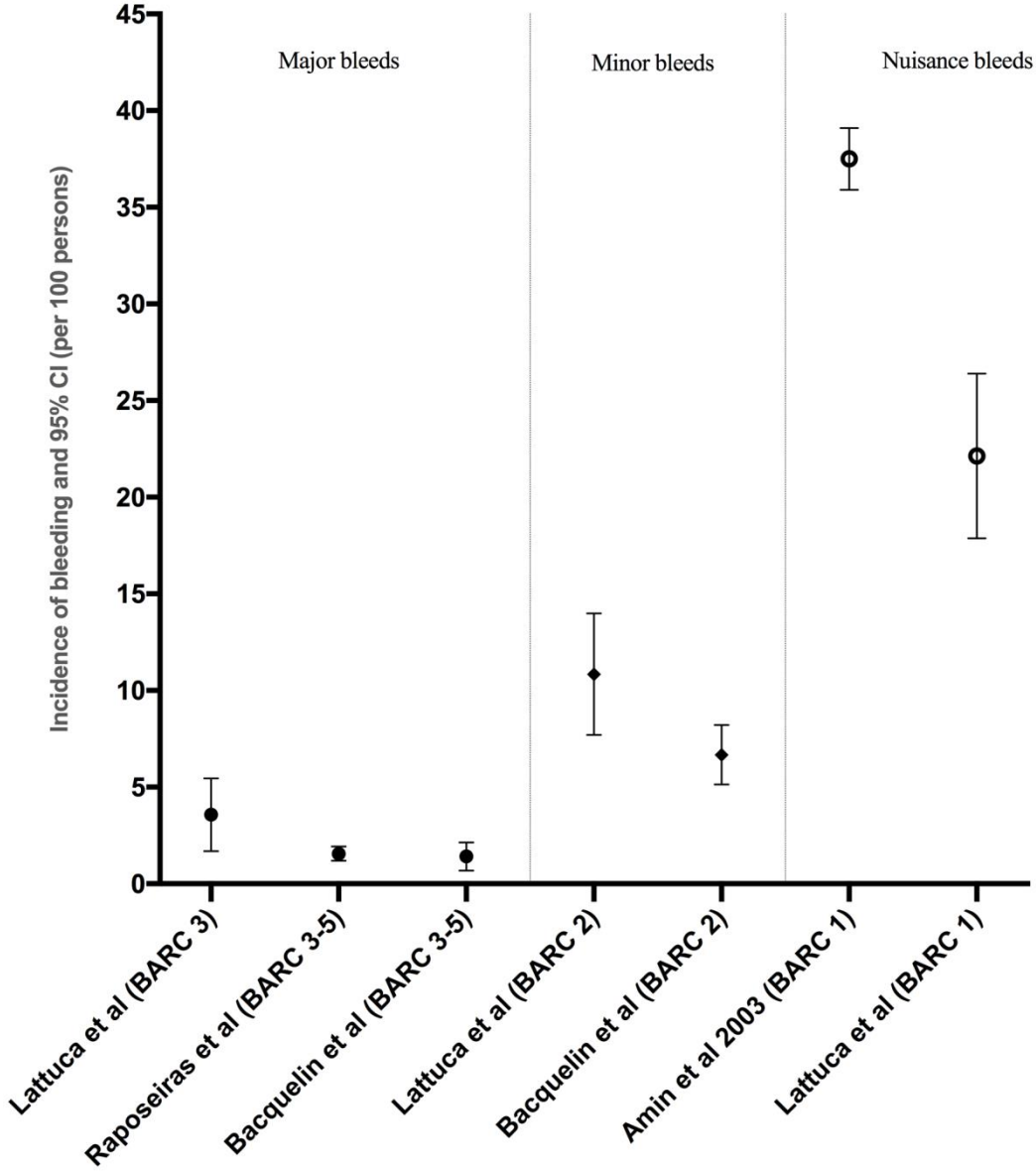
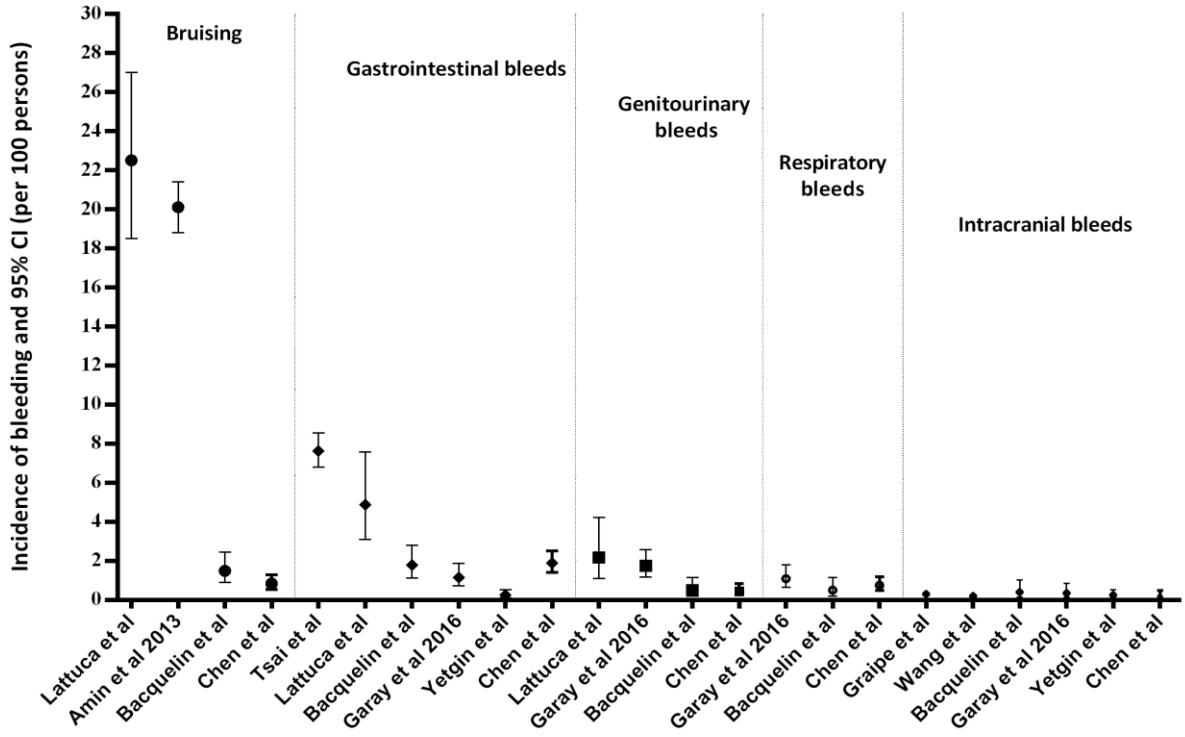


Figure 3.5: Incidence of each type of bleeding event within the first 12 months after hospital discharge in observational studies



3.4.5 Secondary objectives

This section summarises the association of post-discharge bleeding events with the outcomes of mortality, MACE, re-infarction, and rehospitalisation based on results of included studies.

3.4.5.1 Bleeding and risk of mortality

Only six observational studies (Brener et al., 2016; Brinkert et al., 2017; Caneiro-Queija et al., 2018; Chen et al., 2019; Lamberts et al., 2013; Schjerning Olsen et al., 2015) and one RCT (Valgimigli et al., 2016) reported on mortality overall. In these studies, there was consistent reporting of an association between post-discharge bleeding and all-cause mortality (**table 3.4**). Major bleeding was associated with nearly three to sixfold increased risk of mortality in the first 12 months of hospital discharge in three studies (Brinkert et al., 2017; Chen et al., 2019; Lamberts et al., 2013) (**table 3.4**). Nuisance bleeding events defined as BARC 1 were not associated with mortality in one RCT, but there was an increased risk of mortality with BARC 2 and 3 bleeds in the same RCT (Valgimigli et al., 2016), which increased with bleeding severity (**table 3.4**). The SOE for the outcome of mortality was rated low (**table 3.5**).

3.4.5.2 Bleeding and risk of MACE, rehospitalisation and re-infarction.

The adjusted risk of MACE with bleeding (defined as bleeds leading to hospitalisation or death in one study (Sørensen et al., 2009), and BARC ≥ 2 bleeds in another study (Chen et al., 2019)) was nearly threefold in two studies (**table 3.4**). There was a statistically non-significant association between post-discharge bleed (defined as BARC 1 bleeds) and risk of rehospitalisation in one study (adj HR, 1.20 (95% CI 0.95, 1.52) (Amin et al., 2013)

(**table 3.4**). There were no studies examining the association between post-discharge bleeding and subsequent risk of re-infarction. The SOE for the outcomes of MACE and re-hospitalisation were rated insufficient (**table 3.5**).

Table 3.4: Summaries of risk of mortality, MACE and rehospitalisation from included studies by length of follow-up

Author/year	Location	Setting	Length of follow-up	Bleeding criteria	Adjusted/Unadjusted outcomes			Quality score
					Mortality	MACE	Rehospitalisation	
Lamberts et al 2013	Denmark	Registry	12 months	Fatal and non-fatal bleed	Adj HR 2.79 (95% CI: 2.39, 3.26)	NR	NR	6
Brinkert et al 2017	Canada	Registry	12 months	Hospitalisation with major bleeding	Adj OR 2.97 (95% CI: 1.71, 5.15)	NR	NR	5
Chen et al 2019	China	Registry	12 months	BARC ≥ 2	**BARC ≥ 2:** Adj HR 1.68 (95% CI: 0.66, 4.28) **BARC ≥ 3:** Adj HR 5.93 (95% CI: 1.63, 21.52)	**BARC ≥ 2:** Adj HR 2.59 (95% CI: 1.17, 5.74) **BARC ≥ 3:** Adj HR 5.83 (95% CI: 1.72, 19.74)	NR	5
Caneiro-Queija et al 2018	Spain	Registry	455 days (median)	BARC 2 - 3	Adj HR 5.1 (95% CI, 3.6, 7.7)	NR	NR	6
Brener et al 2016	US and Germany	Registry	24 months	TIMI, GUSTO and ACUITY major bleed	**Bleeds between 30-365 days;** Unadj HR 4.61 (95% CI 1.70, 12.49): **Bleeds >365 days;** Unadj HR 2.63 (95% CI 0.86, 8.04)	NR	NR	5
Olsen et al 2015	Denmark	Registry	3.5 years	Bleed leading to death or hospitalisation	Adj HR 1.51 (95% CI: 1.28, 1.79)	NR	NR	6
Valgimigli et al 2017	Multi-centre	RCT	Unclear	BARC 1 - 3	**BARC 1:** Adj HR 0.89 (95% CI: 0.61, 1.31) **BARC 2:** Adj HR 1.70 (95% CI: 1.23, 2.36) **BARC 3a:** Adj HR 2.77 (95% CI: 1.86, 4.12)	NR	NR	3†

Author/year	Location	Setting	Length of follow-up	Bleeding criteria	Adjusted/Unadjusted outcomes			Quality score
					Mortality	MACE	Rehospitalisation	
Valgimigli et al 2017	Multi-centre	RCT	Unclear	BARC 1 - 3	**BARC 3b:** Adj HR 4.51 (95% CI: 2.86, 7.10) **BARC 3c:** Adj HR 28.2 (95% CI: 17.5, 45.7)	NR	NR	3†
Sorensen et al 2009	Denmark	Registry	476.5 days (mean)	Fatal and non-fatal bleed	NR	Adj HR 3.00 (95% CI: 2.75, 3.27)	NR	5
Amin et al 2013	US	Registry	12 months	BARC 1	NR	NR	Adj HR, 1.20 (95% CI 0.95, 1.52)	4

*†; quality assessed by Newcastle Ottawa Scale, **Adj**; adjusted, **unadj**; unadjusted, **HR**; hazard ratio, **OR**; odd ratio, **NR**; not reported, **CI**; confidence interval, **MACE**; Major Adverse Cardiovascular Event, **BARC**; bleeding academic research consortium, **GUSTO**; global use of strategies to open occluded arteries, **TIMI**; thrombolysis in myocardial infarction, **ACUITY**; acute catheterisation and urgent intervention triage strategy*.

Table 3.5: Summary of the assessment of the strength of evidence for each secondary objective

Outcome and length of follow-up post-hospital discharge	Strength of evidence (SOE)
All-cause mortality (within 1 to 3.5 years)	**SOE** = Low (6 observational studies and 1 RCT; 145,326 participants) Low level of evidence due to moderate risk of bias, and residual confounding.
MACE (within 365 to 476 days)	**SOE** = Insufficient (2 observational studies; 43,193 participants) Insufficient, because evidence was derived from only two studies that are at high risk of bias, as such conclusion cannot be drawn.
Rehospitalisation (within 12 months)	**SOE** = Insufficient (1 observational study; 3560 participants) Insufficient, because evidence was derived from only one study that is at high risk of bias, as such conclusion cannot be drawn.

***SOE**: strength of evidence, **MACE**: major adverse cardiovascular event, **RCT**: randomised controlled trial.*

3.5 Discussion

This is a systematic review to study the incidence, timing, and types of post-discharge bleeding events, and their association with mortality, MACE, re-infarction and rehospitalisation. Fifty-five studies were included, comprising 38 observational studies and 17 RCTs with a combined cohort of 721,342 participants for the primary objectives, and 189,698 for the secondary objectives. But, due to the high level of heterogeneity between studies, a narrative synthesis approach was instead used to summarise data. The findings from this review are discussed as follows:

3.5.1 Incidence of bleeding

This study reports that bleeding complications after hospital discharge following ACS are common, with up to one-third of patients reporting to have experienced a bleeding event in the first 12 months after hospital discharge. Incidences of bleeding were generally lower in RCTs than observational studies. In the majority of RCTs, incidence of bleeding mostly varied between 0.96 and 16.7 percent within the first 12 months after hospital discharge, except in one RCT where the reported incidence was 39.4 percent. In this study that reported an incidence of 39.4 percent, the underlying population were generally high-risk patients in which 40% were managed with multi-vessel PCI. These patients were also prescribed prasugrel for 12 months upon hospital discharge. Prasugrel is a potent antiplatelet which has been linked with excess bleeding complications (Wiviott et al., 2007). The majority (95%) of the bleeding events reported in this RCT were BARC types 1 and 2 bleeds. BARC type 1 bleeds especially, are not actionable and do not cause patients to seek treatment by a healthcare professional, and are therefore ascertained based on patient self-reports (Mehran et al., 2011).

This review also found that the incidence of bleeding was slightly higher among patients that presented with STEMI than in those with NSTEMI/UA. Patients with STEMI are high-risk patients who are mostly managed with PCI and discharge on potent antiplatelets (such as prasugrel or ticagrelor) for up to a year or even longer. The longer the duration of antiplatelet therapy, the greater the risk of bleeding complications (Udell et al., 2015). The lowest incidences for bleeding were observed in a US population enrolled in Medicare (Wang et al., 2015) and a Swedish population enrolled in the Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA) (Graipe et al., 2015). These studies mainly reported on intracranial bleeding events. These types of bleeding events are likely to be very rare post ACS (Mahaffey et al., 2015).

3.5.2 Timing of bleeding

This analysis reports that bleeding events following hospital discharge occurred more frequently in the initial three months (based on three studies), but these bleeding events continued to occur even after 1 year. This highlights the first 3 months after hospital discharge as the period for greater vulnerability for bleeding, and a time when resources can be better utilised to improve longer-term patient prognosis. The fact that bleeding events continued even after 1 year generally reflects the elderly comorbid nature of the ACS population, and that, this patient population may have to remain on aspirin therapy indefinitely.

3.5.3 Bleeding by severity

This review found that the incidence of bleeding increased as the severity of bleeding decreased. This is because as the severity gravitates from major and more towards minor

or nuisance bleeds, less stringent criteria are used to ascertain these types of bleeding events. These minor/nuisance bleeding events include overt and actionable sign of haemorrhage which may necessitate non-surgical medical intervention by healthcare professionals, they also include bleeds which are not actionable and do not cause patient to seek treatment by a healthcare professional such as bruising and nose bleeds (Mehran et al., 2011). These latter bleeding events may be common following hospital discharge for ACS, as patients remain on antiplatelet therapy (Amin et al., 2013). It is, therefore, reasonable to infer that, although bleeding events do persist following hospital discharge for ACS, these bleeding events may predominantly be nuisance bleeds.

3.5.4 Site-specific bleeds

This review showed that bruising was the most common type of bleeding event post-hospital discharge, followed by gastrointestinal bleeds. In the case of gastrointestinal bleeding events, prolonged use of antiplatelets may irritate/damage gastrointestinal mucosa (Cryer and Feldman, 1999) resulting in haemorrhagic episodes, especially in patients with undiagnosed asymptomatic gastric ulcer or cancer. Proton pump inhibitors (PPIs) have been shown to reduce the risk of upper gastrointestinal bleeds (Bhatt et al., 2010), and the European Society of Cardiology (ESC) guidelines have advocated the use of PPIs for the management of patients with a history of, or likely to experience gastrointestinal bleeding events (Ibanez et al., 2017). However, it was unclear in the majority of studies whether patients were prescribed PPIs at the time of discharge.

3.5.5 Mortality, MACE, and rehospitalisation

There was some indication in this review that nuisance bleeding events may not be associated with mortality, but minor and major bleeding events may increase the risk of mortality post-hospital discharge, although the strength of the evidence was low and only seven studies reported on this outcome, two of which were conducted on a Danish population. It is, therefore, reasonable to suggest that major bleeding may increase the risk of mortality post-hospital discharge, but the extent and magnitude of the associations of minor and nuisance bleeding events with mortality remain unclear due to limited data. Whether there is an association between post-discharge bleeding and subsequent risk of MACE and rehospitalisation also remain uncertain due to limited number of studies reporting on these outcomes. Although there was an indication of an association with MACE in two studies (Chen et al., 2019; Sørensen et al., 2009) and rehospitalisation in one study (Amin et al., 2013), the latter association did not reach statistical significance.

3.5.6 Reasons for the variation in incidence

The variation in reported incidence in this study may be attributed to differences in length of follow up across studies included in the review. All other things being equal, studies with longer duration of follow-up will have higher incidence of bleeding. However, this relation between length of follow-up and incidence of bleeding may have been obscured by other characteristics such as the severity of bleeding examined. That is to say, a study examining minor bleeding events over a shorter duration of follow-up may report higher incidence than a study examining major bleeds over a similar or longer duration of follow-up. As an example, Amin and colleagues (Amin et al., 2013) who examined only nuisance bleeds over a period of 12 months reported an incidence of 37.5

percent, while Wong and colleagues (Wong et al., 2006) who examined only major bleeding events reported an incidence of 6.7 percent over a period of 21 months. For this reason, assessing the impact of length of follow-up on the incidence of bleeding across studies has not been possible.

Differences in the type of ACS examined across studies may have also contributed to the variation in incidence in this review. Differences may arise from the fact that studies of patients with STEMI may report higher incidence of bleeding than studies of patients with NSTEMI, since patients with STEMI will more likely remain on potent antiplatelet therapy for longer durations (Claeys et al., 2017). Patients with NSTEMI tend to be on average older than those with STEMI at the time of ACS presentation (MINAP, 2017). Therefore, more likely to be discharged on shorter duration of antiplatelet therapy or not prescribed any antiplatelet in the case of those with higher prevalence of comorbidities who are perceived to be at higher risk of bleeding.

Another potential explanation for the variation in reported incidence of bleeding may be differences in types of bleeding examined across studies. Two studies (Graipe et al., 2015; Wang et al., 2015) included in the review only reported on intracranial bleeds, and another three (Atar et al., 2006; Cuschieri et al., 2014; Tsai et al., 2011) only reported on gastrointestinal bleeding events post-hospital discharge. Generally, the reported incidences of bleeding in these studies were lower than those reported in the majority of studies that examined all types of bleeding events. Differences in types, dosage, and duration of discharge antithrombotic drugs across studies may have influenced the overall incidence of bleeding in this review. Differences may arise from the fact that studies of patients discharged on shorter duration of, or lower doses of antiplatelets may report lower incidences of bleeding, while studies of patients discharged on longer

duration of, or higher doses of antiplatelets may report higher incidences of bleeding. Other potential explanation for the variability in reported incidence may be differences in socio-demographic characteristics (such as age and gender), presence/absence of comorbidities, and the severity of bleeding examined across studies included in the review.

3.5.7 Strengths and limitations

The main strength of this review was the number of studies included. This study also has some potential limitations. First, the studies included in the review were heterogeneous in regard to length of follow up, type of ACS presentation, severity, and type of bleeding examined, demographic characteristics of the study participants, discharge anti-platelet and anti-coagulant regimens to pool data to obtain an overall incidence or mortality figures. Second, the duration and dosage of discharge antithrombotic therapy, as well as ACS management strategies, were not specified in the majority of studies (due to selective reporting), as such the impact of these factors on the incidence of bleeding were not assessed. In the majority of studies, episodes of bleeds were extracted to calculate incidence figures. In most of these studies, there was lack of clarity on whether patients were included in the numerator more than once if they had multiple episodes of bleeding events. Similarly, for some studies where episodes of bleeds were reported at different time intervals and the number of people at risk within each time interval was not reported, incidence figures were estimated based on the assumption that there was no attrition; hence incidence may have been underestimated. The study combined evidence from both RCTs and observational studies using registries, and findings may vary between

study designs. However, narrative synthesis was carried out distinctly and reported separately for RCTs and for observational studies.

Data extraction was carried out by NI alone. It is possible that errors may have been made during the extraction process. However, the extraction process was carried out twice and results compared for consistency. There were limited numbers of studies identified that reported on the secondary objectives. Therefore, definitive conclusion could not be drawn, which also limit generalisability.

3.5.8 Implications of the findings of the review for the research in this thesis

As highlighted in the previous chapter (Chapter 2), the incidence and prognostic impact of in-hospital bleeding events have been described in both observational studies and RCTs. The findings in this systematic review indicates that the evidence pool in regards to post-discharge bleeding events is limited. The majority of the studies identified in the course of the review did not report on the incidence of bleeding or were not primarily designed to investigate incidence, but data on episodes of bleeding events were extracted to calculate incidence. It was unclear in the majority of these studies, whether only first bleeding events were counted or multiple episodes of bleeding events (for patients that had more than one bleed) were also included. There was a wide variation in regards to length of follow up, type of ACS presentation, severity, and type of bleeding examined, demographic characteristics of the study participants, discharge anti-platelet and anti-coagulant regimens between the studies identified in the course of the review. All these meant that a definitive conclusion cannot be drawn regarding the incidence of longer-term post-discharge bleeding events. This gap within the literature underscores the need to examine the incidence of these bleeding events (while taking account of person-time

at risk) using a high quality observational study design that will be more reflective of the real-world population encountered in clinical practice, which form the basis for objective 3 (Chapter 7) in this thesis.

The variation in reported incidence between the studies identified in this review indicates that the incidence of post-discharge bleeding may be influenced by baseline patient characteristics. As highlighted in chapter 2, section 2.2.2, the studies that reported on characteristics that may be associated with post-discharge bleeding events were either carried out in the PCI setting in clinical trials, or only considered major bleeding events, or the majority of the study population were patients with stable coronary artery disease or other unspecified cardiovascular diseases. Further investigation on factors which may increase the risk of post-discharge bleeding complications (and site-specific bleeding events) is needed, so that risk stratification tools that may be more representative of the unselected cohorts encountered in clinical practice (often ignored in RCTs) can be developed to identify individuals at higher risk of bleeding following hospital discharge. This gap within the literature was the basis for objective 4 (Chapter 8) in this thesis.

There was also an indication from the present review that evidence on the association of post-discharge bleeding events with mortality is limited. Further research is required to quantify these associations, with particular emphasis on whether minor and nuisance bleeding events (which may be common post-hospital discharge) have a prognostic impact. Future research examining these associations should stratify by the timing of bleeding events in order to determine whether the prognostic impact of bleeding is more pronounced in the early phase of hospital discharge or is equally important in the longer-term after hospital discharge. Finally, further research is required to investigate whether site-specific bleeding events also have prognostic impacts on outcomes such as mortality,

since some sites (such as intracranial bleeds) may more likely be associated with mortality than others (such as bruising). This need for more evidence on the association of post-discharge bleeding with mortality became the basis for objective 5 (Chapter 9) in this thesis.

3.5.9 Conclusion

In this systematic review of 55 studies, bleeding complications following hospital discharge for ACS were found to be common, with bruising the most common. These bleeding complications vary by severity, anatomic source and type of discharge antithrombotic therapy, and whilst most common immediately post-discharge, these bleeds continue to occur in the longer-term. There are limited data around the longer-term outcomes of patients that sustain bleeding events post-hospital discharge for ACS. Further work is required to define the nature, frequency and prognostic impact of such bleeding events. Real-world risk stratification tools will need to be developed that specifically predict the risk of bleeding complications post-discharge to identify high-risk individuals for a more patient-centred approach in managing optimal pharmacotherapy and care.

Leading on from the systematic review, the remainder of the thesis will address the highlighted gaps within the literature by investigating the incidence, risk factors, and association of post-discharge bleeding events with all-cause mortality within the primary care setting, using a national EHR database. But first, the next chapter (Chapter 4) will describe the development of a definition for these bleeding complications following hospital discharge for ACS to be applied within a primary care EHR.

Chapter 4.0: **Defining bleeding following ACS within the primary care setting by means of a consensus strategy**

4.1 Introduction

In the UK primary care setting, over 98% of the general population are registered with GPs, who are the first point of contact for non-emergency health-related issues (Herrett et al., 2015). These health-related issues are either managed within the primary care setting or referred to secondary care (usually the National Health Service (NHS) hospitals which is the main health care provider in the UK and free at the point of care). Feedback mechanisms exist between GPs and the secondary care team where key information such as diagnoses or procedures carried out on a patient while in secondary care are fed back to GP practices (Herrett et al., 2015). This key information, alongside diagnoses and symptoms seen in primary care, and their associated management are recorded in patients' primary care EHR by means of codes, most notably the Read coding system.

Read codes, also known as the Read clinical classification, are a coded thesaurus of clinical terms, which facilitate the storage and retrieval of patient information in primary care EHRs. These Read clinical classifications have a hierarchical structure comprising 5 levels split into chapters. The precision of information/detail captured by a Read code increases as more alpha-numeric characters are added. As an example, the code G…. (level 1) refers to the circulatory system diseases chapter. G3… (level 2) refers to ischaemic heart diseases, and G30.. (level 3) refers to acute myocardial infarction. Each Read code is linked to a Read term, which is a clinical terminology that provide a textual description of the health-related concept representing the code. These Read codes can be cross-referenced to Office of Population Census and Surveys Classification of Surgical Operations and Procedures Version 4.2 (OPCS-4) and the International Classification of Diseases Version 10 (ICD-10) commonly used in UK secondary care.

In these primary care EHRs, bleeding events are not generally recorded using the formally known definitions (such as BARC, TIMI, and GUSTO – described in Chapter 2, section 2.2). Recorded bleeding events within primary care tend to be based only on clinical parameters (such as intracranial bleed) and recorded using the related Read codes. There remains a lack of a standardised definition for bleeding for use in primary care research using EHRs. Previous studies of bleeding complications in the primary care setting have developed their own definitions (Buresly et al., 2005; Raposeiras-Roubín, Faxén, et al., 2018; Valle et al., 2016). But these definitions are conservative in that they do not capture minor and nuisance bleeding events (such as nose bleed and bruising) which patients may be concerned about. To address this drawback, this pilot study will define bleeding events following ACS within the primary care setting using a Delphi consensus strategy.

The Delphi consensus strategy involves the use of questionnaires or checklists to collect data independently from experienced and knowledgeable participants that form the consensus panel (Dalkey and Helmer-Hirschberg, 1962; Hsu, 2007). Multiple iterations of data collection and feedback between the investigator and members of the panel are carried out until agreement is reached on the target issue. The Delphi process can be continually iterated until a consensus is reached, but in most cases, three iterations are sufficient to reach an agreement (Custer et al., 1999; Ludwig, 1997).

Accordingly, the Delphi consensus strategy was used with a panel consisting of an Interventional Cardiologist and three GPs to agree on a Read code based definition of bleeding post ACS within the primary care setting.

4.2 Aim and objectives

4.2.1 Aim

The overall aim was to define bleeding following ACS within the primary care setting by means of a Delphi consensus technique.

4.2.2 Specific objectives

Primary objective:

- To define bleeding post ACS in primary care using Read codes.

Secondary objectives (as an exploratory analysis to inform the main studies of the thesis):

- To explore the prevalence of bleeding in the adult post ACS population in a sample of GP practices in North Staffordshire.
- To explore the median time to bleeding post ACS.
- To explore the types/sites of bleeding events post ACS.

4.3 Methods

4.3.1 Read codes generation

Potential Read codes used to define bleeding complications in the primary care setting were generated in four stages: first, by longitudinally following patients with a discharge diagnosis of ACS in the Consultation in Primary Care Archive (CiPCA) database (described below) to identify codes used in recorded consultations that potentially refer to bleeding events. Second, by systematic search of the literature (which also encompassed studies identified in the systematic review reported in Chapter 3). Third, by search of the website clinicalcodes.org, and finally, by search of the Clinical research using Linked Bespoke studies and Electronic Health Records (CALIBER) collection of codelists for Read codes used to define bleeding events within the primary care setting.

4.3.1.1 The CiPCA database

CiPCA is a primary care electronic medical record database containing anonymised consultation records with GPs within a sample of practices in North Staffordshire. The database (at the time of data request) contained records of patients from 11 general practices covering a registered population of 94,565 people as at 2011. These 11 practices have a research agreement with Keele University to extract pseudo-anonymised records of their patient's consultations, investigations, referrals, and prescriptions for research purposes. All general practice encounters are electronically recorded using the Read coding system (described in section 4.1 above), which is normal in the UK primary care setting. Data are available for each patient registered at a participating practice unless they have asked for their data not to be used in research. Broad use of the CiPCA database for research purposes was initially granted by the North Staffordshire Research

Ethics Committee (reference 03/04) and has been updated regularly since, most recently by Haydock Park Research Ethics Committee (reference 17/NW/0232) in April 2017. Participating practices record clinical activities following the Keele University consultation data audit, training and validation programme. These data are further subjected to regular audits by the CiPCA data manager within the Keele University Research Institute for Primary Care and Health Sciences. Therefore, the data are of high research standard (Jordan et al., 2007; Porcheret et al., 2004), and more than 30 research publications have used this database.

Accordingly, using the CiPCA database, patients with a first recorded primary diagnosis of ACS from 01/01/2005 to date of last data extraction (28/12/2011) at the time of data request were identified from the 11 general practices, regardless of age and gender. Read codes used to identify ACS patients in the CiPCA database were based on code lists used in previous studies of ACS in primary care (Bhattarai et al., 2012; Hawkins et al., 2013; Khan, Perera, et al., 2010; Parisi et al., 2015; Zhong et al., 2018), with the final code list derived via consensus of a GP and an Interventional Cardiologist (see **appendix 4.1** for code list). Identified ACS patients were then followed longitudinally from date of ACS until end of registration at their practice or death or date of last data extraction (whichever came first). All coded consultations during this follow-up period were identified and Read codes that potentially refer to bleeding were then extracted by NI onto an Excel spreadsheet, and duplicates were removed.

4.3.1.2 The literature search

A systematic search of Embase (Ovid SP; 1974 – June 2017) and Medline (Ovid SP; 1946 – June 2017) was carried out to identify studies that have examined or reported on bleeding within the primary care setting using the following search strategy:

1. exp bleeding/ or epistaxis/ or gastrointestinal hemorrhage/ or brain hemorrhage/

2. h?emorrhage.mp.

3. medical record/ or electronic health record/ or primary health care/

4. exp "Read code"/

5. exp United Kingdom/

6. 1 or 2

7. 3 or 4

8. 5 and 6 and 7

9. limit 8 to (human and English language)

Read codes used to define bleeding in studies identified from the literature search were extracted onto a preformatted Excel spreadsheet for Microsoft Windows. Similarly, code list identified from studies, which were either screened full text or included in the systematic review (in Chapter 3) were also extracted onto the preformatted Excel spreadsheet. For studies that reported on bleeding complications using ICD-10 codes, these codes were translated into Read codes using the NHS Read code browser version 2. The extracted Read codes and the translated ICD-10 codes were combined and duplicate Read codes removed.

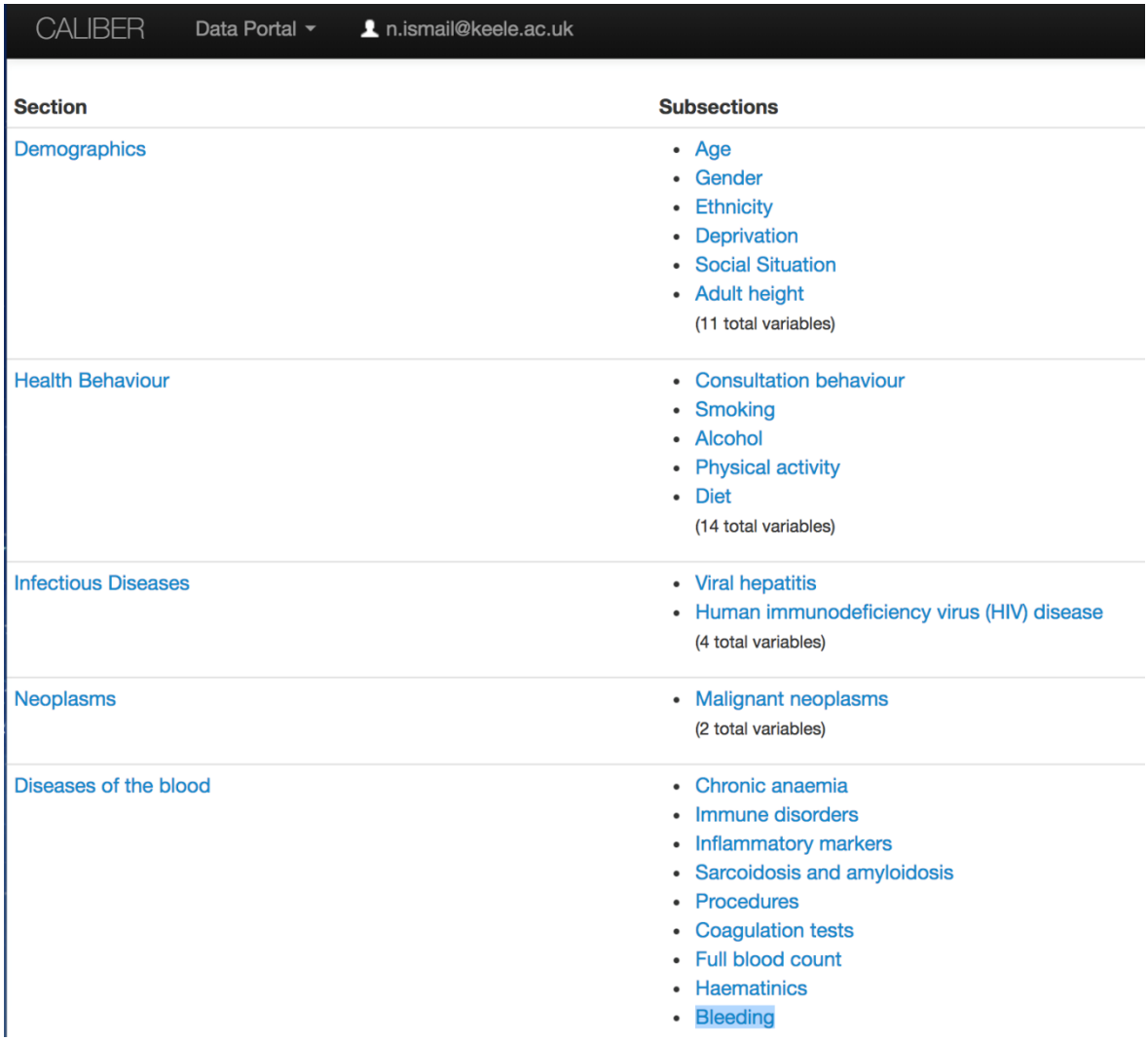
4.3.1.3 Clinicalcodes.org search

Clinicalcodes.org is a website containing compilations of Read codes that were used by previous studies to define morbidities and conditions within the primary care setting. A manual search of this website for studies that have defined bleeding by means of Read codes was carried out.

4.3.1.4 The CALIBER database

The CALIBER database comprised five linked EHRs; specifically, the Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES), Myocardial Ischaemia National Audit Project (MINAP), social deprivation information and Office for National Statistics (ONS) mortality data (Denaxas et al., 2012). The database contains records of over 10 million adults (CALIBER, 2018). These records include patients' consultations with GPs, referrals, investigations, prescriptions, diagnoses, and causes of deaths. The CALIBER data portal also contains secondary and primary care definitions for morbidities and conditions such as ACS and bleeding. The primary care definitions for these conditions are based on Read codes. The CALIBER data portal has a section containing a code list used to define bleeding within the primary care setting (**figure 4.1**). Request to use these Read coded definitions from the CALIBER data portal for the present study was granted by Spiros Denaxas from the Institute for Health Informatics, University College London. Accordingly, these code lists were extracted from the data portal onto a preformatted Excel spreadsheet.

Figure 4.1: The CALIBER data portal



4.3.2 The consensus strategy

Extracted Read codes that potentially refer to bleeding from the CiPCA database, the CALIBER data portal, and from the systematic search of Embase and Medline, as well as those extracted from studies that were either screened full text or included in the systematic review in Chapter 3, were combined and duplicate Read codes removed. After de-duplication, the combined Read codes were tabulated (see **appendix 4.2**) and emailed to a panel consisting of three GPs and an Interventional Cardiologist. The panel were then

asked independently to select from the tabulated list of Read codes which best define bleeding complications post ACS within the primary care setting. The question asked was

- Does the code define a bleed likely to have occurred following ACS?

  Responses were:

  - Yes it does (include in definition)
  - No it doesn't (exclude from definition)
  - Unsure

Each member of the panel was blinded to the results of the others at this stage. Code lists selected by each individual member of the panel were examined after the first iteration. For Read codes where there was 100% concordance or 3/4 of the panel agreed (to include or exclude), these Read codes were extracted and retained, or removed if agreed for exclusion. Read codes where members of the panel disagreed (2 members disagree with the other 2) on whether to include or exclude from the definition were separately emailed to members of the panel (second iteration), alongside results from the first iteration. For these Read codes, the panellists were asked to re-evaluate their initial decision and select which Read codes define a bleed likely to have occurred following ACS within the primary care setting, using the same question above. Overall, two iterations were carried out. For Read codes where the panellist did not agree on whether to include or exclude from the definition following the second iteration, two members of the panel (a GP and an Interventional Cardiologist) decided on whether these Read codes should be included or not.

For Read codes that were agreed for inclusion, the daughter codes of the parent Read code were searched on the NHS Read code browser, and any daughter code that referred

to bleeding was also included in the definition. The final code lists for the definition were classified based on anatomic site of the bleed by NI into bruising; respiratory/ear, nose, throat (ENT); gastrointestinal; genitourinary; intraocular; intracranial; and other (unclassified) bleeds. This classification was built upon the categorisation used in previous studies (Gallagher et al., 2014; Voss et al., 2016). As an example, gastrointestinal bleeds comprised any Read code with associated Read term that referred to bleeding from the gastro-oesophageal tract to the rectum (See **appendix 4.3** for code lists used to define site-specific bleeding event). This classification was validated by a GP and an Interventional Cardiologist.

4.3.3 Exploratory analysis in the CiPCA database

Bleeding events (as defined from the consensus above) were identified from date of ACS until end of patient registration at their practice or death or date of last data collection at the time of data request (28/12/2011). Prevalence of bleeding was then defined as the proportion of individuals with a recorded ACS diagnosis who consulted at least once for bleeding complication post ACS between 01/01/2005 and 28/12/2011. For patients that had consulted with more than one bleeding event, only the first event was counted, and the rest were ignored. Using the number of ACS patients registered at these practices as the denominator, the prevalence of bleeding (bleeding as defined by the code lists in **appendix 4.3**) was determined per 100 registered persons with ACS. Patients with recorded first bleeding consultations post ACS were descriptively compared with those without by socio-demographic characteristics (age and gender). The median time to a first bleeding event (defined as the time from date of ACS consultation to date of first consultation for bleeding) was determined for bleeding overall and for site-specific

bleeding events. The proportion of patients with recorded prescription for 1) aspirin only, 2) clopidogrel only, 3) prasugrel only, 4) warfarin only, 5) aspirin plus clopidogrel, 6) aspirin plus prasugrel, 7) aspirin plus warfarin and, 8) aspirin plus clopidogrel plus warfarin within the first 30, 60 and 90 days after the index ACS date was estimated. All analyses were performed using SPSS version 24.0. Continuous variables are presented as median and interquartile range (IQR) while categorical variables are presented as frequencies and percentages.

4.4 Results

From the CiPCA database, 963 patients with an ACS diagnosis between 2005 and 2011 were identified and followed for a median of 2.59 years (IQR: 0.99, 4.26) post ACS. 70 Read codes that potentially refer to bleeding complication were identified and extracted from consultations of these patients. 289 Read codes that were used to define bleeding in primary care within the CALIBER data portal were also identified. 8 studies were identified from the systematic search of Medline and Embase that reported on bleeding using either Read codes or ICD-10 codes within the primary care setting (see **figure 4.2** for a detailed description). Of these studies, three (Crooks et al., 2012; Gaist et al., 2013; MacDonald et al., 2003) defined bleeding by Read codes and five (Ban et al., 2017; Button et al., 2011; Christensen and Munro, 2008; Jones et al., 2005; Kroll et al., 2016) by ICD-10 criteria. 112 Read codes were extracted from these studies overall after removal of duplicates. A further 109 Read codes were extracted from six studies (Gallagher et al., 2014; Ko et al., 2010; Lamberts et al., 2013; Rapsomaniki et al., 2016; Sørensen et al., 2009; Voss et al., 2016) that were either screened full text or included in the systematic review (in Chapter 3). Overall, 580 Read codes were extracted from CiPCA, CALIBER, systematic search of Medline and Embase, and from studies identified in the course of the systematic review, which altogether yielded 388 Read codes after removal of duplicates (see **figure 4.3**). There were no identified studies of bleeding on the clinicalcodes.org website.

Figure 4.2: A Prisma flow diagram depicting the steps involved in selecting studies that had defined bleeding complication within the primary care setting

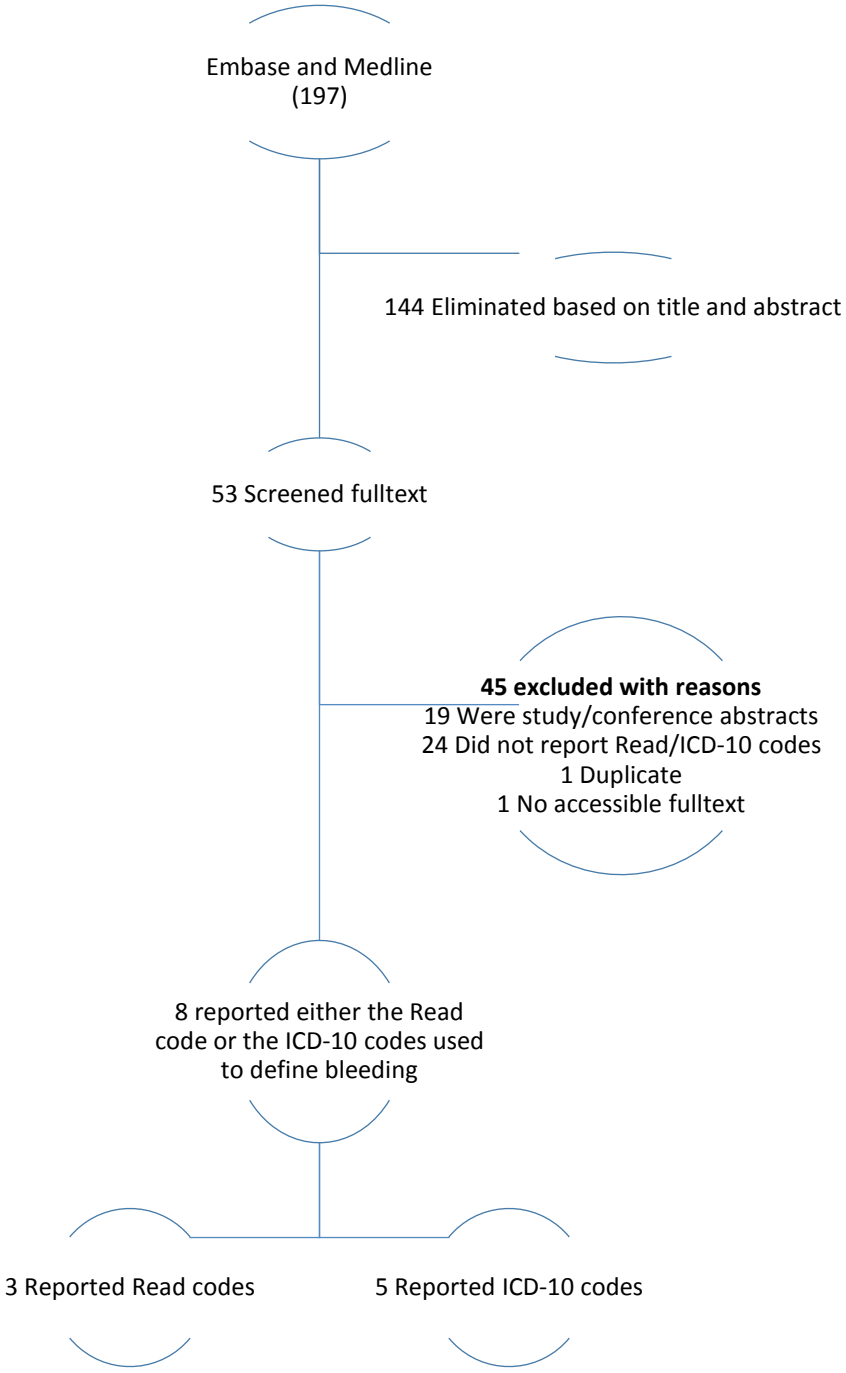


Figure 4.3: A summary of the total number of Read codes extracted from each source

4.4.1 Reaching a consensus

The consensus panel were presented with 388 Read codes in the first iteration and 26 in the second iteration. After the first iteration, the panellists showed concordance on 93% (n = 362) of the Read codes on either to include or exclude from the definition. Of these 362 Read codes, the panel agreed on inclusion of 68% (n = 246) and exclusion of 32% (n = 116). Among Read codes agreed for inclusion (n = 246), the panel showed 100% concordance on 209, whereas 3/4 of the panel showed concordance on the remaining 37 Read codes. For Read codes where the panel agreed on exclusion (n = 116), the panel

showed 100% concordance on 94, whereas 3/4 of the panel showed concordance on the remaining 22 Read codes. After the second iteration, the panel showed concordance on 58% (n = 15) of the remaining 26 Read codes on either to include or exclude from the definition. Among Read codes agreed by the panel for exclusion (n = 13), there was 100% concordance on 6 Read codes, whereas 3/4 of the panel agreed on exclusion of the remaining 7 Read codes. There were only 2 Read codes agreed by 3/4 of the panel for inclusion after the second iteration. Consensus was achieved on the majority of the Read codes (97%, n = 377) after the second iteration except for 11 Read codes. For these 11 Read codes, two members of the consensus panel (a GP and an Interventional Cardiologist) deliberated and decided that two of the 11 Read codes should be included in the definition while the remaining 9 Read codes should be excluded from the final definition. Overall, 250 Read codes were agreed for inclusion in the final definition (see **appendix 4.4** for code list), and the remaining 138 Read codes were excluded (see **appendix 4.5** for code list). After searching the NHS Read code browser for daughter codes of the 250 code list agreed for inclusion, the final definition for bleeding comprised 380 Read codes overall (see **appendix 4.3** for code list). **Table 4.1** summarises the types of bleeding events that were included in the definition, classified based on the anatomic site of the bleed.

Table 4.1: Bleeding events that were included in the definition, stratified by anatomic site

Bleeding term	Classification
Subarachnoid haemorrhage	Intracranial
Intracerebral haemorrhage	Intracranial
CVA - cerebrovascular accid due to intracerebral haemorrhage	Intracranial
Stroke due to intracerebral haemorrhage	Intracranial
Cortical haemorrhage	Intracranial
Internal capsule haemorrhage	Intracranial
Basal nucleus haemorrhage	Intracranial
Cerebellar haemorrhage	Intracranial
Pontine haemorrhage	Intracranial
Bulbar haemorrhage	Intracranial
Ruptured berry aneurysm	Intracranial
External capsule haemorrhage	Intracranial
Lobar cerebral haemorrhage	Intracranial
Other and unspecified intracranial haemorrhage	Intracranial
Extradural haemorrhage - nontraumatic	Intracranial
Subdural haemorrhage - nontraumatic	Intracranial
Intracranial haemorrhage NOS	Intracranial
Epidural haemorrhage	Intracranial
Evacuation of haematoma from temporal lobe of brain	Intracranial
Evacuation of haematoma from cerebellum	Intracranial
Evacuation of intracerebral haematoma	Intracranial
Aspiration of haematoma of brain tissue	Intracranial
Evacuation of subdural haematoma	Intracranial
Evacuation of extradural haematoma	Intracranial
Blood in vomit	Gastrointestinal
Haematochezia	Gastrointestinal
Oesophageal varices with bleeding	Gastrointestinal
Haemorrhage of oesophagus	Gastrointestinal
gastric ulcer with haemorrhage	Gastrointestinal
duodenal ulcer with haemorrhage	Gastrointestinal
peptic ulcer with haemorrhage	Gastrointestinal
Haemorrhagic gastritis	Gastrointestinal
Haemoperitoneum - nontraumatic	Gastrointestinal
Rectal bleeding	Gastrointestinal
Gastrointestinal haemorrhage	Gastrointestinal
Haematemesis	Gastrointestinal
Melaena	Gastrointestinal
Blood in stool	Gastrointestinal
Gastrotomy and ligation of bleeding point of stomach	Gastrointestinal
Oversew of blood vessel of duodenal ulcer	Gastrointestinal

Bleeding term	Classification
Intra-ocular haemorrhage	Intraocular
Haemorrhage - retinal	Intraocular
Unspecified choroidal haemorrhage	Intraocular
Subconjunctival haemorrhage	Intraocular
Vitreous haemorrhage	Intraocular
Haemoptysis	Respiratory/ENT
Epistaxis	Respiratory/ENT
Throat haemorrhage	Respiratory/ENT
Pulmonary haemorrhage NOS	Respiratory/ENT
Otorrhagia	Respiratory/ENT
Haemothorax	Respiratory/ENT
Haematuria	Genitourinary
Prostatic haemorrhage	Genitourinary
Testicular haematoma due to nontraumatic cause	Genitourinary
Male genital haemorrhage NOS	Genitourinary
Haematospermia	Genitourinary
Haematosalpinx	Genitourinary
Haematometra	Genitourinary
Vaginal haematoma	Genitourinary
Haemorrhage of vagina	Genitourinary
Menorrhagia	Genitourinary
Postmenopausal bleeding	Genitourinary
Haematocolpos	Genitourinary
Other abnormal uterine and vaginal bleeding	Genitourinary
Spontaneous bruising	Bruising
Petechiae	Bruising
Spontaneous ecchymosis	Bruising
Anaemia due to chronic blood loss	Other
Haemorrhagic disorder due to circulating anticoagulants	Other
Haemopericardium	Other
Ruptured aortic aneurysm	Other
Haemarthrosis	Other
Haematoma NOS	Other
[X]Haemorrhage, not elsewhere classified	Other

NOS: *not otherwise specified*

4.4.2 Exploratory analysis in the CiPCA database

The study population are summarised by socio-demographic characteristics in **table 4.2** and by discharge antithrombotic therapy in **table 4.3**. There were 963 patients with ACS as at 2011, and the majority were men (64%). Among the 963 ACS patients that constituted the study population, 198 (21%) patients had experienced 565 bleeding events over a median follow up of 2.59 years post ACS. Of these 198 patients, 36% (n = 72) had one bleeding event, 22% (n = 43) had two bleeding events, 14% (n = 28) had three bleeding events, and 28% (n = 55) had four or more bleeding events post ACS. The prevalence of bleeding within the first 30, 60, 90, and 365 days post ACS were 1.5, 2.8, 3.8, and 10.4 percent respectively. Respiratory/ENT (23% of all first bleeds) and genitourinary bleeds (23%) were the more commonly reported first types of bleeding events post ACS (**table 4.4**). The median time to a first bleeding event post ACS was 359 days (IQR: 133, 796). The median time to each site-specific bleeding event post ACS is presented in **table 4.4**. The socio-demographic characteristics of the study population by bleeding are described in **table 4.5**. The majority of the study population were prescribed dual antiplatelet therapy with aspirin and clopidogrel within the first 90 days of ACS.

Table 4.2: Baseline description of the CiPCA study population

Characteristics	**N (%)**
ACS	963
Age (median (IQR))	72 (58, 81)
At least one bleeding event recorded post ACS diagnosis (n, %)	
Yes	198 (21)
No	765 (79)
Gender (n, %)	
Females	351 (36)
Males	612 (64)
Practice (n, %)	
1	144 (15)
2	71 (7)
3	82 (9)
4	96 (10)
5	39 (4)
6	7 (1)
7	175 (18)
8	48 (5)
9	109 (11)
10	61 (6)
11	131 (14)

***N**; total number of patients, **%**; percentage, **IQR**; interquartile range.*

Table 4.3: Baseline antithrombotic therapy of the study population by time from ACS

Antithrombotic Therapy	≤ 30 Days	≤ 60 Days	≤ 90 Days
Aspirin (only) (n, %)	152 (15.7)	184 (19.1)	199 (20.7)
Clopidogrel (only) (n, %)	71 (7.4)	54 (5.6)	49 (5.1)
Prasugrel (only) (n, %)	***	***	***
Warfarin (only) (n, %)	19 (1.9)	21 (2.2)	24 (2.5)
Aspirin + Clopidogrel (n, %)	433 (44.9)	506 (52.5)	523 (54.3)
Aspirin + Prasugrel (n, %)	13 (1.3)	14 (1.5)	14 (1.5)
Aspirin + Warfarin (n, %)	8 (0.8)	15 (1.6)	14 (1.5)
Clopidogrel + Warfarin (n, %)	10 (1.0)	14 (1.5)	15 (1.6)
Aspirin + Clopidogrel + Warfarin (n, %)	5 (0.5)	6 (0.6)	8 (0.8)
None (n, %)	251 (26.0)	149 (15.5)	117 (12.1)

*** *frequency count is < 5,* ***n****; total number of patients,* ***%****; percentage*

Table 4.4: Timing and percentage of patients with each site-specific bleeding event (based on first bleed) over a median follow-up of 2.59 years post ACS within North Staffordshire

Type of bleed	**Bleeding events** n (% of all first bleeds)	**Median time from ACS to first bleed** (in days)
		Median (IQR)
Overall bleeds	**198 (100%)**	**359 (133, 796)**
Genitourinary	46 (23%)	515 (154, 1007)
Respiratory/ENT	45 (23%)	300 (73, 552)
Bruising	33 (17%)	247 (104, 543)
Gastrointestinal	32 (16%)	288 (135, 554)
Other (unclassified)	23 (11%)	845 (168, 1214)
Intraocular	18 (9%)	413 (167, 793)
Intracranial	***	53 (…, …)

*** *frequency count is < 5,* ***ENT;*** *ear, nose, throat,* ***IQR****; interquartile range*

Table 4.5: Socio-demographic characteristics of the CiPCA study population by bleeding complication over a median follow-up of 2.59 years post ACS

Characteristics	**Bleeding**	
	Yes (n = 198)	**No** (n = 765)
Age (median (IQR))	71 (58, 80)	72 (58, 81)
Gender (n, %)		
Females	89 (45)	262 (34)
Males	109 (55)	503 (66)

IQR*; interquartile range****, n****; total number of patients,* ***%****; percentage.*

4.5 Summary

The overall aim of this pilot study was to define bleeding events that are likely to occur following ACS, within the primary care setting, by means of Read codes. A panel consisting of an Interventional Cardiologist and three GPs agreed upon a code list for this definition, which comprised 250 Read codes. After inclusion of daughter codes, the final definition included 380 Read codes overall.

The exploratory descriptive analysis of the CiPCA database revealed that bleeding may be common in primary care, with a prevalence of 10 percent in the first 12 months following the ACS event. The majority of patients were discharged on guideline-recommended dual antiplatelet therapy with aspirin and clopidogrel. Patients discharged on antiplatelet therapy were more likely to have this therapy recorded in their medical records within the first 90 days after the ACS event. The proportion of patients on clopidogrel monotherapy decreased within 60 and 90 days post ACS. This was mainly explained by the fact that the patients who were on clopidogrel monotherapy within the initial 30 days were later prescribed either aspirin or warfarin in the subsequent 60 and 90 days post ACS.

4.5.1 Strength and limitations

A major strength of this pilot study lies in the comprehensive list of Read codes used to define bleeding complications, which is unlikely to have missed any relevant code.

The findings of this pilot study should be interpreted in light of some limitations. First, consensus was reached on the majority of Read codes (97%) after the second iteration, but only two members of the panel decided on whether to include or exclude the remaining 3 percent (11 Read codes). Second, all the descriptive analyses in this study

were mainly exploratory due to limited data and prevalence figures did not take into account time at risk. A study set within the national CPRD database will incorporate a larger sample size.

In summary, bleeding following ACS within the primary care setting has been defined by consensus of GPs and an Interventional Cardiologist. This definition, which comprised 380 Read codes, will be used to address the main objectives of the thesis. But first, the next chapter (Chapter 5) will describe the datasets and the methods that will be employed in addressing these objectives.

Chapter 5.0: **Methods for the studies using the Clinical Practice Research Datalink**

5.1 Introduction

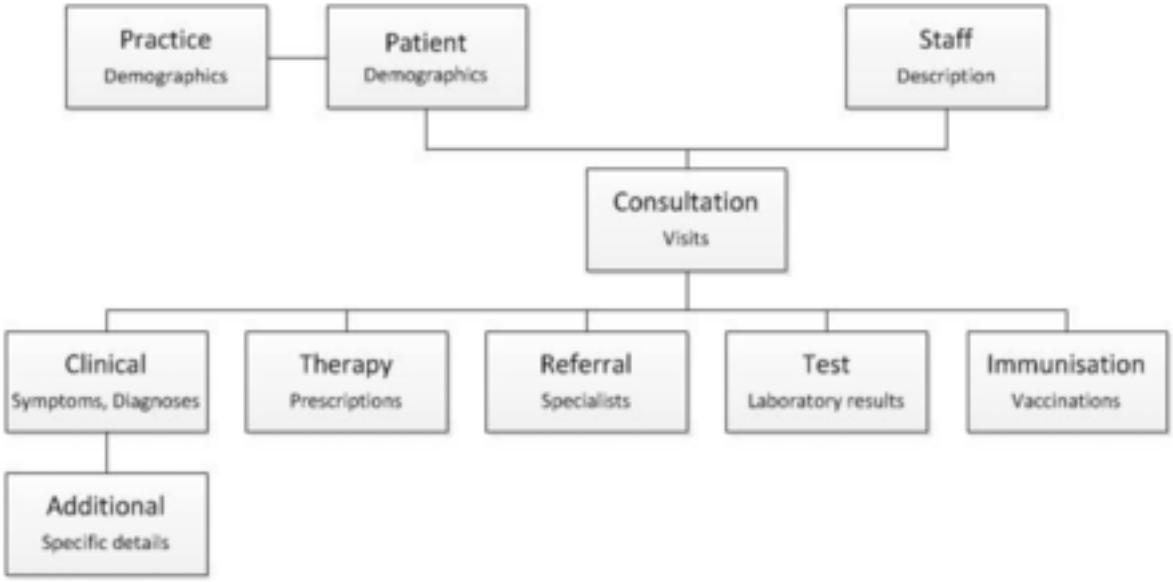
In the previous chapter, post-discharge bleeding following ACS was defined by consensus of GPs and an Interventional Cardiologist using resources from the literature and data from the CiPCA database. Limited exploratory analysis was likewise carried out on the CiPCA database. However, the size of the CiPCA database means a study utilising it would not be adequately powered to address the main objectives of this thesis. Therefore, in this chapter, a brief overview of the datasets that will be used for the remainder of the thesis, study design, inclusion and exclusion criteria for the study population, key variable definitions, and approaches to analyses and handling missing data are outlined.

5.2 Description of the study data source

5.2.1 The Clinical Practice Research Datalink (CPRD)

The CPRD is a UK government not for profit research service that combined EHRs across GP practices into a research-ready dataset known as the CPRD GOLD. **Figure 5.1** shows the structural overview of the CPRD GOLD data. The CPRD GOLD contains anonymised individual patient records on demographics, tests, clinical events, referrals, prescriptions, and immunisation from a subset of over 600 UK general practices (as at 2013) that had consented at the practice level to periodically provide data for research purposes. Each patient's consultation records (registered at a consenting practice) are available for research purposes unless they have requested for their data not to be used. Broad use of the CPRD data for observational research was approved by the National Research Ethics Service Committee (NRES). Over 2000 publications have used the CPRD data both nationally and internationally since its inception (CPRD, 2019).

Figure 5.1: Structural overview of the CPRD GOLD data



(figure adapted from (Herrett et al., 2015))

The CPRD GOLD contains consultation records of over 14 million patients, of which over 4 million were deemed active and alive as at 2013, representing almost 7% of the UK population (Herrett et al., 2015). CPRD is generally representative of the UK population on age, gender, and ethnicity (Herrett et al., 2015; Mathur et al., 2014). The CPRD data are of high research standard, and this standard has been regularly maintained through feedback mechanisms between CPRD and participating GP practices. Feedback reports highlighting inconsistencies and deficiencies in the data are fed to practices that do not meet these standards, along with instructions on how to rectify these anomalies. Practices which do not conform no longer have their data uploaded onto the CPRD database, and any previously uploaded data which may have anomalies are flagged to ensure researchers are aware of this issue.

Two further quality checks employed by CPRD ensure that practices, which provide data, are up to standard and the patients registered at these practices are acceptable for research. A patient is deemed "acceptable for research" if all quality checks on the validity of his/her age, gender, medical record and registration status are satisfied, while

a practice is flagged as “up to standard for research” if it meets the minimum quality checks on the continuity of data recording and the number of recorded deaths at that practice (Williams et al., 2012). The validity of diagnostic coding for conditions such as ACS is high in the CPRD database (Herrett et al., 2013; Herrett, Thomas, et al., 2010; Khan, Harrison, et al., 2010). A comparison of the validity of ACS diagnosis within CPRD against those recorded in the Myocardial Ischaemia National Audit Project ((MINAP) a national database of patients admitted to hospitals in England and Wales with a diagnosis of ACS (Herrett, Smeeth, et al., 2010)) which is regarded as containing the gold standard registry diagnostic record for this condition showed 92.2% positive predictive value (Herrett et al., 2013). The CPRD database has been shown to provide the more complete source of ACS records than MINAP or Hospital Episode Statistics ((HES) described below) (Herrett et al., 2013).

5.2.1.1 Linkage

CPRD is one of the largest primary care consultation records databases in the world, with a median prospective follow-up of 9.4 years (IQR: 2.3, 13.9 years) at the individual patient level as at 2013 (Herrett et al., 2015). It covers England, Wales, Scotland, and Northern Ireland, but for a subset of English practices that have consented to linkage (75% of all English practices that contribute data to CPRD), CPRD provides linked primary care consultation data to Hospital Episode Statistics (HES) data, English Index of Multiple Deprivation (IMD) data, and the Office for National Statistics (ONS) mortality data. Linkage to these datasets is carried out by a trusted third party (NHS digital, formerly known as the Health and Social Care Information Centre) (CPRD, 2018) using an eight-step deterministic algorithm to match patient records by all or some of the following: NHS

number, date of birth, sex, and postcode. Practices with and without such linkage are similar in respect of demographic data, years of follow-up, and prescribing (Gallagher et al., 2011). The richness of the information recorded in these linked datasets will provide an opportunity to: 1) carry out a population-based study that will allow the inclusion of elderly multi-morbid patients, which tend to be excluded in RCTs (Steg et al., 2007); 2) provide an opportunity to longitudinally follow the transition of patients from primary care to secondary care and back to primary care, thus allowing the study of longer-term complications such as bleeding events following hospital discharge post ACS; 3) provide records of individual patient's past/present diagnoses, prescriptions, investigations, laboratory measurements, and major morbidities; and 4) provide adequate sample size to detect meaningful associations. An application to use the CPRD data and these linked datasets to address the main objectives of the thesis was submitted to the Independent Scientific Advisory Committee (ISAC), and was approved, ISAC protocol number 17_181 (see **appendix 5.1** for protocol).

5.2.2 HES (admitted patient care (APC)) data

HES is a data warehouse containing detailed information on all hospitalisations, diagnoses, procedures, demographic information, and dates of hospital discharge from NHS or independent hospitals where the costs of care are reimbursed by the NHS. The data is structured by financial year, and each row of the data represents a finished consultant episode, which is the period under which a patient is cared for by one consultant, specified by a start and an end date (Herbert et al., 2017). Each hospitalisation is represented by a unique spell number, and each spell number may have multiple finished consultant episodes if a patient was cared for by more than one consultant

during hospitalisation (Herbert et al., 2017). Diagnoses in each episode of care are defined by ICD-10 codes and procedures by OPCS codes. The HES data also contains other geographical variables mapped from patient's postcode. It covers all NHS trusts within England, including primary care trusts, acute hospitals, and mental health trusts (NHS Digital, 2017a). The validity of diagnoses for conditions such as ACS is high in the HES database (Herrett et al., 2013). When compared to the MINAP registry (as gold standard), the HES database showed 91.5% positive predictive value for ACS diagnosis (Herrett et al., 2013).

5.2.3 ONS mortality data

The ONS mortality data contains information on the official date and cause of death of deceased persons in the UK. Each death within the ONS mortality data is recorded following the World Health Organisation ICD-10 classification. For each deceased person, the data contains the underlying cause of death and up to six other causes as recorded on the medical certificate of causes of death (ONS, 2016). The legal requirement to certify deaths (within 5 days) in England and Wales means that the ONS mortality data provide the most up to date (gold standard) record for deaths within the UK. But in situations where a coroner is involved, registration may be delayed until all enquiries have been completed, which may cause delayed recording in ONS (ONS, 2016). The linked ONS data provides a unique opportunity to study the prognostic impact of longer-term complications such as bleeding events on risk of mortality following ACS.

5.2.4 IMD data

IMD is a weighted combination of seven indices of deprivation, namely: income, employment, living environment, crime, barriers to housing and services, health and disability, and education, skills and training (Department for Communities and Local Government, 2015). It is an overall measure of deprivation experienced by people living in an area, estimated at the lower layer super output area, which comprised of units of output areas. The output area is the lowest geographical level built from clusters of adjacent units of postcodes to provide census estimates. These output areas are socially homogenous, similar in size and on average contains 110 to 139 households (ONS, 2017a). Every lower layer super output area is ranked according to its level of deprivation relative to that of other areas. The linked IMD data (based on a patient's lower layer super output area) is categorised based on quintile scores, with 1 representing the least deprived areas in England and 5 indicating the most deprived areas nationally. In this thesis, the English IMD 2015 was used as a proxy for individual level measure of deprivation.

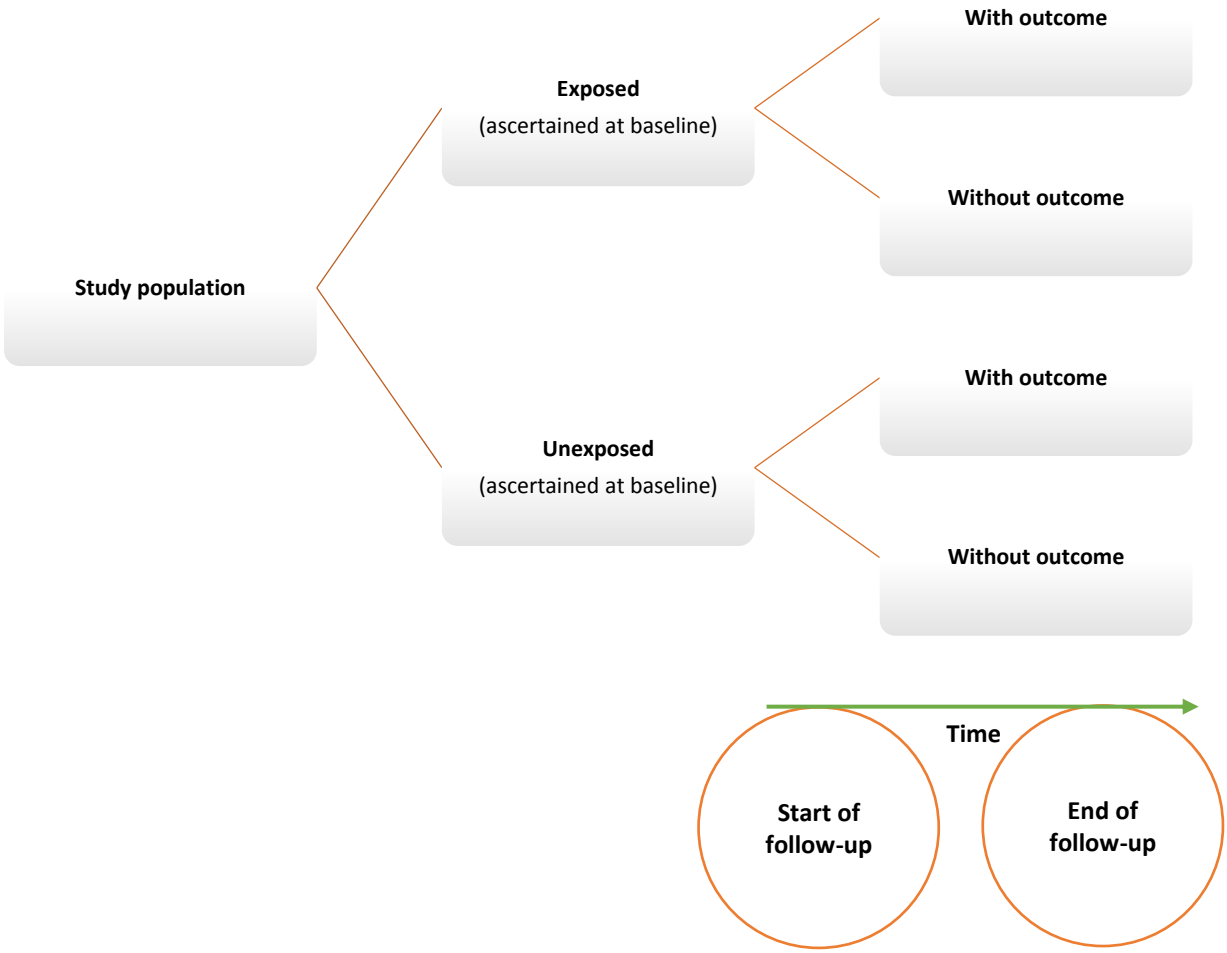
5.3 Study design

An open and dynamic cohort study design was the design adopted for all studies in this thesis. **Figure 5.2** gives a detailed illustration of this study design. Generally, in such a cohort design, individuals are defined as exposed or unexposed based on the presence or absence of a specific risk factor for an outcome at baseline. At the time of exposure ascertainment, patients are free from the outcome of interest. The exposed and unexposed individuals are then followed over some time to assess the occurrence of the outcome. Because individuals are free from the outcome of interest at the time their

exposure status is ascertained, the cohort study design allows temporal sequence between the exposure and the outcome to be established (Hennekens and Buring, 1987). The cohort study design also allows measuring of the incidence of the outcome in the exposed and unexposed groups (Hennekens and Buring, 1987). Three cohort studies all set within the linked CPRD database were carried out in this thesis in the following order:

I. The incidence, types, and timing of bleeding, and mortality study (Chapter 7)
II. The risk factors for bleeding study (Chapter 8), and finally
III. The prognostic impact of bleeding on all-cause mortality study (Chapter 9).

Figure 5.2: Schematic description of the cohort study design



5.3.1 The study population

5.3.1.1 Inclusion criteria

CPRD and HES were the datasets used to define the inclusion criteria for the study population, and patients were included if:

- ✓ They have a primary care record for ACS diagnosis (STEMI or NSTEMI) in CPRD between 01/01/2006 and 31/12/2016, and without a prior record for ACS in the preceding two years (the same Read code list used to ascertain ACS status in the CiPCA database in the analysis in Chapter 4 were used to ascertain ACS status in the CPRD database (see appendix 4.1)).

- ✓ They were aged 18 years and over at the time of ACS diagnosis, and designated as “acceptable for research” within CPRD.
- ✓ They were registered at a participating practice that was designated as “up to standard for research” within CPRD.
- ✓ They have at least two prior years of “up to standard” data within CPRD before the index ACS date and complete continuous registration in this period.
- ✓ They were registered at one of the 407 English practices that had consented to linkage with HES, ONS mortality data and IMD deprivation data (as at 2017).
- ✓ Had a matching ACS record in HES within 31 days before or after the date of the primary care ACS event. The 31-days window was selected because an episode of ACS might first be recorded by a GP in primary care before the patient is referred to a hospital, or it might be coded first in the hospital before informing the respective GP. In situations where ACS is first diagnosed in the in-hospital setting, a discharge letter containing a minimum of the primary diagnosis is dispatched to the patient’s GP within 24 hours of hospital discharge (Department of Health, 2003). To allow for delays from receipt of these letters to coding of ACS diagnosis into patient’s EHR records, the 31-days window was adjudged sufficient by consensus of NI, UTK, MAM, and KPJ. This time frame has also been shown to be sufficient in identifying matching ACS events between CPRD, HES, MINAP, and ONS (Herrett et al., 2013).

5.3.1.2 Exclusion criteria

The CPRD, HES, and ONS mortality data were the datasets used to define the exclusion criteria from the study population. Patients were excluded if:

- ✓ They did not have a matching ACS record in HES within 31 days before or after the primary care ACS event.
- ✓ They did not have a discharge date recorded in HES.
- ✓ They did not survive to hospital discharge.
- ✓ Their index ACS event preceded the date their registered practice was deemed to have up to standard data in CPRD.
- ✓ The date of transfer out of their registered practice was the same as or preceded the date of hospital discharge from the index ACS event.

5.3.1.3 Start point/index date of the study population

For each patient that fulfilled the criteria for the study population above, the start point/index date for that patient was the date of hospital discharge following the matched ACS event in HES. The steps taken to identify the study population and their index date are described further in Chapter 6.

5.3.1.4 Exit point of the study population

For each patient that fulfilled the criteria for the study population, the exit point of the study was determined as the earliest of the following dates:

- ➢ Date of death
- ➢ Date of last data collection from their registered practice
- ➢ Date of transfer out of practice

- End of the study period (20/09/2017).

5.4 Defining key variables using CPRD, HES, IMD and ONS data

The risk factors, outcomes, and covariates included in the analyses in this thesis are defined as follows.

5.4.1 The outcomes

5.4.1.1 Bleeding post-hospital discharge

Bleeding following ACS was defined as a record within the patient's primary care record with a Read code from the code list developed using the process described in Chapter 4 (and listed in **appendix 4.3)** post-hospital discharge, or a death record in the ONS mortality data with bleeding as the primary underlying cause post-hospital discharge. Bleeding was used interchangeably as an outcome (in Chapter 8) and as an exposure (in Chapter 9) in this thesis, and the definition remained the same throughout. All analyses in this thesis were based on the first bleeding event for a patient following hospital discharge. For patients with multiple first bleeds (that is, multiple bleeds recorded on the first day of bleeding) the most severe bleeding event was selected for these patients. For example, if a patient had intracranial bleeding and nose bleed recorded on the same day, the intracranial bleed was given preference. For those with a record of anaemia, this was only counted as a bleeding event if a patient did not have a prior record of anaemia in the 3 months before hospital discharge, and there was no record of other bleeding events (such as gastrointestinal bleed) within 2 days before or after the anaemia record (this rule was based on the clinical judgement of an Interventional Cardiologist (MAM)). For the remainder of the thesis, emphasis will be on bleeding events occurring within the first 12 months following hospital discharge for ACS. This

time frame was chosen because the majority of the study population will be on guideline-recommended dual antiplatelet therapy in this period, whose main side effect is bleeding (Wallentin et al., 2009; Wiviott et al., 2007; Yusuf et al., 2001). All bleeding events within this period were categorised based on the severity of the bleed by a GP (UTK) into typically/potentially serious bleeding events (referred to as serious bleeds in this thesis) and typically non-serious bleeding events (referred to as non-serious bleeds in this thesis) based on clinical judgement and the typical nature of the bleeds. See **appendix 5.2** for a full list of all the different bleeding events that constituted serious and non-serious bleeding events. **Table 5.1** summarises these bleeding events based on severity.

Table 5.1: Bleeding events categorised based on severity

Bleeding term	Site	Severity
Subarachnoid haemorrhage	Intracranial	Serious
Intracerebral haemorrhage	Intracranial	Serious
CVA - cerebrovascular accid due to intracerebral haemorrhage	Intracranial	Serious
Subdural haemorrhage - nontraumatic	Intracranial	Serious
Pontine haemorrhage	Intracranial	Serious
Other and unspecified intracranial haemorrhage	Intracranial	Serious
Sequelae of other nontraumatic intracranial haemorrhage	Intracranial	Serious
Evacuation of subdural haematoma	Intracranial	Serious
Gastrointestinal bleeding NOS	Gastrointestinal	Serious
Haematemesis	Gastrointestinal	Serious
Melaena	Gastrointestinal	Serious
Bleeding gastric ulcer	Gastrointestinal	Serious
Bleeding duodenal ulcer	Gastrointestinal	Serious
Rectal bleeding	Gastrointestinal	Serious
Blood in stool	Gastrointestinal	Serious
Haemorrhage - retinal	Intraocular	Serious
Subconjunctival haemorrhage	Intraocular	Non-serious
Vitreous haemorrhage	Intraocular	Serious
Conjunctival haemorrhage NOS	Intraocular	Non-serious
Subretinal haemorrhage	Intraocular	Serious
Epistaxis	Respiratory/ENT	Non-serious
Haemoptysis	Respiratory/ENT	Serious
Haemothorax	Respiratory/ENT	Serious
Haematuria	Genitourinary	Serious
Haematospermia	Genitourinary	Serious
Menorrhagia	Genitourinary	Serious
Postmenopausal bleeding	Genitourinary	Serious
Other abnormal uterine and vaginal bleeding	Genitourinary	Serious
Spontaneous bruising	Bruising	Non-serious
Anaemia due to chronic blood loss	Other	Serious
Haemarthrosis	Other	Serious
Haematoma NOS	Other	Serious

NOS; *not otherwise specified,* ***ENT;*** *ear, nose, throat.*

5.4.1.2 All-cause mortality

All-cause mortality was defined as having a death record in the ONS mortality data within the first 12 months following hospital discharge for ACS. The motivation for selecting this time frame (the first 12 months after hospital discharge) is described in detail in Chapter 9, section 9.3.1.2. The ONS mortality data contains the most up to date record of all deceased individuals in the UK, and all mortality records used in the analyses in this thesis were based on records from the ONS mortality data. For patients with recorded causes of deaths in ONS, the primary cause for each patient was classified as either bleeding, cardiovascular, or non-cardiovascular and non-bleeding related. Causes of deaths were coded using ICD-10 codes in the ONS data. For each code, the associated ICD term was reviewed, and for each term that referred to bleeding (as defined in Chapter 4), the underlying death was then classified as bleeding related. For terms that referred to the heart or the vascular system such as heart failure, cardiomyopathy, stroke or myocardial infarction, these deaths were classified as cardiovascular related. For terms that did not refer to bleeding or the heart/vascular system, such as road traffic accident, tuberculosis, and cancer, these deaths were classified as non-cardiovascular and non-bleeding related. These classifications were cross-validated by a cardiologist (MR) within the Research Institute.

5.4.2 Risk factors and covariates

The motivation for selecting these variables was based upon characteristics identified from the literature and the clinical judgement of an Interventional Cardiologist and a GP (see Chapter 8, section 8.3.1.3). These characteristics were grouped into socio-

demographic, comorbidities, in-hospital procedures, and pharmacological characteristics, and defined as follows:

5.4.2.1 Socio-demographic characteristics

All socio-demographic characteristics were identified from primary care records within CPRD except ethnicity, which was identified from HES data, and deprivation, which was based on IMD data.

5.4.2.1.1 Age

Age was derived by subtracting year of birth from year of index ACS diagnosis. Day and month of birth were not recorded in the CPRD patient data file.

5.4.2.1.2 Gender

Gender was identified from primary care records within CPRD as males, females, and indeterminate. For the main objectives of this thesis, gender was defined as males and females.

5.4.2.1.3 Geographical region

Geographical region was defined as North East, North West, Yorkshire and The Humber, East Midlands, West Midlands, East of England, South West, South Central, London, and South East as recorded within patient's primary care records in the CPRD practice data file.

5.4.2.1.4 Deprivation

Social deprivation was defined by IMD (2015) based on patient's postcode linked at lower layer super output area, as has been described above. The IMD was categorised based on quintile scores recorded within the area based deprivation data file, with 1 representing the least deprived areas in England and 5 indicating the most deprived areas nationally.

5.4.2.1.5 Ethnicity

Ethnicity was defined as Whites, Chinese, Other, Bangladeshi, Pakistani, Indian, Asian other, Black African/Caribbean/Other and mixed, in the HES patient data file. In this thesis, ethnicity was defined as White, Black, Asian, and other.

5.4.2.1.6 Body Mass Index

In CPRD, BMI may be recorded in kg/m^2, or weights (in kilograms) and heights (in metres) may be recorded in the additional clinical details data file. In this thesis, BMI was defined using the last recorded weight and height measurement for a patient until 30 days after hospital discharge. For patients whose BMI has already been calculated within CPRD, but are missing height or weight measurement, BMI was defined as the last recorded BMI measurement until 30 days after hospital discharge. Because the BMI of a patient may fluctuate with time, the cut-off of 30 days post-hospital discharge was used in order to capture the most recent BMI for a patient. BMI was then categorised into underweight (< 18.5 kg/m^2), normal weight (18.5 to < 25.0 kg/m^2), overweight (25.0 to < 30 kg/m^2) and obese (≥ 30 kg/m^2) following the World Health Organisation classification (WHO, 2017).

5.4.2.1.7 Smoking

Smoking was defined as the last recorded smoking status for a patient within 2 years prior to index date. Smoking status was then categorised into non-smoker, ex-smoker, and current smoker following the same classification used by Kontopantelis *et al*, Joseph *et al* and, as previously done in the CALIBER data portal (Joseph et al., 2016; Kontopantelis et al., 2014). Read codes used to define smoking were based on previous studies (Doran et al., 2011; Fairhurst et al., 2014, 2016; Joseph et al., 2017; Kontopantelis et al., 2014; Kontopantelis, Springate, et al., 2015; Reeves et al., 2014; Springate et al., 2015; Stocks et al., 2015) and are attached in **appendix 5.3**.

5.4.2.2 Comorbidities

Baseline comorbidities including hypertension, prior heart failure, peripheral vascular disease (PVD), gastroduodenal ulcer, chronic obstructive pulmonary disease (COPD), atrial fibrillation, and cancer were identified from patient's primary care records within CPRD, and defined as having the relevant diagnostic Read code in the 2 years before index date (see **appendix 5.3** for code lists). Code list for these morbidities/conditions were based on:

1) Read codes used in previous studies of these conditions within the primary care setting (Din et al., 2015; Doran et al., 2011; Fairhurst et al., 2014, 2016; Khan, Perera, et al., 2010; Kontopantelis et al., 2013, 2014; Kontopantelis, Olier, et al., 2015; Kontopantelis, Springate, et al., 2015; Mansfield et al., 2016; Reeves et al., 2014; Reilly et al., 2015; Springate et al., 2015; Stocks et al., 2015; Zhong et al., 2018)

2) Read codes used to define these conditions in the CALIBER data portal (the CALIBER data portal has been described in Chapter 4, section 4.3.1.4)
3) The Quality and Outcome Framework (QOF) definition, which is an incentive program designed to improve the quality of care given to patients by rewarding GP practices for the quality of care they provide to their patients (NHS Digital, 2017b).

   For each of these conditions/morbidities, the absence of a relevant Read code in patient primary care record was assumed to imply the absence of the condition/morbidity.

5.4.2.2.1 Diabetes

Diabetes was identified from primary care records within CPRD and defined as having:

1) A diagnostic Read code within 2 years prior to index date, or
2) A prescription for blood sugar-lowering medication such as Insulin, Metformin, Sulphonylureas, Meglitinides, within 2 years prior to index date. Read and product code lists used in ascertaining diabetes status were based on previous studies (Doran et al., 2011; Joseph et al., 2016, 2017; Khan, Perera, et al., 2010; Kontopantelis et al., 2013, 2014; Kontopantelis, Springate, et al., 2015; Mansfield et al., 2016; Matthews et al., 2016; Reeves et al., 2014; Reilly et al., 2015; Zhong et al., 2018) and those used in the CALIBER data portal. These code lists are presented in **appendix 5.3** and **5.4**.

5.4.2.2.2 History of bleeding

History of bleeding complications prior to index date was defined as having any of the codes included in the code list generated from the consensus exercise in Chapter 4, **appendix 4.3** in a patient's primary care record within 2 years prior to index date.

5.4.2.2.3 Chronic Kidney Disease (CKD)

Some patients had serum creatinine measurements recorded in their medical record within the tests data file in CPRD. Some had diagnostic Read codes for CKD in their clinical files, while others had both. In this thesis, CKD was defined as follows:

1) For patients with diagnostic Read codes for CKD within their clinical file, CKD was defined following the QOF criteria as having any of the Read codes for CKD in **appendix 5.3** within two years prior to index date. Staging of CKD for these patients followed the QOF classification, with those in stages 1 and 2 being categorised as not having CKD, and those in stages 3 to 5 as having CKD (NHS Digital, 2017c).
2) For patients without a recorded diagnostic Read code for CKD in CPRD, CKD was defined by estimated Glomerular Filtration Rate (eGFR), estimated using the last recorded serum creatinine measurement (for patients with a record) within 2 years prior to index date. eGFR was calculated for each patient using the Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) (see **table 5.2**). Patients with an eGFR greater than or equal to 60 mL/min per 1.73 m^2 were categorised as not having CKD, while those with an eGFR less than 60 mL/min per 1.73 m^2 were categorised as having a CKD based on the classification by kidney disease improving global outcome guideline (Stevens and Levin, 2013).

Patients without a diagnostic code for CKD in their primary care record within CPRD and without serum creatinine measurements were assumed to have normal kidney function.

Table 5.2: Formulas used in estimating GFR using serum creatinine

Race and Sex	eGFR equations when serum creatinine measured in µmol/L
Black	
Female	$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]
Male	$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.159$ [if black]
White or other	
Female	$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female]
Male	$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age}$

where Scr is serum creatinine, κ is 61.9 for females and 79.6 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1

(Adapted from Levey et al (Levey et al., 2009))

5.4.2.2.4 Hyperlipidaemia

Hyperlipidaemia was identified from primary care records within CPRD and defined as having any of the following criteria within 2 years prior to index date:

1) A total serum cholesterol level > 5 mmol/L (NHS Digital, 2017d; ScotPHO, 2017) or
2) A diagnostic code for hyperlipidaemia (see **appendix 5.3** for code lists) or
3) A prescription for lipid-lowering drugs (see **appendix 5.4** for product code lists). Read and product code lists used in ascertaining hyperlipidaemia status were based on those used within the Research Institute and the CALIBER data portal.

5.4.2.2.5 Baseline haemoglobin, white cell count, systolic and diastolic blood pressure

These were defined as the last recorded measurements in a patient's primary care record in CPRD within 2 years prior to index date. For total white cell count and baseline haemoglobin values where the units of measurement differ from the norm, these values were converted to the standard unit (for example, haemoglobin recorded in g/dL was converted to the standard unit of g/L by multiplying by 10). For values where the unit of measurement cannot be converted, these values were regarded as missing.

5.4.2.3 In-hospital procedures

5.4.2.3.1 PCI during the index ACS hospitalisation

The HES procedure data file contains the list of all procedures carried out on a patient during each hospitalisation stay. In this thesis, PCI during the index ACS hospitalisation was defined as having any of the OPCS codes listed **in appendix 5.5** for a PCI procedure in a patient's secondary care record (within HES datafile) between the index ACS admission date and discharge. These OPCS code lists were based on the consensus of two Interventional Cardiologists (MR and AS) within the Research Institute.

5.4.2.3.2 Coronary angiography during the index ACS hospitalisation

Coronary angiography during the index ACS hospitalisation was defined using secondary care records within the HES procedure data file, as having a record for any of the OPCS codes listed in **appendix 5.5** in HES between the index ACS admission date

and discharge. These OPCS code lists were also based on consensus of the two Interventional Cardiologists MR and AS.

5.4.2.4 Pharmacological characteristics

A GP (UTK) highlighted that a patient discharged with antithrombotic medication will normally have this recorded in his/her medical record within 30 days of hospital discharge. To allow discharge antithrombotic medication to be fully characterised, a period of 90 days (based on the exploratory analysis in Chapter 4) was adjudged sufficient enough (by consensus of NI, UTK, MAM and KPJ) for defining a patient's discharge medication. Antithrombotic medication at discharge was therefore defined and categorised as follows:

Single antiplatelet therapy: defined from patient primary care record in CPRD as having a recorded prescription for one of aspirin, clopidogrel, prasugrel or ticagrelor within 90 days post index date.

Dual antiplatelet therapy: defined from patient primary care record in CPRD as having a recorded prescription for aspirin and one of clopidogrel, prasugrel or ticagrelor within 90 days post index date.

Oral anticoagulant: defined from patient primary care record in CPRD as having a recorded prescription for one of warfarin, apixaban, rivaroxaban or dabigatran (with or without concomitant antiplatelets) within 90 days post index date.

5.4.2.4.1 Selective Serotonin Re-uptake Inhibitors (SSRIs)

The duration of treatment with SSRIs usually last up to six months or indefinite in the case of recurrent depression (NHS, 2015). Baseline SSRI was therefore defined using

primary care records in CPRD as having a recorded prescription for one of Fluoxetine, Paroxetine, Citalopram, Escitalopram, Sertraline or Fluvoxamine within 6 months prior to index date.

5.4.2.4.2 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Baseline NSAID use was defined using primary care records within CPRD as having a recorded prescription for one of Ibuprofen, Naproxen, Diclofenac, Celecoxib, Mefenamic acid, Etoricoxib or any other non-topical NSAID within 6 months prior to index date. The period of six months was adjudged sufficient to capture patients on longer-term NSAID use, such as those with underlying Rheumatoid Arthritis.

The code lists used to define baseline SSRIs, NSAIDs, and discharge antithrombotic medications are attached in **appendix 5.4.**

5.5 Analysis

I. The incidence, types, and timing of bleeding, and mortality study (*Objective 3*) – The description of the analytic approach for this study is outlined in Chapter 7.

II. The risk factors for bleeding study (*Objective 4*) – A competing risk regression model was used to determine independent associations between baseline patient characteristics and bleeding events (in Chapter 8).

III. The prognostic impact of bleeding on all-cause mortality study (*Objective 5*) – Cox proportional hazard regression model was used to determine independent associations between bleeding events and all-cause mortality (in Chapter 9).

Specific details of these analyses are described in the relevant chapters. The statistical models used in these analyses are described below. In order of complexity, the Cox

proportional hazard model is described first followed by the competing risk regression model.

5.5.1 The Cox proportional hazard regression model

The open and dynamic study design chosen for all the studies in this thesis means that patients can enter and exit the study at various times during follow-up. Therefore, the analysis of data generated from such a study design must take into account of; 1) the time of occurrence of the outcome event, 2) the time of censoring for the participants who were observed for the entire duration of follow-up but did not have the outcome event, and 3) the time of censoring for the participants who were lost to follow up.

The Cox proportional hazard regression model is suitable for this type of analysis and has been described in detail in Cox 1972 (Cox, 1972). The Cox model was used for objective 5 in that it can assess the effect of bleeding events on the hazard function, which is the probability that a patient will experience the outcome of mortality within the first 12 months after hospital discharge, conditional upon surviving up to the time of hospital discharge. The hazard function is then interpreted as the hazard or risk of mortality within the first 12 months following hospital discharge (Bland, 2015). Equation 1 illustrates the Cox proportional hazard regression model.

$$\ln\left\{\frac{h_{(t)}}{h_{0(t)}}\right\} = b_1X_1 + b_2X_2 + \cdots b_kX_k \qquad \boldsymbol{Eq\ 1}$$

equation adapted from Bland (Bland, 2015)

$h_{(t)}$= the hazard or risk of mortality at time t.

$h_{0(t)}$= the baseline hazard, that is to say, the hazard or risk of mortality when bleeding and all

other variables $X_1, X_2 \ldots X_k$ are set to zero.

$X_1, X_2 \ldots X_k$= the exposure of bleeding and all other covariates.

$\mathbf{ln}\left\{\frac{h_{(t)}}{h_{0(t)}}\right\}$ = log relative hazard of mortality in relation to the exposure of bleeding.

$b_1, b_2 + \cdots b_k$= coefficients quantifying the association of bleeding and all other covariates with the outcome of mortality.

Exponentiation of the regression coefficients results in hazard ratios, which represents the proportional increase or decrease in the hazard or risk of mortality per unit change in bleeding events while controlling for the effect of all the other variables included in the model. All associations are quantified by crude or adjusted hazard ratios and associated 95% confidence intervals.

5.5.2 The competing risk regression model

In the situation where the aim is to estimate the risk of bleeding events, and the outcome of bleeding is precluded from happening by the occurrence of other events (such as mortality), the Cox proportional hazard model will not be suitable in such a setting. Patients that died before experiencing a bleeding event will be censored in the same way as those who were still alive but were not observed for the entire duration of the study period. However, this will violate the Cox model assumption of independence of censoring and survival, since patients that die before experiencing a bleeding event will not have the same risk of the outcome of bleeding (their risk will be zero) after censoring as those that remained under observation or those that were still alive but were lost to follow-up.

A more suitable approach to estimate the risk of the outcome of bleeding (objective 4) in the presence of competing events such as death is to use a competing risk model, where the data to be analysed is expanded so that each patient has a record for the outcome of bleeding and the competing event (death from any cause). The association of baseline patient characteristics (e.g. female gender) with the outcome of bleeding are then assessed while simultaneously accounting for the effect of these baseline characteristics on the competing event. This approach gives a more robust effect estimate that is more reflective of the real-world setting (Lau et al., 2009). This effect estimate often referred to as the sub-distribution hazard ratio can then be interpreted as the risk of the outcome of bleeding within the first 12 months after hospital discharge in those with the baseline risk feature of interest (e.g. being a female) who have not yet had a bleeding event or have had the competing event (have died from any cause). In this thesis, the Fine and Gray competing risk regression model (Fine and Gray, 1999) was used to determine independent associations between baseline patient characteristics and bleeding events following hospital discharge post ACS. For a detailed description of the Fine and Gray competing risk regression model, the reader is referred to Fine and Gray 1999 (Fine and Gray, 1999). All associations were quantified by crude or adjusted subhazard ratios and associated 95% confidence intervals.

5.5.3 Assumptions of the Cox and competing risk regression models

For each fitted model, the two fundamental assumptions that are vital to the use and interpretation of the Cox and the competing risk regression models, namely, the proportional hazard assumption and the linearity assumption were examined. The

former assumes that the relative hazard of the outcome of interest among patients exposed to a particular risk factor is constant over the whole duration of follow up, while the latter assumes a linear relation between the relative hazard of the outcome and each risk factor on a continuous scale (Hosmer et al., 2008). Details of the diagnostic methods employed to assess these assumptions and results of these assessments are reported in the relevant chapters (Chapters 8 and 9).

5.6 Missing data

Generally, missing data are broadly categorised into three distinct types, depending on the mechanism giving rise to the missingness. The data may be missing completely at random (MCAR) or at random (MAR) or not at random (MNAR). When the probability that the data are missing does not depend on the observed and the missing data, this is referred to as MCAR. When the probability that the data are missing does depend on the observed but not the missing data, this is then referred to as MAR. When the probability that the data are missing does depend on both the observed and the missing data, this is then referred to as MNAR (Hosmer et al., 2008; Little and Rubin, 2002).

The CPRD dataset contains incomplete or missing data: for example, on smoking status and BMI. Ignoring patients with missing data in subsequent analyses may result in biased or inefficient measures of associations due to loss of power and precision. There are several approaches to dealing with missing data in epidemiological studies, some of which have been implemented in most statistical software packages (Horton and Kleinman, 2007). One of the most widely applied approaches is multiple imputation. Multiple imputation uses the distribution of the observed data to predict plausible

values for the missing data (White et al., 2011). Prediction errors are then added to account for any uncertainty in the imputed values (White et al., 2011). There is no consensus regarding the optimal number of imputations required, but as a rule of thumb, it should at least equal the percentage of incomplete cases in the dataset (White et al., 2011). Each imputed dataset is analysed separately but identically to generate measures of associations (such as hazard ratios and their associated confidence intervals). These measures of associations (from each imputed dataset) are then combined using Rubin's rule to obtain an overall estimate (White et al., 2011). Generally, analyses based on a multiply imputed dataset produces an unbiased and efficient measure of association (White et al., 2011).

Multiple imputation is based on the assumption that the mechanism giving rise to the missing data is MAR. While it is impossible to postulate whether the mechanism giving rise to the missingness is MAR or MNAR from the observed data, the MAR assumption can be made plausible by including variables which are significant predictors of the incomplete variable, and those which significantly predict whether the incomplete variable is missing (White et al., 2011).

Accordingly, multiple imputation (10 imputations) by chained equations was carried out to address missing data in this thesis (in Chapter 8). Only 10 imputed datasets were created due to the time and computational power required to carry out the intended analyses in this thesis. The variables smoking and BMI status were imputed, and the following variables were included in the imputation model: age, gender, year of hospital discharge following ACS, geographic region, CKD, diabetes, hypertension, heart failure, cancer, PVD, stroke, gastroduodenal ulcer, COPD, anaemia, atrial fibrillation, prior history of bleeding, type of ACS presentation, hyperlipidaemia, NSAID, SSRI,

discharged antithrombotic drug combination, coronary angiography, and PCI during the index ACS hospitalisation. The outcomes of bleeding and all-cause mortality, and the times to both bleeding and all-cause mortality within the first 12 months following hospital discharge were also included in the imputation model, so as not to weaken any potential association between the outcomes of bleeding or mortality with smoking and BMI status (Sterne et al., 2009). Analyses were then carried out on each imputed dataset and results combined using Rubin's rule to obtain an overall measure of association (hazard ratios and their associated confidence intervals). Results from the imputed datasets were then compared with those from the complete case analyses (analysis where only patients with complete data on all variables were considered) (in Chapters 8 and 9).

5.7 Statistical software

All statistical analyses for the main objectives of this thesis were carried out in Stata version 14.2 (Stata Corporation, College Station, Texas, USA).

5.8 Summary

This chapter outlined the study datasets, the study design, the inclusion and exclusion criteria for the study population, definitions for key variables, and finally the analytic approaches employed to address the main objectives of the thesis. The next chapter (Chapter 6) will describe the study population and descriptively compare their baseline characteristics to those patients with recorded ACS who did not fulfil the inclusion criteria for the study population. The baseline characteristics of those with missing data and those without will likewise be compared.

Chapter 6.0: **The study population and their baseline characteristics**

6.1 Introduction

In the previous chapter (Chapter 5), the study datasets, the study design, the inclusion and exclusion criteria for the study population, definitions for key variables, general approach to analysis, and approaches to handling missing data were described. In this chapter, the study population are derived, described, and compared descriptively to patients with primary care recorded ACS who did not fulfil the inclusion criteria for the study population. The level of missing data is examined and baseline characteristics of those who have missing data and those who did not are descriptively compared by socio-demographic, comorbidities, in-hospital procedures, and pharmacological characteristics.

6.2 Methods

6.2.1 Identification of the study population and their index date from CPRD and HES

The inclusion and exclusion criteria for the study population has been described in Chapter 5, section 5.3.1. Patients that fulfil the criteria for the study population were first identified from primary care records within CPRD. Of these patients, those that have linkage to secondary care records in HES were determined, and all hospital admissions with an ACS coded diagnosis in HES (defined by the ICD-10 code lists in **appendix 6.1**) were retrieved for these patients. To be included, the ACS must be recorded as either the primary or secondary diagnosis. For each patient with a linked record in HES, the primary care ACS event date was matched to an admission date with an ACS coded diagnosis in HES. Matching was within 31 days before or after the primary care event (recorded in CPRD) as previously done by Herrett *et al* (Herrett et al., 2013). A record longer than 31 days of the primary care event date was assumed to

be a different event (rule decided by consensus of NI, MAM, UTK, and KPJ), and was therefore not included as a matched event. When the primary care ACS event date was matched to an admission date with an ACS coded diagnosis in HES, the hospital discharge date became the **index date** for that patient. Matching was carried out in five stages (as follows) so that the level of agreement between the primary care (CPRD) and the secondary care records (HES) could be examined at each stage. Initially, patients were examined for

- exact match on HES admission date (with an ACS coded diagnosis) between CPRD and HES
- HES admission date with an ACS coded diagnosis between 1 and 7 days before or after the CPRD ACS date
- HES admission date with an ACS coded diagnosis between 8 and 14 days before or after the CPRD ACS date
- HES admission date with an ACS coded diagnosis between 15 and 21 days before or after the CPRD ACS date
- HES admission date with an ACS coded diagnosis between 22 and 31 days before or after the CPRD ACS date.

6.2.1.1 Sensitivity cohort

The sensitivity cohort is referred to as those with a primary care record of ACS that did not fulfil the inclusion criteria for the study population. That is to say, those that had a primary care record for ACS between 2006 and 2016, but either had no linkage to HES records or did not have a matching ACS event in HES within 31 days of the primary care

ACS date. For the purpose of comparisons between the sensitivity cohort and the study population, the sensitivity cohort were given an index date equivalent to the primary care ACS event date plus 5 days. This was based on reports from HES (NHS Digital, 2015) and MINAP (Weston et al., 2015) which indicated that the median length of hospital stay for patients with ACS was between 3 and 5 days.

6.2.2 Baseline descriptive comparisons

The study population were described and compared descriptively with the sensitivity cohort by baseline socio-demographic, comorbidities, in-hospital procedures, and pharmacological characteristics. Baseline definition for these characteristics has been described in Chapter 5, section 5.4. The level of missing data was assessed, and the baseline characteristics of those who have missing data and those who did not were descriptively compared. Continuous variables are presented as mean and standard deviation or median and IQR where the data were not normally distributed, and categorical variables as frequencies and percentages.

6.3 Results

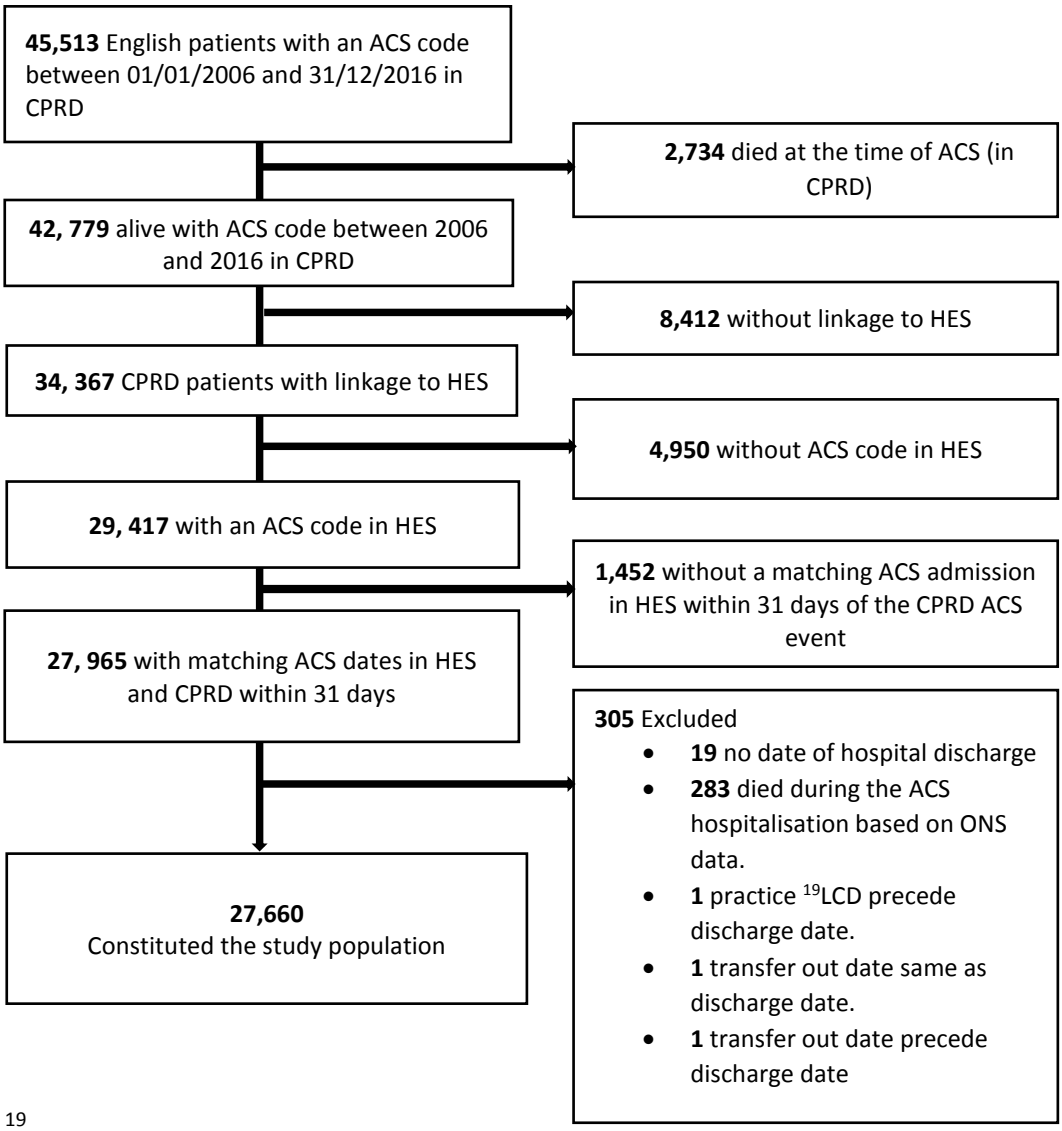
6.3.1 The study population

Figure 6.1 summarises the steps involved in identifying the study population and **appendix figure 6.1** describes these steps in more detail. Overall, 45,513 English patients aged 18 years and over had a primary care record for ACS (within CPRD) between 01/01/2006 and 31/12/2016, without a previous record in the preceding 2 years, and had 2 prior years of up to standard data within CPRD. 2,734 (6.0%) of these patients died on the date of the ACS event (recorded in CPRD). Of the remaining 42,779 patients, 34,367 (80.3%) had linkage to secondary care records in HES.

Of the 34,367 patients with HES linkage, 29,417 (86.0%) had an ACS code recorded in HES. Among patients with recorded ACS code in HES, 19,377 (65.9%) had an ACS admission date which exactly matched the first primary care ACS date in CPRD, 6,695 (22.8%) had an ACS admission date within 1 and 7 days before or after the primary care ACS date, 1,055 (3.6%) between 8 and 14 days, 475 (1.6%) between 15 and 21 days, and 363 (1.2%) between 22 and 31 days. 1452 (4.9%) did not have an ACS record in HES within 31 days of the primary care ACS date recorded in CPRD.

Of the 27,965 patients with a matching ACS record in HES and CPRD within 31 days, 19 did not have a hospital discharge date. For 3 patients, the last collection date for the practice or the transfer out date was either the same as or preceded the hospital discharge date, and a further 283 patients died during the ACS hospitalisation stay (based on ONS data), leaving 27,660 patients. These 27,660 patients constituted the study population for the analysis in this thesis. 14,648 patients who did not fit the criteria for the study population were used as a sensitivity cohort, mainly for descriptive purposes.

Figure 6.1: Flow diagram describing the steps involved in identifying the study population



19

[19] Last collection date

6.3.2 Baseline descriptive comparisons between the study population and the sensitivity cohort

6.3.2.1 Socio-demographic characteristics

The socio-demographic characteristics of the study population and the sensitivity cohort are described in **table 6.1**. The mean age of the study population was 70 years, and were more commonly men (65%), from the white ethnic background (96%), with higher percentages residing in the North West and Southern parts of England. The sensitivity cohort and the study population did not generally differ on demographic characteristics, although there were small differences in distribution by geographical region.

Table 6.1: Descriptive comparisons between the study population and the sensitivity cohort by socio-demographic characteristics

Demographics	**Study population** *(n = 27,660)*	**Sensitivity cohort** *(n = 14,648)*	**Overall** *(N = 42308)*
Age (years) (Mean ± SD)	69.9 ± 13.6	70.3 ± 13.6	70.1 ± 13.6
Gender (n, %)			
Male	17855 (64.6)	9152 (62.5)	27007 (63.8)
Female	9805 (35.4)	5495 (37.5)	15300 (36.2)
BMI (kg/m^2) (n, %)			
Normal weight (*BMI 18.50 to < 25)*	5924 (30.4)	3100 (30.9)	9024 (30.5)
Underweight *(BMI < 18.50)*	387 (2.0)	227 (2.3)	614 (2.1)
Overweight *(BMI 25 to < 30)*	7829 (40.1)	3926 (39.1)	11755 (39.8)
Obese *(BMI ≥ 30)*	5367 (27.5)	2794 (27.8)	8161 (27.6)
Smoking Status (n, %)			
Non smoker	7460 (33.2)	4241 (35.7)	11701 (34.1)
Ex-smoker	8701 (38.7)	4739 (39.9)	13440 (39.1)
Current smoker	6311 (28.1)	2907 (24.5)	9218 (26.8)
Ethnicity (n, %)			
White	26051 (95.6)	5769 (93.8)	31820 (95.3)
Black	135 (0.5)	52 (0.8)	187 (0.6)
Asian	806 (3.0)	235 (3.8)	1041 (3.1)
Other	251 (0.9)	95 (1.5)	346 (1.0)
IMD Quintiles (n, %)			
Least deprived	5545 (20.1)	1389 (21.0)	6934 (20.2)
2	6057 (21.9)	1459 (22.1)	7516 (21.9)
3	5817 (21.0)	1403 (21.3)	7220 (21.1)
4	5330 (19.3)	1253 (19.0)	6583 (19.2)
Most deprived	4893 (17.7)	1096 (16.6)	5989 (17.5)
Geographical region (n, %)			
North East	712 (2.6)	272 (1.9)	984 (2.3)
North West	5105 (18.5)	2179 (14.9)	7284 (17.2)
Yorkshire & The Humber	1087 (3.9)	431 (2.9)	1518 (3.6)
East Midlands	745 (2.7)	885 (6.0)	1630 (3.9)
West Midlands	3346 (12.1)	1721 (11.7)	5067 (12.0)
East of England	3072 (11.1)	1380 (9.4)	4452 (10.5)
South West	3794 (13.7)	1520 (10.4)	5314 (12.6)
South Central	3537 (12.8)	2364 (16.1)	5901 (13.9)
London	2592 (9.4)	1874 (12.8)	4466 (10.6)
South East Coast	3670 (13.3)	2022 (13.8)	5692 (13.5)

***SD**: standard deviation, **N:** overall patients in CPRD, **BMI:** body mass index, **IMD:** index of multiple deprivation.*

6.3.2.2 Comorbidities, in-hospital procedures, and pharmacological characteristics

The characteristics of the study population and sensitivity cohort are described by baseline comorbidities, in-hospital procedures, and pharmacological characteristics in **table 6.2**. Thirty percent of the study population had baseline CKD. The majority of the study population were discharged on guideline-recommended dual antiplatelet therapy with aspirin and a P2Y12 inhibitor (mostly clopidogrel), and 5.6 percent were managed with oral anticoagulants. The sensitivity cohort and the study population did not generally differ on comorbidities except for the higher prevalence of hyperlipidaemia (in the sensitivity cohort) and CKD (in the study population). There were more patients discharged on dual antiplatelet therapy in the study population than the sensitivity cohort (59.5% versus 45.6%), and the sensitivity cohort were twice as likely as the study population to have no recorded antithrombotic prescription at the time of hospital discharge for ACS (16.9% versus 9.7%). For a detailed description of the combinations of discharge antithrombotic drugs of the study population, the reader is referred to **appendix table 6.1.**

Twenty-five percent of the study population had experienced bleeding complications following hospital discharge (discussed in more detail in Chapter 7, section 7.1.3), which was similar to the sensitivity cohort (23%).

Table 6.2: Descriptive comparisons between the study population and the sensitivity cohort on comorbidities, in-hospital procedures, and pharmacological characteristics

Comorbidities	**Study population** *(n = 27,660)*	**Sensitivity cohort** *(n = 14,648)*	**Overall** *(N = 42308)*
Diabetes (n, %)	5816 (21.0)	3178 (21.7)	8994 (21.3)
Hypertension (n, %)	7103 (25.7)	3771 (25.7)	10874 (25.7)
Heart failure (n, %)	2521 (9.1)	1451 (9.9)	3972 (9.4)
Cancer (n, %)	2957 (10.7)	1614 (11.0)	4571 (10.8)
PVD (n, %)	987 (3.6)	537 (3.7)	1524 (3.6)
Gastroduodenal ulcer (n, %)	171 (0.6)	124 (0.8)	295 (0.7)
COPD (n, %)	5560 (20.1)	3017 (20.6)	8577 (20.3)
Atrial fibrillation (n, %)	1734 (6.3)	1119 (7.6)	2853 (6.7)
Hyperlipidaemia (n, %)	17808 (64.4)	10309 (70.4)	28117 (66.5)
History of bleeding (n, %)	3322 (12.0)	1875 (12.8)	5197 (12.3)
Bleeding Post-discharge (n, %)	**6891 (25.0)**	**3326 (22.7)**	**10217 (24.1)**
CKD (eGFR < 60 mL/min/1.73 m^2) (n, %)	8407 (30.4)	2759 (18.8)	11166 (26.4)
ACS presentation (n, %)			
STEMI	3632 (13.1)	1320 (9.0)	4952 (11.7)
NSTEMI	10415 (37.7)	4182 (28.5)	14597 (34.5)
Not otherwise specified	13613 (49.2)	9146 (62.4)	22759 (53.8)
Haemoglobin (g/L (Mean ± SD))	135 ± 18.9	134 ± 18.9	135 ± 18.9
Diastolic (mm Hg (Mean ± SD))	77.1 ± 12.0	76.2 ± 11.5	76.8 ± 11.8
Systolic (mm Hg (Mean ± SD))	137 ± 19.5	135 ± 19.3	136 ± 19.4
White cell count ($x10^9$/L (Median + IQR))	7.4 (6.2, 9.1)	7.4 (6.1, 9.0)	7.4 (6.2, 9.0)
In-hospital procedures			
Coronary angiography (only) (n, %)	4260 (15.4)	*450 (3.1)	4710 (11.1)
PCI (n, %)	9685 (35.0)	*400 (2.7)	10085 (23.8)
Drug therapy (n, %)			
Baseline NSAIDs	3483 (12.6)	1802 (12.3)	5285 (12.5)
Baseline SSRIs	2091 (7.6)	1247 (8.5)	3338 (7.9)
Discharge Antithrombotic			
Single antiplatelet	6954 (25.1)	4478 (30.6)	11432 (27.0)
Dual antiplatelet	16470 (59.5)	6680 (45.6)	23150 (54.7)
Oral anticoagulant	1559 (5.6)	1012 (6.9)	2571 (6.1)
No record	2677 (9.7)	2478 (16.9)	5155 (12.2)

* *majority of patients did not have linkage to HES records, therefore in-hospital procedures only ascertained for the few with linkage to HES data,* ***eGFR:*** *estimated glomerular filtration rate,* ***ACS:*** *acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***SD:*** *standard deviation,* ***IQR****: interquartile range.*

6.3.3 Missing data

Table 6.3 describes the extent of missing data on baseline characteristics. Generally, there was no difference in the prevalence of missing data between the study population and the sensitivity cohort. Baseline haemoglobin, white cell count, systolic, and diastolic blood pressure had the highest prevalence of missing data for both the study population and the sensitivity cohort. **Table 6.4** descriptively summarises the study population with any missing data and those without missing data by socio-demographic, comorbidities, in-hospital procedures, and pharmacological characteristics. Patients who had missing data were on average younger (mean 68 years versus 73 years), with lower prevalence of comorbidities such as diabetes, hypertension, COPD, hyperlipidaemia, history of bleeding complications, and CKD. These patients who had missing data were more commonly managed with PCI during the ACS hospitalisation stay and dual antiplatelet therapy with aspirin and a P2Y12 inhibitor post-hospital discharge.

Twenty-seven percent of the study population that did not have any missing data had experienced bleeding complications following hospital discharge, which was slightly higher than that of the population with missing data (23%).

Table 6.3: Prevalence of missing data for baseline characteristics

Characteristic	Frequency and percentage of missing		
	Study population *(n = 27,660)*	**Sensitivity cohort** *(n = 14,648)*	**Overall** *(N = 42308)*
BMI (kg/m^2) (n, %)	8153 (29.5)	4601 (31.4)	12754 (30.1)
Smoking Status (n, %)	5188 (18.8)	2761 (18.8)	7949 (18.8)
Ethnicity (n, %)	417 (1.5)	*8497 (58.0)	8914 (21.1)
IMD (n, %)	18 (0.1)	*8048 (54.9)	8066 (19.1)
Haemoglobin (g/L) (n, %)	8703 (31.5)	4479 (30.5)	13182 (31.2)
Diastolic (mm Hg) (n, %)	9592 (34.7)	5325 (36.4)	14917 (35.3)
Systolic (mm Hg) (n, %)	9592 (34.7)	5325 (36.4)	14917 (35.3)
White cell count (x10^9/L) (n, %)	8914 (32.2)	4643 (31.7)	13557 (32.0)

** Majority of patients did not have linkage to HES records,* ***BMI:*** *body mass index,* ***CKD:*** *chronic kidney disease,* ***IMD:*** *index of multiple deprivation.*

Table 6.4: Baseline descriptive comparisons between those with any missing data and those without in the study population

Demographics	**Missing** (n = 16614)	**Non-missing** (11046)
Age (years) (Mean ± SD)	68.2 ± 14.2	72.5 ± 12.4
Gender (n, %)		
Male	11007 (66.3)	6848 (62.0)
Female	5607 (33.7)	4198 (38.0)
BMI (kg/m^2) (n, %)		
Underweight *(BMI < 18.50)*	138 (1.6)	249 (2.3)
Normal weight (*BMI 18.50 to < 25)*	2642 (31.2)	3282 (29.7)
Overweight *(BMI 25 to < 30)*	3405 (40.2)	4424 (40.1)
Obese *(BMI ≥ 30)*	2276 (26.9)	3091 (28.0)
Smoking Status (n, %)		
Non smoker	3540 (31.0)	3920 (35.5)
Ex-smoker	4023 (35.2)	4678 (42.4)
Current smoker	3863 (33.8)	2448 (22.2)
Comorbidities		
Diabetes (n, %)	2548 (15.3)	3268 (29.6)
Hypertension (n, %)	3499 (21.1)	3604 (32.6)
Heart failure (n, %)	1273 (7.7)	1248 (11.3)
Cancer (n, %)	1627 (9.8)	1330 (12.0)
PVD (n, %)	436 (2.6)	551 (5.0)
Gastroduodenal ulcer (n, %)	75 (0.5)	96 (0.9)
COPD (n, %)	2716 (16.3)	2844 (25.7)
Atrial fibrillation (n, %)	825 (5.0)	909 (8.2)
Hyperlipidaemia (n, %)	8990 (54.1)	8818 (79.8)
History of bleeding (n, %)	1517 (9.1)	1805 (16.3)
Bleeding post-discharge (n, %)	**3945 (23.7)**	**2984 (27.0)**
CKD (eGFR < 60 mL/min/1.73 m^2) (n, %)	3947 (23.8)	4460 (40.4)
ACS presentation (n, %)		
STEMI	2401 (14.5)	1231 (11.1)
NSTEMI	5747 (34.6)	4668 (42.3)
Not otherwise specified	8466 (51.0)	5147 (46.6)
Haemoglobin (g/L (Mean ± SD))	135 ± 19.4	135 ± 18.6
Diastolic (mm Hg (Mean ± SD))	78.5 ± 12.1	76.1 ± 11.8
Systolic (mm Hg (Mean ± SD))	138 ± 19.6	137 ± 19.4
White cell count (x10^9/L (Median + IQR))	7.3 (6.1, 9.0)	7.5 (6.2, 9.1)

Continuation	Missing (n = 16614)	Non-missing (11046)
In-hospital procedures		
Coronary angiography (only) (n, %)	2511 (15.1)	1749 (15.8)
PCI (n, %)	6477 (39.0)	3208 (29.0)
Drug therapy (n, %)		
Baseline NSAIDs	2009 (12.1)	1474 (13.3)
Baseline SSRIs	1075 (6.5)	1016 (9.2)
Discharge antithrombotic		
Single antiplatelet	3886 (23.4)	3068 (27.8)
Dual antiplatelet	10390 (62.5)	6080 (55.0)
Oral anticoagulant	796 (4.8)	763 (6.9)
No record	1542 (9.3)	1135 (10.3)

eGFR: *estimated glomerular filtration rate,* ***ACS:*** *acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***SD:*** *standard deviation,* ***IQR****: interquartile range.*

6.3.4 Conclusion

There were 27,660 patients that fulfilled the study inclusion criteria and 14,648 that constituted the sensitivity cohort. Overall, the study population and the sensitivity cohort did not differ on the majority of baseline characteristics. Hence, results of subsequent analyses should be generalisable to the wider English ACS population in primary care. However, among those that fulfilled the inclusion criteria for the study population, those that had missing data appeared to be younger and healthier than those who did not. Ignoring these patients with missing data in subsequent analyses may result in biased or inefficient measures of associations due to loss of power and precision. Multiple imputation (described in detail in Chapter 5, section 5.6) will, therefore, be carried out and all analyses for the remainder of the thesis will be based on these imputed datasets.

But first, using the identified study population, the next chapter (Chapter 7) will examine the incidence, types, and timing of bleeding and mortality following hospital discharge post ACS.

Chapter 7.0: **Incidence, timing and types of bleeding events and mortality post-hospital discharge for ACS**

In the previous chapter, the study population was derived and described on baseline characteristics. In this chapter, the crude incidence, timing, and types of bleeding events and mortality post-hospital discharge are detailed (objective 3). The chapter is divided into 2 sections: the first section (section 7.1) determines the incidence, timing, and types/sites of bleeding events following hospital discharge post ACS. The second section (section 7.2) determines mortality rates after hospital discharge following ACS.

7.1 The incidence, timing, and types/sites of bleeding events

The motivation for the descriptive study described in this chapter has been outlined in detail in Chapters 1 and 3 of this thesis. But to recap, these are summarised as follows:

- The incidence of bleeding following hospital discharge after ACS is unclear.
- The majority of previous studies in the post-discharge setting reported only episodes of bleeding events and not incidence of bleeding.
- The emphasis in the majority of the previous studies have been on major bleeding, with little consideration for minor and nuisance bleeding events, which may be common post-discharge.
- In the majority of the previous studies that reported on the episodes of bleeding events, it was unclear whether patients were counted more than once if they had more than one episode of bleeding.
- There was wide variation in regards to length of follow up, type of ACS presentation, severity and type of bleeding examined, demographic characteristics of the study participants, and discharge antithrombotic regimen

between the studies that reported on episodes of bleeding events post-hospital discharge.

- There is uncertainty regarding the timing and types/sites of bleeding events following hospital discharge post ACS.

To address these gaps in knowledge, this section reports on the descriptive study determining the incidence, timing, and types/sites of bleeding events following hospital discharge post ACS. Baseline characteristics are also descriptively compared between those who sustained bleeding complications and those who did not, following hospital discharge for ACS.

7.1.1 **Aim and Objectives**

7.1.1.1 Aim

The overall aim was to determine the incidence, timing, and types/sites of bleeding events following hospital discharge for ACS.

7.1.1.2 Specific objectives

- To determine the incidence of bleeding events in the first 12 months after hospital discharge following ACS.
- To determine the incidence of bleeding events by time within the first 12 months after hospital discharge following ACS.
- To determine the types/sites of bleeding events in the first 12 months after hospital discharge following ACS.
- To determine the baseline characteristics of those that experienced bleeding complications in the first 12 months after hospital discharge following ACS.

7.1.2 **Methods**

The method for determining the incidence of bleeding is described below. All analyses described in this section are based on a first bleeding event for a patient following hospital discharge for ACS.

7.1.2.1 Study design

This was a descriptive cohort study set within CPRD with linkage to HES and ONS mortality data. Patients with a coded diagnosis for ACS between 1/1/2006 and 31/12/2016 were identified and followed prospectively for recorded bleeding consultations post-hospital discharge for ACS. Identified patients had no prior diagnostic record of ACS in the preceding 2 years (see inclusion criteria for the study population, Chapter 5, section 5.3.1.1).

For the incidence of bleeding analysis, follow up started from the index date of hospital discharge until date of first bleeding event within 12 months, or date patient ceased contributing to CPRD due to death or leaving practice or practice leaving CPRD or the end of 12 months from the index date of hospital discharge or the date of last data collection at the time of data request. The incidence of bleeding within the first 12 months following hospital discharge was then determined per 1000 person-years with associated 95% confidence intervals. The numerator for the incidence was the number of patients with at least one episode of bleed following hospital discharge, and the denominator was the total person-time at risk. The incidence of bleeding in the first 12 months following hospital discharge by timing of the bleeding events from the date of hospital discharge were likewise determined (that is, incidence in each of the following time periods: discharge – 30 days, 31 – 60 days, 61 – 90 days, 91 – 120 days, 121 – 150

days, 151 – 180 days, 181 – 210 days, 211 – 240 days, 241 – 270 days, 271 – 300 days, 301 – 330 days, 331 – 365 days post-discharge, with the numerator being the number of patients having first bleed within each time period and the denominator being the total person-time at risk in each time period). The incidence of bleeding within the first 12 months after hospital discharge by severity (see Chapter 5 table 5.1 for bleeding events that constituted serious and non-serious bleeds) and site of the bleeding events were determined. When estimating the incidence of bleeding by severity and site, only the relevant bleeding event was counted as a bleed and all others were ignored. For example, when estimating the incidence of gastrointestinal bleeds, only first episodes of these types of bleeding events were counted as bleeds and all other bleeding events (such as intracranial bleeds) before or after the gastrointestinal bleed were ignored (i.e. not counted as bleeding events).

7.1.2.2 Baseline characteristics of patients with bleeding complications

The baseline characteristics of patients who experienced bleeding in the first 12 months after hospital discharge for ACS were descriptively compared with those who did not, followed by stratification (based on all first bleeds within 12 months) by severity (serious and non-serious bleeds), timing of the bleed (bleeds within the first 30 days after hospital discharge, referred to as “early bleeds” and bleeds between 31 and 365 days post-hospital discharge referred to as “late bleeds” in this thesis), and types/site-specific bleeding events post hospital discharge.

The definition for each of the baseline characteristics are detailed in Chapter 5, section 5.4. For socio-demographic characteristics and comorbidities, the baseline was defined as the last recorded measurement or status in the previous 2 years prior to the date of

hospital discharge, except BMI, which was defined as the last record until 30 days after hospital discharge in order to capture the most recent BMI for a patient. In-hospital procedure was defined as having the relevant procedure during hospitalisation. Baseline for pharmacological characteristics was defined as having a relevant recorded prescription in the previous 6 months prior to hospital discharge in the case of NSAIDs and SSRIs, or within 90 days post-hospital discharge in the case of antithrombotic drugs (see Chapter 5, section 5.4.2.4). Continuous variables are presented as mean and standard deviation or median and IQR where the data were not normally distributed, and categorical variables as frequencies and percentages.

7.1.3 **Results**

7.1.3.1 Incidence of bleeding

Of the 27,660 patients that constituted the study population, 6,891 (25%) patients experienced 12,034 bleeding events over a median follow-up of 1.96 years (IQR: 0.67, 4.19) post-hospital discharge. A greater proportion of the bleeding events (53% of all first bleeds (3,620/6,891)) occurred within the first 12 months following hospital discharge. Of the 3,620 patients with first bleeding events in the first 12 months after hospital discharge, 74% (n = 2,673) only had one bleeding event, 18% (n = 654) had two bleeding events, 5.4% (n = 197) had three bleeding events, and 2.6% had four or more bleeding events within 12 months after discharge.

Overall, 13% (3,620/27,660) of patients had a bleeding event within 12 months after hospital discharge. The median time to a first bleeding event within 12 months post-hospital discharge was 123 days (IQR: 45, 223). The incidence of bleeding in the first 12 months of hospital discharge was 162/1000 person-years at risk (95% CI: 157, 167), and bleeding events occurred more frequently in the first 30 days following discharge (**figure 7.1**). Nineteen percent of patients that had a bleeding event within the first 12 months after hospital discharge had their first bleeding event in the first 30 days. **Figure 7.2** illustrates the crude incidence of bleeding within 12 months after hospital discharge for ACS by year of index hospital discharge. The incidence within this period ranged from 153 to 201/1000 person-years at risk. The incidence fluctuated but remained reasonably steady between 2006 and 2014, and peaked in 2015.

Figure 7.1: Crude incidence rates (per 1000 person-years at risk) of bleeding within 12 months after hospital discharge by time from date of hospital discharge

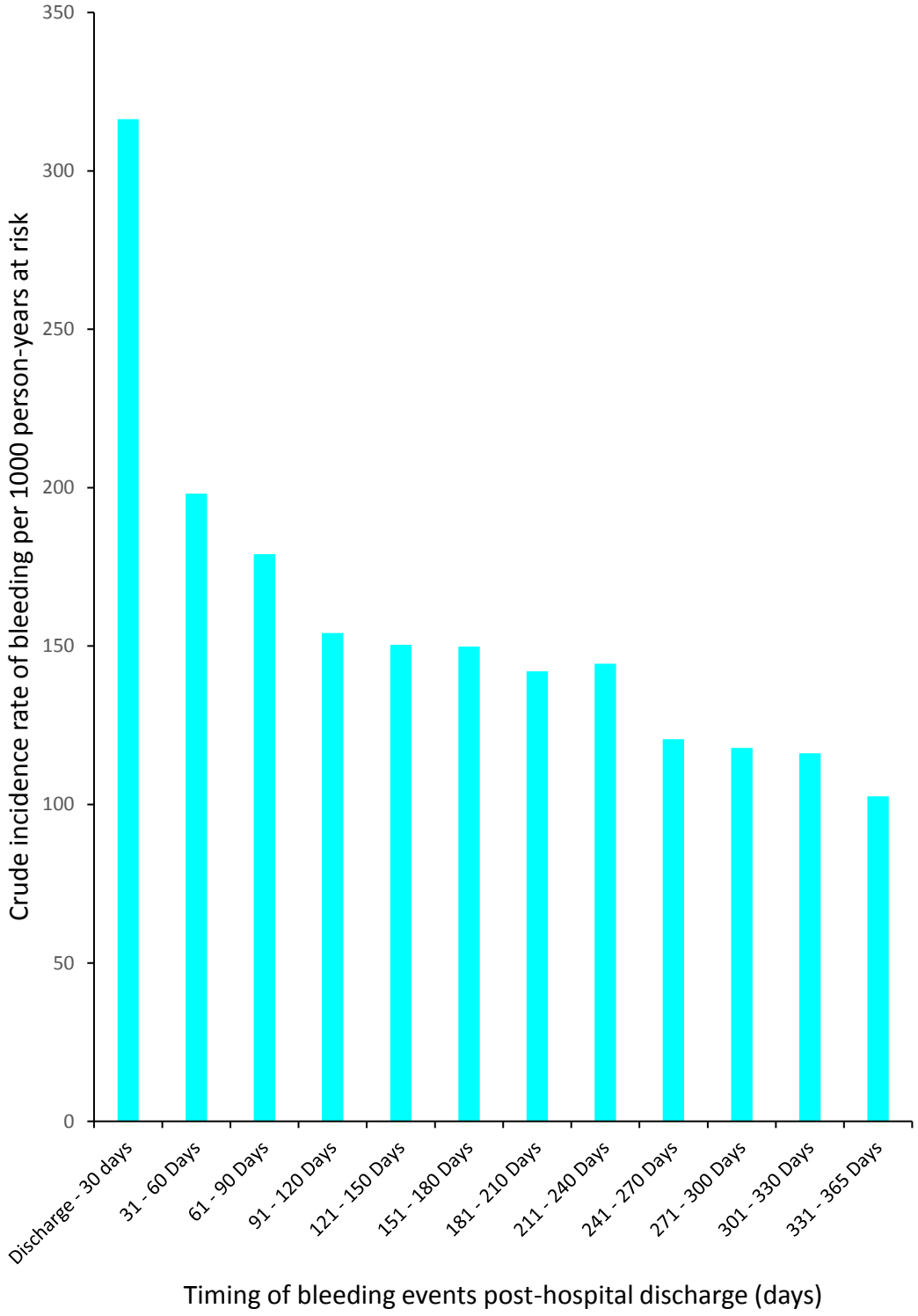
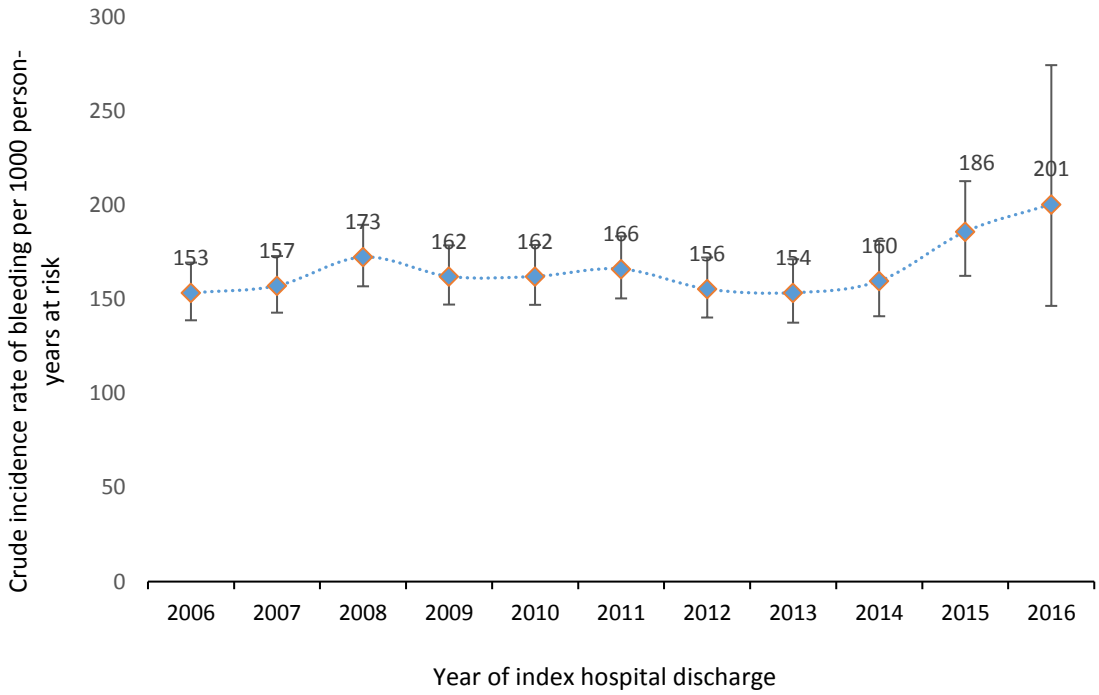


Figure 7.2: Crude incidence rates (per 1000 person-years at risk) of bleeding within 12 months after hospital discharge by year of index hospital discharge



7.1.3.2 Bleeding by severity

When the incidence of bleeding within the first 12 months following hospital discharge was split by severity, the incidence of a severe first bleed was 96/1000 person-years (95% CI: 92, 100) and 67/1000 person-years (95% CI: 63, 70) for non-serious first bleeds. The median time to a serious first bleeding event in the first 12 months following hospital discharge was 121 days (IQR: 43, 233), and 134 days (IQR: 51, 220) for non-serious first bleeding events. Both serious and non-serious bleeding events occurred more frequently in the first 30 days following hospital discharge for ACS.

7.1.3.3 Types/site-specific bleeding events

Table 7.1 summarises the incidence and timing of site-specific bleeding events within the first 12 months following hospital discharge for ACS. In this period, bruising was the most common type of first bleeding event post-hospital discharge (26% of all first bleeds), followed by gastrointestinal (20%) and other unclassified bleeds (19%, defined as ruptured aneurysms, haemarthrosis, haematoma, anaemia, and haemopericardium). Generally, the incidence of site-specific bleeds was highest for bruising (42/1000 person-years at risk), and lowest for intracranial bleeds (3/1000 person-years at risk).

Table 7.1: Incidence and timing of each type of bleeding event within 12 months post-hospital discharge

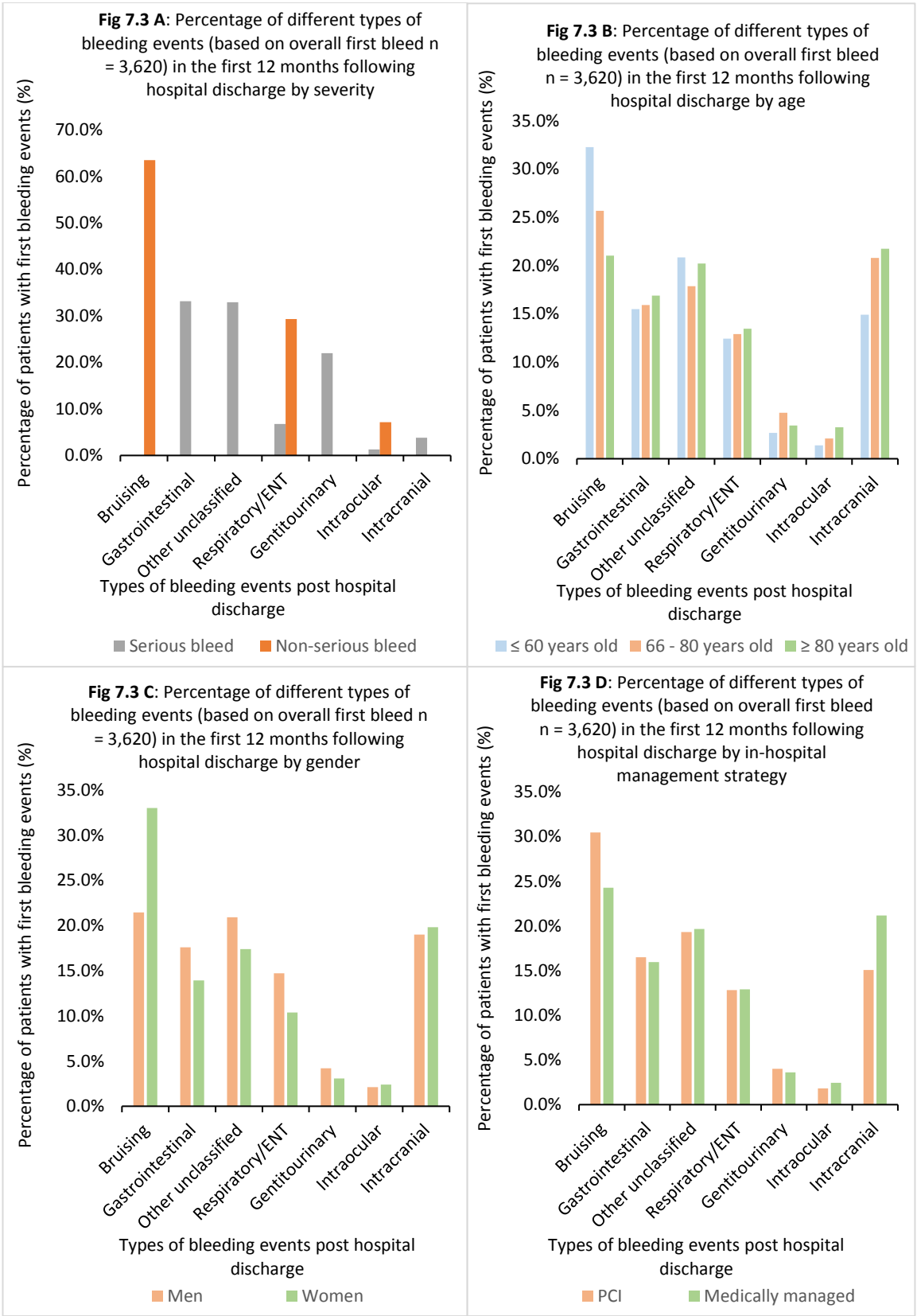
Type of bleed	**Bleeding events** n (% of all first bleeds)	**Incidence rate** (per 1000 person-years)	**Timing of bleed within 12 months** (days)
		Rate (95% CI)	Median (IQR)
Bruising	949 (26%)	42 (40 to 45)	132 (51 to 217)
Gastrointestinal	705 (20%)	32 (30 to 35)	123 (44 to 235)
Other unclassified	700 (19%)	32 (30 to 35)	125 (48 to 239)
Respiratory/ENT	582 (16%)	27 (25 to 29)	135 (54 to 229)
Genitourinary	468 (13%)	22 (20 to 24)	129 (46 to 239)
Intraocular	135 (4%)	6 (5 to 7)	167 (61 to 243)
Intracranial	81 (2%)	3 (3 to 4)	113 (44 to 220)

IQR; *interquartile range,* ***ENT;*** *ear, nose, throat*

Figure 7.3 summarises the percentage of different types of bleeding events (based on overall first bleeds n = 3,620) within the first 12 months following hospital discharge stratified by bleeding severity, age, gender, in-hospital management strategy, and discharge antithrombotic therapy. Generally, gastrointestinal, respiratory/ENT and other unclassified bleeds were more common among men than women (**figure 7.3 C**). Intracranial bleeds were more common in those managed medically during the index

ACS hospitalisation (**figure 7.3 D**). **Figure 7.3 A** shows that 64% of all non-serious bleeding events were bruising. **Figure 7.3 B** shows that in those aged 80 years and over, 22% of first bleeds were intracranial, compared to only 15% in those aged 60 years and under.

Figure 7.3: Percentage of different types of bleeding events (based on overall first bleeds n = 3,620) in the first 12 months following hospital discharge by bleeding severity, age, gender, in-hospital management strategy, and discharge antithrombotic drugs combination



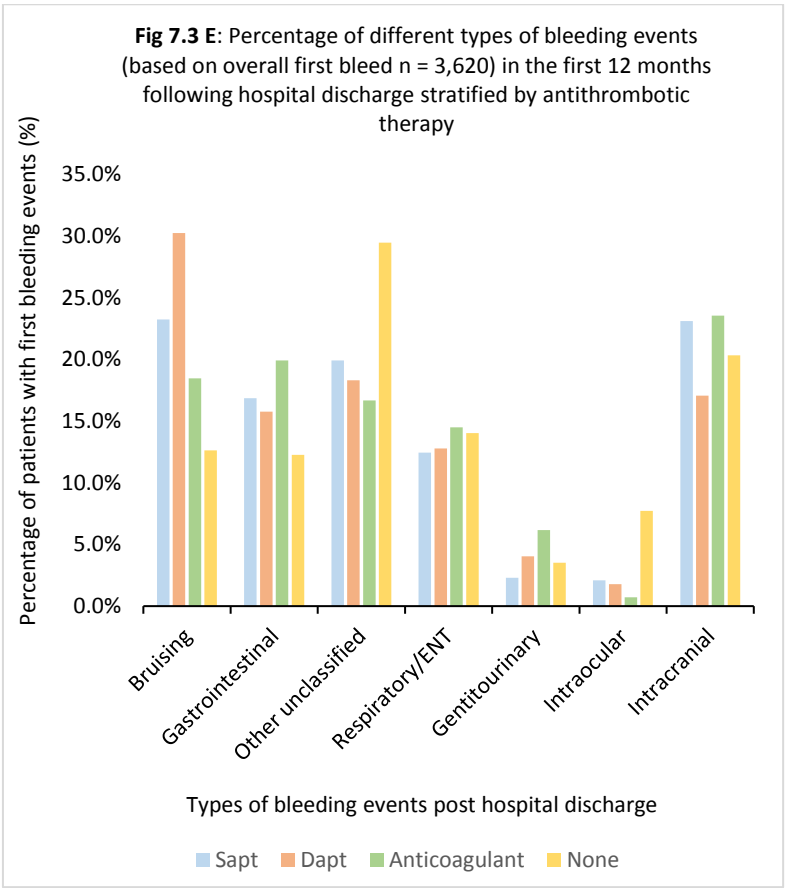


Fig 7.3 E: Percentage of different types of bleeding events (based on overall first bleed n = 3,620) in the first 12 months following hospital discharge stratified by antithrombotic therapy
Percentage of patients with first bleeding events (%)
35.0%
30.0%
25.0%
20.0%
15.0%
10.0%
5.0%
0.0%
Bruising
Gastrointestinal
Other unclassified
Respiratory/ENT
Genitourinary
Intraocular
Intracranial
Types of bleeding events post hospital discharge
Sapt
Dapt
Anticoagulant
None

7.1.3.4 Baseline characteristics of patients with bleeding complications

7.1.3.4.1 Characteristics of patients that experienced bleeding complications in the first 12 months following hospital discharge for ACS.

Of the overall 27,660 patients that comprised the study population, 3,620 (13%) experienced bleeding complications in the first 12 months following hospital discharge. **Table 7.2** summarises the baseline characteristics of those that experienced bleeding complications and those that did not within the first 12 months after hospital discharge for ACS. Those that experienced bleeding complications following hospital discharge for ACS were on average older (mean 72 vs 70 years), and more commonly ex-smokers, with higher prevalence of baseline hypertension, COPD, hyperlipidaemia, CKD, history of bleeding complications (in the previous 2 years prior to hospital discharge), and lower levels of haemoglobin. Those that experienced bleeding events were also more commonly treated with oral anticoagulants post-discharge. Of the 3,620 patients that experienced bleeding complications in the first 12 months, 21% had a history of bleeding, of which 8% consulted with the same type of bleeding event post discharge and the remaining 13% consulted with a different type of bleeding event.

These baseline characteristics are also summarised in appendix **tables 7.1** and **7.2** by age, gender, in-hospital management strategy, and discharge antithrombotic therapy.

Table 7.2: Baseline characteristics of the study population by bleeding events within 12 months post-hospital discharge

Demographic characteristics	Bleeding post-discharge	
	Bleed (n = 3620)	**No bleed** (n = 24040)
Age (year) (Mean ± SD)	72.1 ± 12.9	69.6 ± 13.7
Age (n, %)		
≤ 65	1079 (29.8)	9309 (38.7)
66 - 80	1433 (39.6)	8614 (35.8)
> 80	1108 (30.6)	6117 (25.4)
Gender (n, %)		
Male	2126 (58.7)	15729 (65.4)
Female	1494 (41.3)	8311 (34.6)
BMI (kg/m^2) (n, %)		
Underweight (BMI < 18.50)	62 (2.3)	325 (1.9)
Normal weight (BMI 18.50 to < 25)	828 (31.4)	5096 (30.2)
Overweight (BMI 25 to < 30)	1031 (39.0)	6798 (40.3)
Obese (BMI ≥ 30)	720 (27.3)	4647 (27.6)
Smoking Status (n, %)		
Non-smoker	1032 (34.0)	6428 (33.1)
Ex-smoker	1269 (41.8)	7432 (38.2)
Current smoker	735 (24.2)	5576 (28.7)
Comorbidities		
Diabetes (n, %)	814 (22.5)	5002 (20.8)
Hypertension (n, %)	1075 (29.7)	6028 (25.1)
Heart failure (n, %)	337 (9.3)	2184 (9.1)
Cancer (n, %)	431 (11.9)	2526 (10.5)
PVD (n, %)	174 (4.8)	776 (3.2)
Gastroduodenal ulcer (n, %)	30 (0.8)	141 (0.6)
COPD (n, %)	944 (26.1)	4616 (19.2)
Atrial fibrillation (n, %)	284 (7.8)	1450 (6.0)
Hyperlipidaemia (n, %)	2499 (69.0)	15309 (63.7)
History of bleeding (n, %)	759 (21.0)	2563 (10.7)
CKD (eGFR < 60 mL/min/1.73 m^2 (n, %))	1314 (36.3)	7093 (29.5)
ACS presentation (n, %)		
STEMI	439 (12.1)	3193 (13.3)
NSTEMI	1452 (40.1)	8963 (37.3)
ACS Not otherwise specified	1729 (47.8)	11884 (49.4)
Haemoglobin (g/L (Mean ± SD))	132 ± 19.8	136 ± 18.7
Diastolic (mm Hg (Mean ± SD))	76.2 ± 12.1	77.2 ± 12.0
Systolic (mm Hg (Mean ± SD))	137 ± 19.8	137 ± 19.4
White cell count ($x10^9$/L (Median ± IQR))	7.4 (6.2, 8.9)	7.4 (6.2, 9.1)
In-hospital procedures		
Coronary angiography (only) (n, %)	567 (15.7)	3693 (15.4)

Continuation	Bleeding post-discharge	
	Bleed (n = 3620)	**No bleed** (n = 24040)
In-hospital procedures		
PCI (n, %)	1201 (33.2)	8484 (35.3)
Drug therapy (n, %)		
Baseline NSAIDs	500 (13.8)	2983 (12.4)
Baseline SSRIs	320 (8.8)	1771 (7.4)
Discharge antithrombotic		
Single antiplatelet	908 (25.1)	6046 (25.1)
Dual antiplatelet	2151 (59.4)	14319 (59.6)
Oral anticoagulant	276 (7.6)	1283 (5.3)
No record	285 (7.9)	2392 (10.0)

SD: *standard deviation,* ***n:*** *number of patients in each category,* ***ACS:*** *acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***IQR:*** *interquartile range,* ***MI:*** *myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***eGFR:*** *estimated glomerular filtration rate,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index..*

7.1.3.4.2 Characteristics of patients that experienced bleeding complications in the first 12 months following hospital discharge by severity and timing of bleed (based on first bleeds)

Table 7.3 describes the baseline characteristics of those that experienced serious, non-serious, early, and late bleeding events post-hospital discharge. Compared to patients that experienced serious bleeding events, those that experienced non-serious bleeding events were on average younger (mean 71 vs 73 years), with a higher proportion of women, and lower prevalence of comorbidities (**table 7.3**). Those that experienced non-serious bleeding events were also more commonly discharged on dual antiplatelet therapy (65% vs 56%).

Patients who experienced early bleeding events (defined as bleeds within the first 30 days after hospital discharge) in comparison to those experiencing these bleeding events at a later time point post-hospital discharge were on average older (mean age 73 vs 72 years),

with higher prevalence of cancer, CKD, and lower levels of haemoglobin. A lower percentage of the patients that experienced early bleeding events were managed with coronary angiography during the index ACS hospitalisation. Those that experienced early bleeding events were also less commonly discharged on dual antiplatelets, and had a higher percentage of patients without recorded antithrombotic prescription at the time of hospital discharge (13% vs 7%) (**table 7.3**).

Table 7.3: Characteristics of patients that experienced bleeding complications in the first 12 months following hospital discharge by severity and timing of bleed (based on first bleeds)

Demographic characteristics	Bleeding post-discharge				
	No bleed (n = 24040)	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Late bleeds** (n = 2922)
Age (year) (Mean ± SD)	69.6 ± 13.7	72.9 ± 12.8	70.9 ± 13.0	73.3 ± 13.3	71.8 ± 12.8
Gender (n, %)					
Male	15729 (65.4)	1324 (62.3)	802 (53.7)	403 (57.7)	1723 (59.0)
Female	8311 (34.6)	802 (37.7)	692 (46.3)	295 (42.3)	1199 (41.0)
BMI (kg/m^2) (n, %)					
Underweight (BMI < 18.50)	325 (1.9)	32 (2.1)	30 (2.8)	11 (2.1)	51 (2.4)
Normal weight (BMI 18.50 to < 25)	5096 (30.2)	496 (31.9)	332 (30.5)	175 (33.6)	653 (30.8)
Overweight (BMI 25 to < 30)	6798 (40.3)	582 (37.5)	449 (41.3)	202 (38.8)	829 (39.1)
Obese (BMI ≥ 30)	4647 (27.6)	444 (28.6)	276 (25.4)	133 (25.5)	587 (27.7)
Smoking Status (n, %)					
Non-smoker	6428 (33.1)	591 (32.9)	441 (35.6)	202 (35.1)	830 (33.7)
Ex-smoker	7432 (38.2)	766 (42.7)	503 (40.6)	236 (41.0)	1033 (42.0)
Current smoker	5576 (28.7)	439 (24.4)	296 (23.9)	138 (24.0)	597 (24.3)
Comorbidities					
Diabetes (n, %)	5002 (20.8)	546 (25.7)	268 (17.9)	152 (21.8)	662 (22.7)
Hypertension (n, %)	6028 (25.1)	647 (30.4)	428 (28.6)	215 (30.8)	860 (29.4)
Heart failure (n, %)	2184 (9.1)	221 (10.4)	116 (7.8)	70 (10.0)	267 (9.1)
Cancer (n, %)	2526 (10.5)	272 (12.8)	159 (10.6)	104 (14.9)	327 (11.2)
PVD (n, %)	776 (3.2)	110 (5.2)	64 (4.3)	29 (4.2)	145 (5.0)
Gastroduodenal ulcer (n, %)	141 (0.6)	25 (1.2)	5 (0.3)	***	27 (0.9)
COPD (n, %)	4616 (19.2)	581 (27.3)	363 (24.3)	178 (25.5)	766 (26.2)
Atrial fibrillation (n, %)	1450 (6.0)	179 (8.4)	105 (7.0)	57 (8.2)	227 (7.8)
Hyperlipidaemia (n, %)	15309 (63.7)	1493 (70.2)	1006 (67.3)	464 (66.5)	2035 (69.6)
History of bleeding (n, %)	2563 (10.7)	511 (24.0)	248 (16.6)	158 (22.6)	601 (20.6)
CKD (eGFR < 60 mL/min/1.73 m^2 (n, %))	7093 (29.5)	819 (38.5)	495 (33.1)	280 (40.1)	1034 (35.4)
ACS presentation (n, %)					
STEMI	3193 (13.3)	236 (11.1)	203 (13.6)	73 (10.5)	366 (12.5)
NSTEMI	8963 (37.3)	880 (41.4)	572 (38.3)	290 (41.5)	1162 (39.8)
Not otherwise specified	11884 (49.4)	1010 (47.5)	719 (48.1)	335 (48.0)	1394 (47.7)
Haemoglobin (g/L (Mean ± SD))	136 ± 18.7	130 ± 20.0	135 ± 19.2	129 ± 23.2	133 ± 18.9
Diastolic (mm Hg (Mean ± SD))	77.2 ± 12.0	75.7 ± 12.3	76.8 ± 11.8	75.9 ± 11.9	76.2 ± 12.2
Systolic (mm Hg (Mean ± SD))	137 ± 19.4	137 ± 20.8	137 ± 18.4	137 ± 19.5	137 ± 19.9

Continuation	Bleeding post-discharge				
	No bleed (n = 24040)	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Late bleeds** (n = 2922)
White cell count ($x10^9$/L (Median ± IQR))	7.4 (6.2, 9.1)	7.5 (6.2, 9.1)	7.2 (6.1, 8.7)	7.4 (6.2, 9.0)	7.4 (6.2, 8.9)
In-hospital procedures					
Coronary angiography (only) (n, %)	3693 (15.4)	346 (16.3)	221 (14.8)	90 (12.9)	477 (16.3)
PCI (n, %)	8484 (35.3)	644 (30.3)	557 (37.3)	227 (32.5)	974 (33.3)
Drug therapy (n, %)					
Baseline NSAIDs	2983 (12.4)	290 (13.6)	210 (14.1)	82 (11.7)	418 (14.3)
Baseline SSRIs	1771 (7.4)	186 (8.7)	134 (9.0)	61 (8.7)	259 (8.9)
Discharge antithrombotic					
Single antiplatelet	6046 (25.1)	559 (26.3)	349 (23.4)	213 (30.5)	695 (23.8)
Dual antiplatelet	14319 (59.6)	1184 (55.7)	967 (64.7)	336 (48.1)	1815 (62.1)
Oral anticoagulant	1283 (5.3)	172 (8.1)	104 (7.0)	58 (8.3)	218 (7.5)
No record	2392 (10.0)	211 (9.9)	74 (5.0)	91 (13.0)	194 (6.6)

**** frequency count is < 5, **SD:** standard deviation, **n:** number of patients in each category, **ACS:** acute coronary syndrome, **STEMI:** ST-elevation myocardial infarction, **NSTEMI:** Non ST-elevation myocardial infarction, **IQR:** interquartile range, **MI:** myocardial infarction, **PVD:** peripheral vascular disease, **COPD:** chronic obstructive pulmonary disease, **CKD:** chronic kidney disease, **eGFR:** estimated glomerular filtration rate, **NSAID:** non-steroidal anti-inflammatory drugs, **SSRI:** selective serotonin re-uptake inhibitors, **PCI:** percutaneous coronary intervention, **BMI:** body mass index, **Early bleeds**: defined as first bleeds within the first 30 days after hospital discharge, **Late bleeds:** defined as first bleeds between 31 and 365 days post-hospital discharge.*

7.1.3.4.3 Characteristics of patients that experienced bleeding complications in the first 12 months following hospital discharge by type/site of bleeding (based on first bleeds)

Table 7.4 summarises the baseline characteristics of the study population by type/site of first bleeding event within 12 months after hospital discharge. The majority of patients whose first bleeding events post-hospital discharge were intracranial, or other unclassified bleeds (mainly: ruptured aneurysms, haemarthrosis, haematoma, anaemia, and haemopericardium) were on average older (mean age of 76 years for intracranial bleeds and 74 years for other unclassified bleeds). More females commonly reported

minor bruising than their male counterparts' post-hospital discharge, whereas the opposite is true for all other bleeds. Patients that experienced intracranial bleeding events post-hospital discharge had higher prevalence of baseline diabetes, atrial fibrillation, CKD, and a lower percentage were managed with PCI during the index ACS hospitalisation. This group of patients were also less commonly discharged on dual antiplatelets or oral anticoagulants, and 27% did not have any record of an antithrombotic prescription at discharge. Patients who experienced gastrointestinal bleeding events post-hospital discharge had a higher prevalence of baseline hypertension, cancer, gastroduodenal ulcer, and CKD. Whereas those that experienced respiratory/ENT bleeds had a higher prevalence of heart failure, cancer, hypertension, and COPD in the previous 2 years before hospital discharge (**table 7.4**).

Table 7.4: Characteristics of patients with bleeding complications in the first 12 months following hospital discharge by first type/site of bleeding event

Demographic characteristics	Types/site-specific bleeding events post-discharge						
	Bruising (n = 949)	**Respiratory/ENT** (n = 582)	**Gastrointestinal** (n = 705)	**Genitourinary** (n = 468)	**Intraocular** (n = 135)	**Intracranial** (n = 81)	**Other unclassified bleeds** (n = 700)
Age (year) (Mean ± SD)	69.6 ± 13.0	72.6 ± 12.7	71.9 ± 13.6	72.1 ± 13.5	72.4 ± 10.9	76.3 ± 11.8	74.4 ± 11.6
Gender (n, %)							
Male	456 (48.1)	374 (64.3)	445 (63.1)	313 (66.9)	89 (65.9)	45 (55.6)	404 (57.7)
Female	493 (51.9)	208 (35.7)	260 (36.9)	155 (33.1)	46 (34.1)	36 (44.4)	296 (42.3)
BMI (kg/m^2) (n, %)							
Underweight (BMI < 18.50)	20 (2.9)	12 (2.9)	9 (1.8)	5 (1.5)	***	***	11 (2.1)
Normal weight (BMI 18.50 to < 25)	202 (29.5)	133 (31.6)	154 (30.0)	101 (30.4)	36 (35.3)	29 (48.3)	173 (32.8)
Overweight (BMI 25 to < 30)	286 (41.8)	165 (39.2)	202 (39.4)	123 (37.0)	36 (35.3)	20 (33.3)	199 (37.7)
Obese (BMI ≥ 30)	177 (25.8)	111 (26.4)	148 (28.8)	103 (31.0)	28 (27.5)	8 (13.3)	145 (27.5)
Smoking Status (n, %)							
Non-smoker	288 (36.5)	152 (31.3)	201 (34.0)	126 (32.4)	39 (34.8)	24 (38.7)	202 (33.4)
Ex-smoker	290 (36.7)	221 (45.5)	235 (39.7)	175 (45.0)	51 (45.5)	27 (43.5)	270 (44.6)
Current smoker	212 (26.8)	113 (23.3)	156 (26.4)	88 (22.6)	22 (19.6)	11 (17.7)	133 (22.0)
Comorbidities							
Diabetes (n, %)	159 (16.8)	121 (20.8)	155 (22.0)	104 (22.2)	35 (25.9)	22 (27.2)	218 (31.1)
Hypertension (n, %)	254 (26.8)	200 (34.4)	206 (29.2)	123 (26.3)	48 (35.6)	22 (27.2)	222 (31.7)
Heart failure (n, %)	65 (6.8)	67 (11.5)	67 (9.5)	41 (8.8)	8 (5.9)	***	85 (12.1)
Cancer (n, %)	95 (10.0)	78 (13.4)	95 (13.5)	61 (13.0)	13 (9.6)	7 (8.6)	82 (11.7)
PVD (n, %)	36 (3.8)	29 (5.0)	28 (4.0)	23 (4.9)	6 (4.4)	***	49 (7.0)
Gastroduodenal ulcer (n, %)	***	***	10 (1.4)	***	***	***	9 (1.3)
COPD (n, %)	216 (22.8)	178 (30.6)	182 (25.8)	121 (25.9)	30 (22.2)	20 (24.7)	197 (28.1)
Atrial fibrillation (n, %)	60 (6.3)	51 (8.8)	49 (7.0)	45 (9.6)	9 (6.7)	15 (18.5)	55 (7.9)

Continuation	Types/site-specific bleeding events post-discharge						
	Bruising (n = 949)	**Respiratory/ENT** (n = 582)	**Gastrointestinal** (n = 705)	**Genitourinary** (n = 468)	**Intraocular** (n = 135)	**Intracranial** (n = 81)	**Other unclassified bleeds** (n = 700)
Hyperlipidaemia (n, %)	626 (66.0)	405 (69.6)	497 (70.5)	313 (66.9)	101 (74.8)	49 (60.5)	508 (72.6)
History of bleeding (n, %)	138 (14.5)	127 (21.8)	162 (23.0)	126 (26.9)	30 (22.2)	18 (22.2)	158 (22.6)
CKD (eGFR < 60 mL/min/1.73 m^2 (n, %))	305 (32.1)	188 (32.3)	258 (36.6)	158 (33.8)	63 (46.7)	34 (42.0)	308 (44.0)
ACS presentation (n, %)							
STEMI	122 (12.9)	81 (13.9)	103 (14.6)	50 (10.7)	16 (11.9)	12 (14.8)	55 (7.9)
NSTEMI	370 (39.0)	225 (38.7)	271 (38.4)	184 (39.3)	53 (39.3)	32 (39.5)	317 (45.3)
Not otherwise specified	457 (48.2)	276 (47.4)	331 (47.0)	234 (50.0)	66 (48.9)	37 (45.7)	328 (46.9)
Haemoglobin (g/L (Mean ± SD))	136 ± 17.6	133 ± 21.2	133 ± 20.5	133 ± 19.0	134 ± 19.0	130 ± 23.5	125 ± 19.0
Diastolic (mm Hg (Mean ± SD))	77.4 ± 11.7	75.9 ± 11.6	76.9 ± 12.2	75.4 ± 12.0	75.3 ± 10.9	78.6 ± 14.2	74.4 ± 12.6
Systolic (mm Hg (Mean ± SD))	137 ± 18.1	136 ± 19.1	137 ± 20.4	136 ± 20.0	136 ± 18.2	142 ± 22.7	138 ± 21.8
White cell count (x10^9/L (Median ± IQR))	7.2 (6.1, 8.7)	7.5 (6.2, 9.1)	7.6 (6.3, 9.0)	7.5 (6.2, 9.2)	7.3 (6.0, 8.6)	7.4 (6.1, 9.8)	7.5 (6.2, 8.9)
In-hospital procedures							
Coronary angiography (only) (n, %)	154 (16.2)	78 (13.4)	105 (14.9)	80 (17.1)	19 (14.1)	7 (8.6)	124 (17.7)
PCI (n, %)	366 (38.6)	198 (34.0)	232 (32.9)	154 (32.9)	48 (35.6)	22 (27.2)	181 (25.9)
Drug therapy (n, %)							
Baseline NSAIDs	131 (13.8)	88 (15.1)	95 (13.5)	70 (15.0)	16 (11.9)	6 (7.4)	94 (13.4)
Baseline SSRIs	96 (10.1)	43 (7.4)	64 (9.1)	44 (9.4)	15 (11.1)	6 (7.4)	52 (7.4)
Discharge antithrombotic							
Single antiplatelet	211 (22.2)	153 (26.3)	181 (25.7)	113 (24.1)	21 (15.6)	19 (23.5)	210 (30.0)
Dual antiplatelet	651 (68.6)	339 (58.2)	394 (55.9)	275 (58.8)	87 (64.4)	38 (46.9)	367 (52.4)
Oral anticoagulant	51 (5.4)	55 (9.5)	46 (6.5)	40 (8.5)	17 (12.6)	***	65 (9.3)
No record	36 (3.8)	35 (6.0)	84 (11.9)	40 (8.5)	10 (7.4)	22 (27.2)	58 (8.3)

**** frequency count is < 5, **SD:** standard deviation, **n:** number of patients in each category, **ENT:** ear nose throat, **ACS:** acute coronary syndrome, **STEMI:** ST-elevation myocardial infarction, **NSTEMI:** Non ST-elevation myocardial infarction, **IQR:** interquartile range, **MI:** myocardial infarction, **PVD:** peripheral vascular disease, **COPD:** chronic obstructive*

pulmonary disease, ***CKD:*** *chronic kidney disease,* ***eGFR:*** *estimated glomerular filtration rate,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index.*

7.2 Mortality

In this section, mortality rates after hospital discharge following ACS are determined, mainly to inform the analysis investigating the association of bleeding with all-cause mortality in Chapter 9. The motivation for the present descriptive study has been outlined in Chapters 1, 3, and in more detail in Chapter 9 of this thesis.

7.2.1 Aim and Objectives

7.2.1.1 Aim

The overall aim was to determine the rate and timing of mortality following bleeding events after hospital discharge post ACS.

7.2.1.2 Specific objectives

- To determine the rate of mortality following bleeding complications in the first 12 months after hospital discharge post ACS.
- To determine the rate of mortality by time from the bleeding events within the first 12 months after hospital discharge following ACS.
- To determine the rate of mortality by type/site of bleeding in the first 12 months after hospital discharge following ACS.

7.2.2 **Methods**

The method for determining mortality rate is described below. All analyses described in this section are based on a first bleeding event for a patient post-hospital discharge for ACS, and all deaths are based on ONS mortality records. The comparison of death recording between ONS and CPRD was mainly carried out for completeness.

7.2.2.1 Study design

This was a descriptive cohort study set within CPRD with linkage to HES and ONS mortality data. Patients with a coded diagnosis for ACS between 1/1/2006 and 31/12/2016 were identified and followed prospectively for recorded bleeding consultations post-hospital discharge for ACS. Identified patients had no prior diagnostic record of ACS in the preceding 2 years (see inclusion criteria for the study population, Chapter 5, section 5.3.1.1).

For the mortality rate analysis, bleeding was treated as a time-varying variable, so that patients contributed to the no bleeding group before the date of their first bleeding event and then to the bleeding group thereafter. Follow up, therefore, started from date of hospital discharge until death or date patient ceased contributing to CPRD due to the patient leaving practice or the practice leaving CPRD or the end of 12 months from the index date of hospital discharge or the date of last data collection at the time of data request. Mortality rates within the first 12 months following hospital discharge were then determined among those that experienced bleeding complications and those that did not, using the same procedure described above for incidence of bleeding. For those that did not experience bleeding events, the numerator for the mortality rate was the number of patients dying without a bleed. Person-time at risk

was the time from hospital discharge to the earliest of death, censoring or first bleed. The denominator was the sum of the individual person-time at risk. For those that experienced bleeding events, the numerator was the number of patients dying after a bleed. Person-time at risk was the time from first bleeding event to the earliest of death or censoring. The denominator was the sum of the individual person-time at risk. The rate of mortality after a bleed, by timing of death from the date of the bleeding event was determined (that is, rate in each of the following time periods: 0 – 30 days, 31 – 60 days, 61 – 90 days, 91 – 120 days, 121 – 150 days, 151 – 180 days, 181 – 210 days, 211 – 240 days, 241 – 270 days, 271 – 300 days, 301 – 330 days, 331 – 365 days post-bleed, with the numerator being the number of patients dying after a bleed within each time period and the denominator being the sum of the individual person-time at risk in each time period). The rate of mortality in the first 12 months after hospital discharge by severity and site of the bleeding event (based on all first bleeds) were likewise determined.

7.2.3 **Results**

Of the 27,660 patients that constituted the study population, 6,692 had a death record in ONS and 5,399 in CPRD. Ninety-nine percent (n = 5,366) of those with a record in CPRD also have a corresponding record in ONS. Of those with a record in CPRD (n = 5,366), 96.7 percent (n = 5,190) had a date of death which exactly matched the ONS date, 3 percent (n = 159) had a match within 31 days before or after the ONS date, and for the remaining 0.3 percent (n = 16), the CPRD date of death did not match the ONS date within 31 days.

Overall, 24 percent (n = 6,692) of the study population died over a median follow-up of 1.48 years after hospital discharge following ACS. 9.6% (n = 2,657) of the study population died within the first 12 months of hospital discharge for ACS. **Table 7.5** summarises the percentage of patients that died as a result of bleeding, cardiovascular, or non-cardiovascular and non-bleeding causes over the whole duration of follow up, and at 12 months following hospital discharge for ACS. In the first 12 months, 2.4% of patients that died had a bleeding-related cause of death, and 55% of patients died from cardiovascular causes. While in 43% of patients, the underlying cause of death was recorded as non-cardiovascular and non-bleeding related. Among patients that died as a result of bleeding complications in the first 12 months following hospital discharge (n = 63), 89 percent (n = 56) died from their first bleeding event, and the remaining 11 percent (n = 7) died from a subsequent bleed which was different from the first bleeding event. Overall, 2.5% (n = 66) of patients that died within the first 12 months following hospital discharge died on the day of bleed and 4.6% (n = 121) died within 30 days of the bleeding event.

Table 7.5: Primary causes of deaths over the whole duration of follow up, and at 12 months after hospital discharge for ACS in the overall study population

Primary cause of death	All deaths over the whole duration of follow up	Deaths within 12 months following hospital discharge
	n (%) (N = 6,692)	**n (%) (**N = 2,657)
Bleeding	**167 (2.5)**	**63 (2.4)**
Intracranial	*81 (1.2)*	*31 (1.2)*
Ruptured aneurysm	*46 (0.7)*	*14 (0.5)*
Respiratory	*****	*****
Gastrointestinal	*39 (0.6)*	*17 (0.6)*
Cardiovascular	**3185 (47.6)**	**1448 (54.5)**
Non-cardiovascular/bleeding	**3340 (49.9)**	**1146 (43.1)**

**** frequency count is < 5,*

The rate of mortality within the first 12 months following hospital discharge was 109/1000 person-years at risk (95% CI: 105, 113) overall. Among those that experienced bleeding complications following hospital discharge, the rate of mortality after the bleed in the first 12 months following discharge was 184/1000 person-years at risk (95% CI: 166, 204), and mortality was more frequent in the first 30 days following the bleeding event (**figure 7.4**). Among patients that experienced bleeding complications and died within the first 12 months after hospital discharge, 18% of all deaths occurred on the day of bleed and 33% within 30 days of the bleeding event. Compared to patients who did not experience bleeding complications, those that did experience bleeding events in the first 12 months following hospital discharge had a higher rate of mortality (**figure 7.5**). In patients that experienced bleeding complications and died within the first 12 months following hospital discharge, 17% of all deaths were attributed to bleeding, 38% to cardiovascular, and 45% to non-cardiovascular and non-bleeding causes. Whereas in those that did not experience any bleeding event, 57% of all deaths were due to cardiovascular causes and the remaining 43% to non-cardiovascular and non-bleeding causes.

Figure 7.4: Rate of mortality in patients with first bleed within 12 months following hospital discharge for ACS by timing of death post-bleed

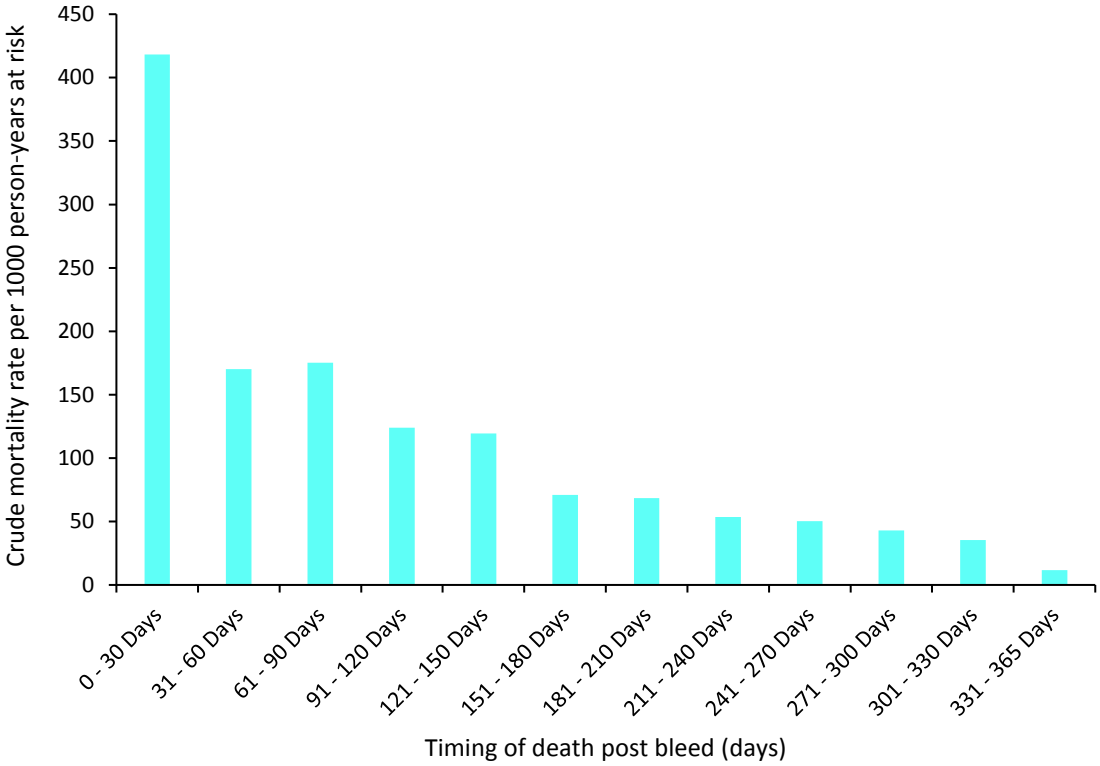
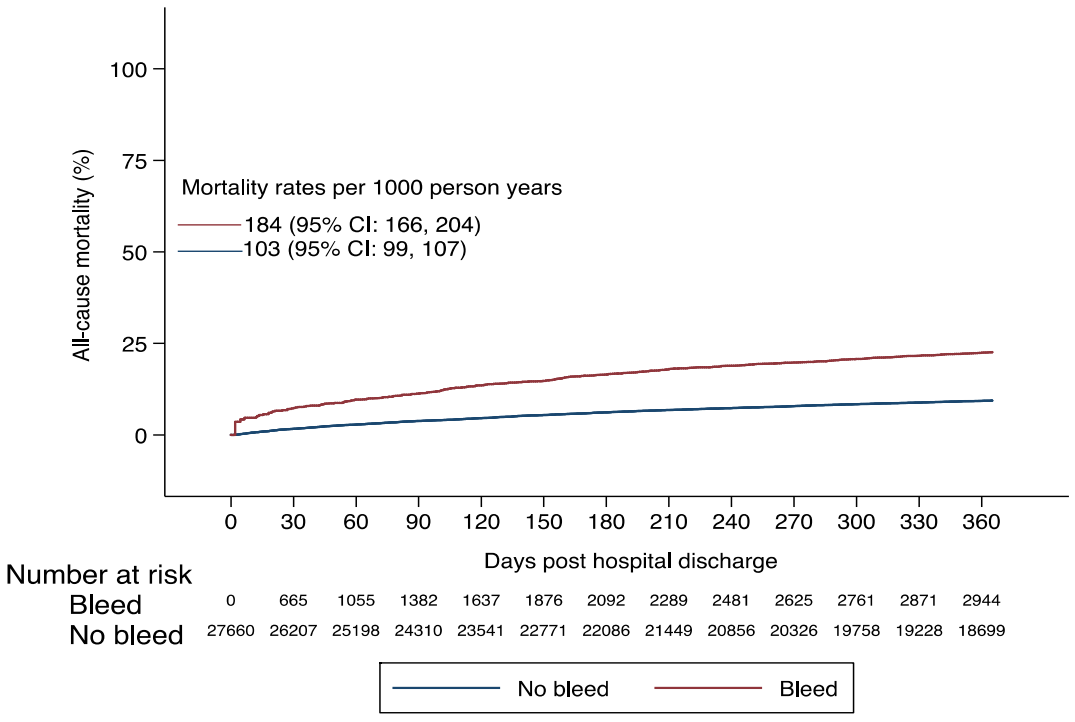


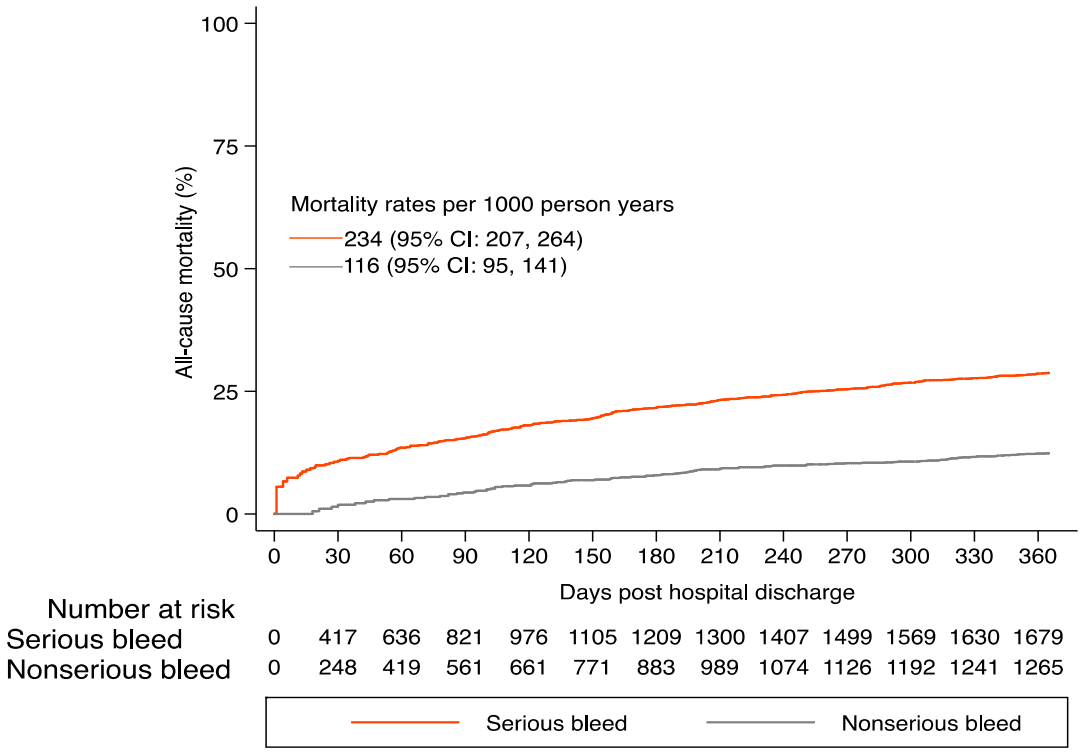
Figure 7.5: Mortality rate in the first 12 months following hospital discharge by bleeding



7.2.3.1 Mortality by bleeding severity

When rate of mortality was stratified by bleeding severity within the first 12 months following hospital discharge, the rate was higher among those that experienced serious bleeding events as their first bleed (234/1000 person-years at risk (95% CI: 207, 264)) than in those experiencing non-serious bleeds (116/1000 person-years at risk (95% CI: 95, 141), **figure 7.6**). Among patients that experienced serious bleeding events and died within the first 12 months following hospital discharge, 21% of all deaths were attributed to bleeding, 33% to cardiovascular, and 46% to non-cardiovascular and non-bleeding causes. Whereas in those that experienced non-serious bleeds, 6% of all deaths were due to bleeding, 52% to cardiovascular, and the remaining 42% to non-cardiovascular and non-bleeding causes.

Figure 7.6: Mortality rate within the first 12 months following hospital discharge by bleeding severity



7.2.3.2 Mortality by type/site-specific bleeds

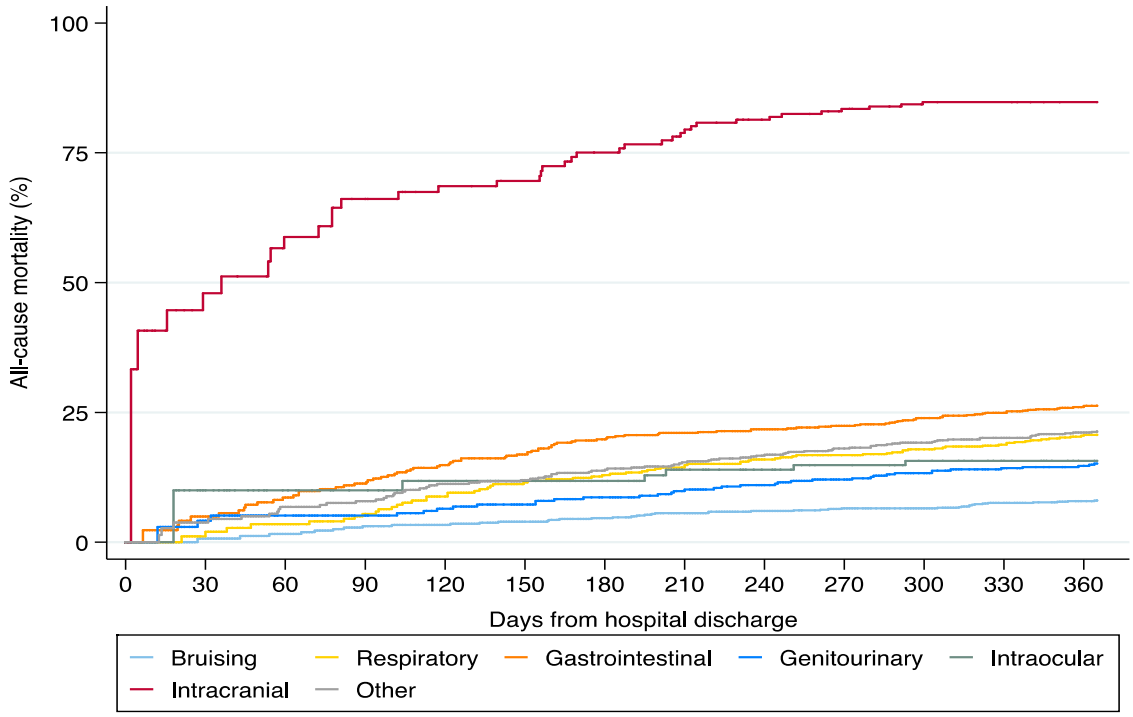
Table 7.6 summarises the mortality rate for each site-specific bleeding event (based on first bleeds) in the first 12 months following hospital discharge for ACS. Overall, mortality rates were higher among those that experienced gastrointestinal, respiratory, and other unclassified bleeding events, and highest in those experiencing intracranial bleeds post-hospital discharge (**figure 7.7**).

Table 7.6: Mortality rates and causes of death within the first 12 months following hospital discharge by type/site of first bleed

Type/site-specific bleeds	**No: with bleed**	**No: of death**	**No: of person-years of observation**	**Mortality rate per 1000 person-years** (95% CI)	**Cause of death within 12 months post-hospital discharge**		
					Bleeding (n, %)	Cardiovascular (n, %)	Non-cardiovascular/non-bleeding (n, %)
Bruising	949	42	541	*78 (57, 105)*	***	24 (57.2)	15 (35.7)
Respiratory/ENT	582	68	312	**218 (172, 277)**	5 (7.4)	29 (42.7)	34 (50.0)
Gastrointestinal	705	92	368	**250 (204, 306)**	16 (17.4)	39 (42.4)	37 (40.2)
Genitourinary	468	37	260	**142 (103, 196)**	***	13 (35.1)	24 (64.9)
Intraocular	135	6	71	*85 (38, 189)*	***	***	***
Intracranial	81	37	29	**1292 (936, 1784)**	27 (73.0)	5 (13.5)	5 (13.5)
Other unclassified	700	80	377	**212 (168, 261)**	12 (15.0)	25 (31.3)	43 (53.7)

*** *frequency count is < 5,* ***CI****: confidence interval,* ***No:*** *number,* ***ENT:*** *ear nose throat,* ***Bold****: indicates higher mortality in those with bleeding complications.*

Figure 7.7: Mortality rates within the first 12 months following hospital discharge by type/site-specific bleeding events



7.2.3.3 Mortality from bleeding by age, gender, in-hospital management strategy, and discharge antithrombotic therapy.

Among those that experienced bleeding complications in the first 12 months following hospital discharge for ACS, rate of mortality following the bleeding event increased with age and was higher among men than women, and in those managed medically during the index ACS hospitalisation (**figures 7.8**).

Figure 7.8: Mortality rates within the first 12 months following hospital discharge among those that experienced bleeding complications (based on first bleed) stratified by age, gender, in-hospital management strategy, and discharge antithrombotic therapy

Fig 7.8A: Mortality rate in those that experienced bleeding events stratified by age

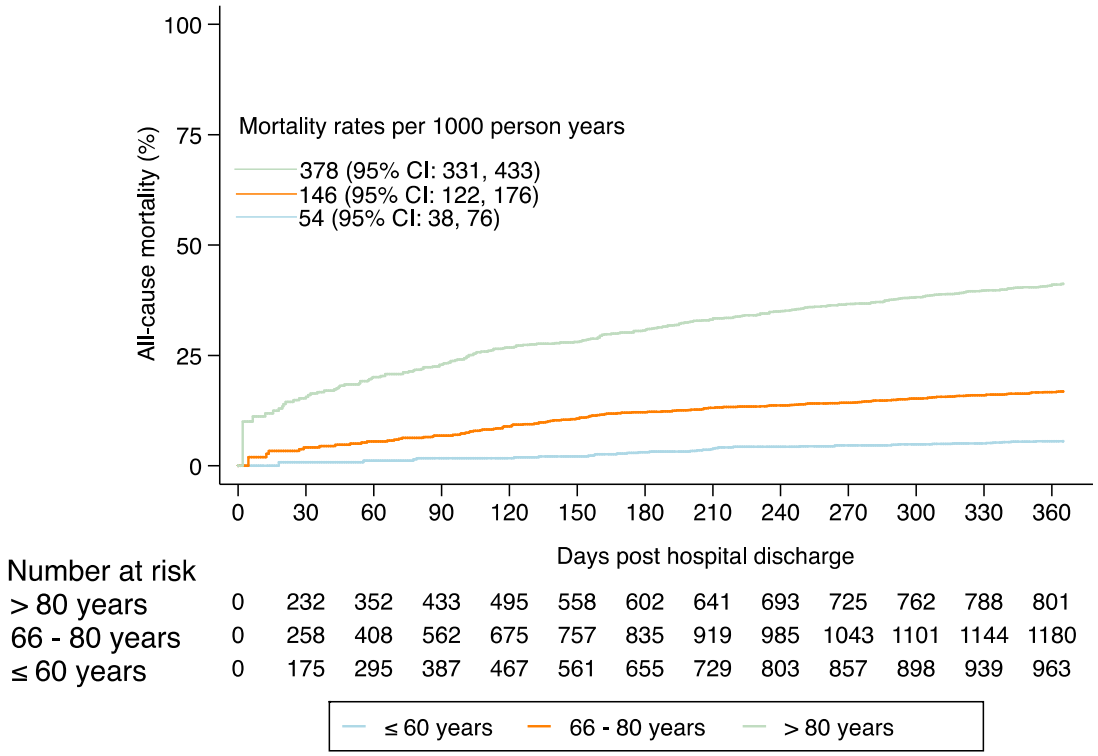


Fig 7.8B: Mortality rate in those that experienced bleeding events stratified by gender

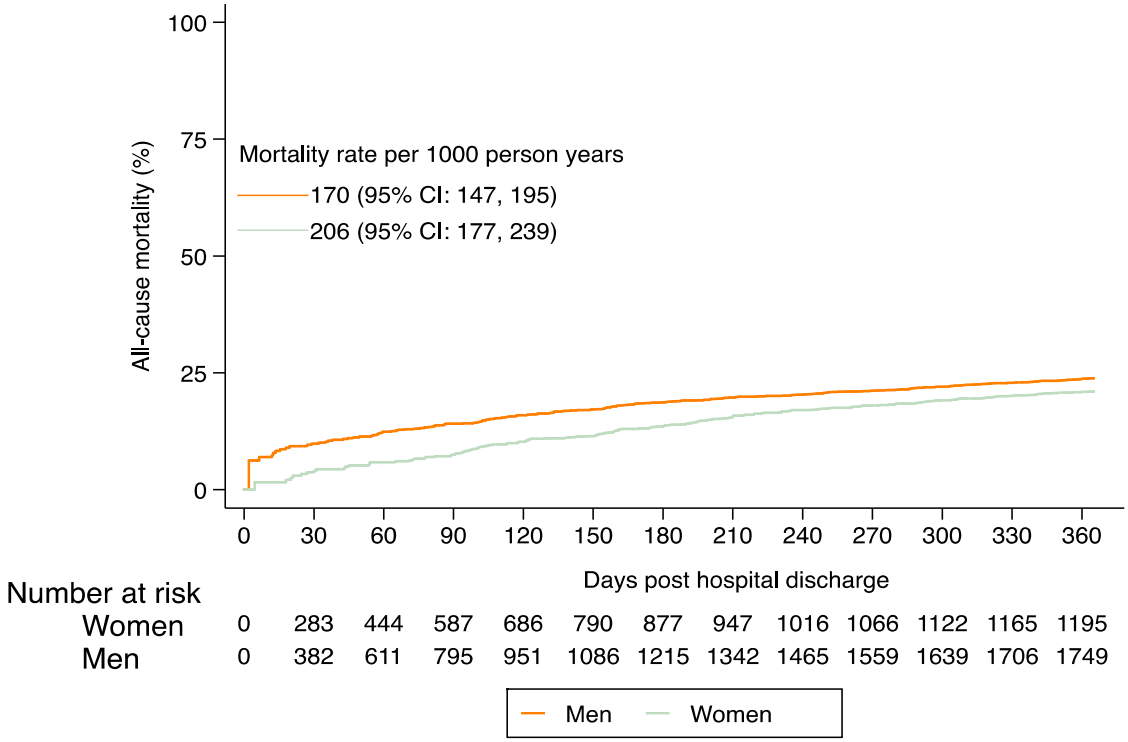
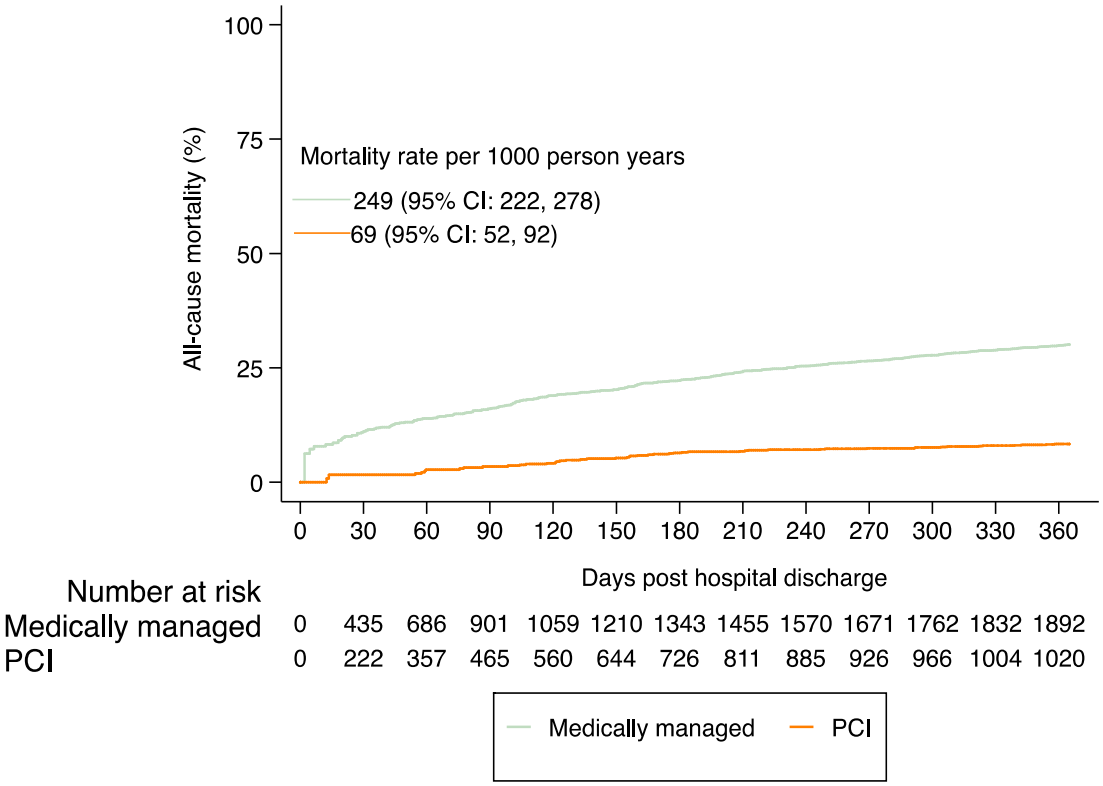


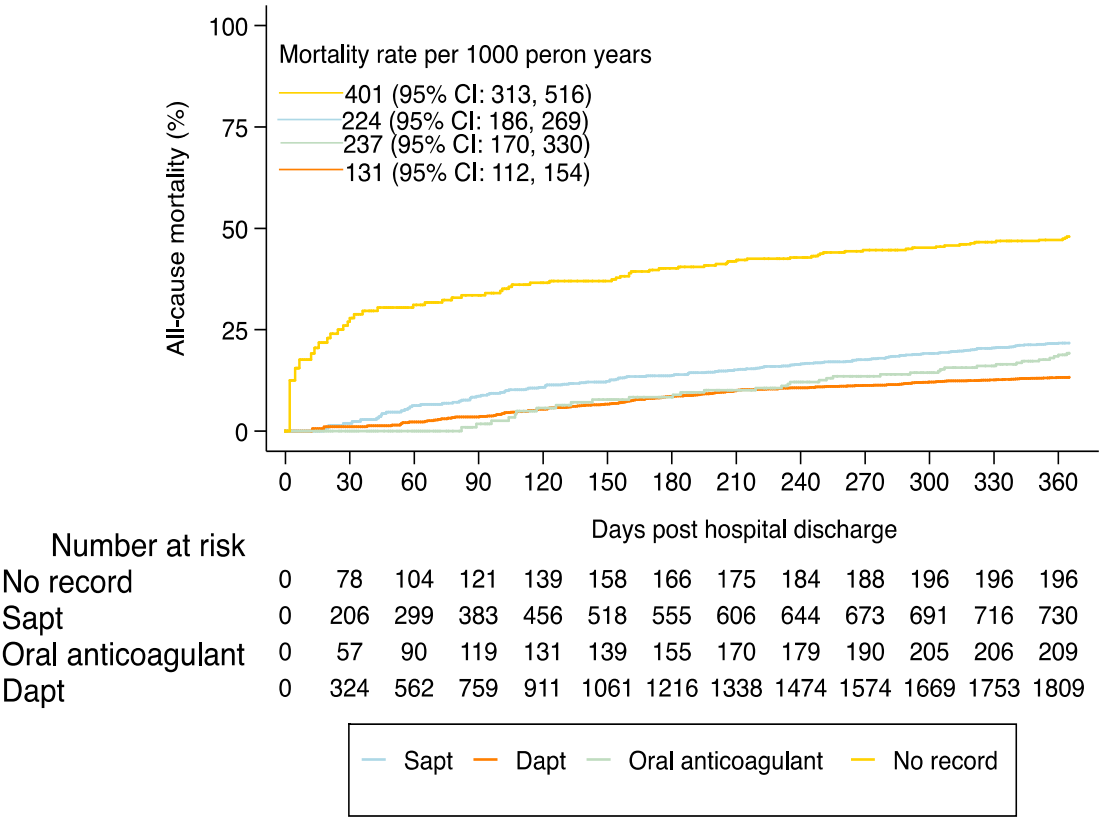
Fig 7.8C: Mortality rate in those that experienced bleeding events stratified by in-hospital management strategy



Number at risk

Medically managed	0	435	686	901	1059	1210	1343	1455	1570	1671	1762	1832	1892
PCI	0	222	357	465	560	644	726	811	885	926	966	1004	1020

Fig 7.8D: Mortality rate in those that experienced bleeding events stratified by discharge antithrombotic therapy



Number at risk

No record	0	78	104	121	139	158	166	175	184	188	196	196	196
Sapt	0	206	299	383	456	518	555	606	644	673	691	716	730
Oral anticoagulant	0	57	90	119	131	139	155	170	179	190	205	206	209
Dapt	0	324	562	759	911	1061	1216	1338	1474	1574	1669	1753	1809

7.3 Discussion

This study reports that bleeding complications following hospital discharge for ACS are common and occur in more than 1 in 10 patients within the first 12 months after hospital discharge, with bruising and gastrointestinal bleeds the most common first type of bleeding events. The median time to a first bleeding event within 12 months was 123 days, and bleeding occurred more frequently in the first 30 days following hospital discharge (19% of all first bleeds). There was a higher prevalence of bleeding in older patients (mean age 72 years and over), ex-smokers, and those with baseline hypertension, COPD, hyperlipidaemia, CKD, prior bleeding complications, and lower level of haemoglobin in the 2 years prior to hospital discharge. Those that experienced bleeding complications within 12 months after hospital discharge had a higher rate of mortality, which was more pronounced in those that experienced intracranial bleeding events. Mortality from bleeding was more frequent in the first 30 days following the bleeding events.

7.3.1 The incidence of bleeding

The result of this study add granularity to the growing body of literature evaluating the incidence of bleeding complications post-hospital discharge for ACS. The finding in this study that 13% of patients had experienced bleeding complications in the year after discharge was within the range reported in the systematic review in Chapter 3 (range: 0.2% to 37.5%). This 13%, however, appeared lower than what has been reported in some studies (identified in the review) with similar length of follow up (Amin et al., 2013; Lattuca et al., 2016). This lower proportion of bleeding events in the present study may be attributed to differences in the methods used in ascertaining bleeding events between

the present study and the previous studies, which will be discussed further in the concluding chapter of this thesis (Chapter 10). It is also important to note that there are differences in relation to patient characteristics, discharge antithrombotic therapy, length of follow-up, severity, and the definition of bleeding used between the present study and previous studies.

7.3.2 Types of bleeding events

Consistent with the findings of the systematic review in Chapter 3, this study reports that, within the first 12 months after hospital discharge, bruising was the most common type of first bleeding events, followed by gastrointestinal bleeds. Bruising is likely to be a common complication within the primary care setting. However, in this study, these events occurred when the majority of patients were on guideline-recommended dual antiplatelet therapy, which can be hypothesised that these events are unlikely to be due to other factors but this maintenance regimen. This was further reinforced by the bruising events becoming very infrequent after the initial 12 months of hospital discharge (results after 12 months not shown), when the majority of patients will mostly be on single antiplatelet therapy with aspirin. Intracranial bleeds were found to be relatively infrequent following hospital discharge. This reflects the paucity of these types of bleeding events post ACS (Mahaffey et al., 2015).

7.3.3 Timing of bleeding events

The median time to a first bleeding event in the first 12 months following hospital discharge for ACS was 123 days, and first bleeding events occurred more frequently in the first 30 days following hospital discharge. The finding that bleeding events occurred more

frequently in the first 30 days after hospital discharge was consistent with those of two previous studies in the post-discharge setting which also identified the first 30 days as the period for greater vulnerability for bleeding complications (Généreux et al., 2015; Valle et al., 2016). Thus, highlighting the time when resources can be better utilised to improve longer-term patient prognosis.

7.3.4 Characteristics of patients who experience bleeding events

Another finding from this descriptive analysis was that patients who experienced bleeding complications following hospital discharge for ACS appeared to have distinct baseline characteristics to those who did not. Owing to the descriptive nature of this analysis, this is only the first step towards understanding the subgroup of patients who are more vulnerable to these complications. A further study, whose main objective was to determine the independent characteristics associated with these bleeding events is presented in the next chapter (Chapter 8).

7.3.5 Mortality

The descriptive results of this study suggest that patients who sustained bleeding complications following hospital discharge for ACS had a higher rate of mortality than those who did not, and these differences in rates may differ depending on the severity and type/site of the bleeding event. A further study whose main objective was to determine whether bleeding events following hospital discharge for ACS are independently associated with all-cause mortality is undertaken (Chapter 9) to explore this relationship further. As the definition of ACS was restricted to high risk patients with

a diagnosis of STEMI or NSTEMI, the mortality rate reported in this study may be higher than for an ACS population including UA in its definition.

7.3.6 Strengths and limitations

This is the first study to examine the incidence of bleeding post ACS from the primary care perspective using a large national EHR database. The study included elderly multi-morbid patients commonly encountered in routine clinical practice, the likes of which have been excluded in previous studies.

This descriptive analysis also has some limitations that warrant mentioning. The study population comprised patients who were mostly elderly with higher prevalence of comorbidities, and may have a higher propensity for bleeding. The extent to which the bleeding events in this study can be attributed to ACS and its management is therefore unclear, and there has not been a study that has examined the incidence of bleeding events in the general population (population without ACS) to compare with this study. The study did not capture bleeding events that were not actionable and did not cause patients to seek medical advice. Therefore, it is likely that the incidence of bleeding may have been underestimated.

The next chapter (Chapter 8) will expand on the findings of this descriptive analysis by exploring in detail the independent associations of baseline patient characteristics with bleeding events within the first 12 months following hospital discharge for ACS.

Chapter 8.0: **Risk factors for bleeding post-hospital discharge for ACS**

8.1 Introduction

This chapter examines the associations of baseline patient characteristics with bleeding complications following hospital discharge after ACS (objective 4). The motivation for the current study has been outlined in detail in Chapters 1 and 2 of this thesis. But to recap, these are summarised as follows:

- There is uncertainty on whether the risk factors identified for in-hospital bleeding events will also be predictive of bleeding post-hospital discharge, since characteristics such as those related to in-hospital procedures may no longer be relevant post-discharge.
- The majority of the previous studies on risk factors for both in-hospital and post-discharge bleeding events have been carried out in the PCI setting, mostly within RCTs. RCTs in the ACS setting have been shown to exclude elderly multi-morbid patients who may be more susceptible to bleeding complications (Steg et al., 2007).
- The majority of the previous studies have excluded minor bleeding events and patients on oral anticoagulants.
- In the majority of previous studies in the post-discharge setting, only a small proportion of the study cohort were ACS patients, with the majority being patients with stable coronary artery disease or other unspecified cardiovascular diseases.

Therefore, to address the drawbacks of the previous studies, this chapter expands on the results of the descriptive analysis from the previous chapter (Chapter 7) which highlighted that patients who experience bleeding complications post-hospital discharge may have

distinct baseline characteristics to those who did not. Using a competing risk framework (see Chapter 5, section 5.5, for a detailed description), characteristics independently associated with an increased risk of bleeding within the first 12 months after hospital discharge following ACS were identified. A paper arising from this study has been published and is attached in **Appendix 8.1**.

8.2 Aim and Objectives

8.2.1 Aim

The overall aim was to determine the baseline characteristics that are independently associated with bleeding following hospital discharge for ACS.

8.2.2 Specific objectives

Primary objective:

To determine independent associations of bleeding (any bleed) within the first 12 months after hospital discharge for ACS with baseline socio-demographic, pharmacological, comorbidities, and in-hospital procedural characteristics.

Secondary objectives:

To determine independent associations between baseline socio-demographic, pharmacological, comorbidities, and in-hospital procedural characteristics with:

- Early bleeding events (bleeds within the first 30 days after hospital discharge for ACS).
- Serious and non-serious bleeding events within the first 12 months after hospital discharge for ACS.
- Each type/site-specific bleeding event within the first 12 months after hospital discharge for ACS.

8.3 Methods

The data source, risk factors and outcome definitions, and baseline characteristics of the study population are described in detail in Chapters 5, 6 and 7.

8.3.1 Study design

This was a cohort study set within CPRD with linkage to HES and ONS mortality data.

8.3.1.1 Study population

The steps involved in identifying the study population were described in Chapter 6, section 6.3.1. Briefly, the study population comprised 27,660 patients with a coded ACS diagnosis between 2006 and 2016.

8.3.1.2 The outcome of bleeding

For the primary objective of the analysis described in this chapter, the outcome of bleeding was defined as having a coded consultation record for any first bleeding event in the patient's primary care record within the first 12 months after hospital discharge for ACS or a death record in the ONS mortality data with bleeding as the primary underlying cause post-hospital discharge.

For the secondary objectives of this analysis, the definition for the outcome of any first bleeding event remained the same but was categorised based on severity (serious and non-serious) (see Chapter 5 table 5.1 for what constituted serious and non-serious bleeds), site (such as intracranial), and timing of the bleeding event (early bleed defined as first bleed within the first 30 days following hospital discharge). The motivation for

categorising bleeding was based on the hypothesis that the independent risk factors for bleeding may vary depending on the severity, site, and timing of the bleeding events.

8.3.1.3 Identifying candidate risk factors for bleeding

Potential risk factors for bleeding complications were identified in three stages: First, by reviewing previously published risk scores of longer-term bleeding events (Alfredsson et al., 2017; Baber et al., 2016; Barra et al., 2013; Chen et al., 2019; Costa et al., 2017; Raposeiras-Roubín, Faxén, et al., 2018; Yeh et al., 2016). Second, by examining studies identified in the course of the systematic review (in Chapter 3) that had also reported on risk factors for bleeding (Buresly et al., 2005; Généreux et al., 2015; Khan et al., 2015; Lattuca et al., 2016; Valle et al., 2016). Third, by reviewing previously published in-hospital bleeding risk scores for characteristics independently associated with bleeding events (Mathews et al., 2011; Mehran et al., 2010; Moscucci et al., 2003; Nikolsky et al., 2007; Subherwal et al., 2009). Risk scores which were reviewed included the CRUSADE, REPLACE, ACUITY/HORIZON, ACTION, GRACE, DAPT, precise-DAPT, TRILOGY-ACS, BLEED-MI, PARIS, BRIC-ACS, and the BleeMAC scores (Alfredsson et al., 2017; Baber et al., 2016; Barra et al., 2013; Chen et al., 2019; Costa et al., 2017; Mathews et al., 2011; Mehran et al., 2010; Moscucci et al., 2003; Nikolsky et al., 2007; Raposeiras-Roubín, Faxén, et al., 2018; Subherwal et al., 2009; Yeh et al., 2016). Overall, twenty-eight independent risk factors were identified, and sixteen were selected for inclusion in this study by consensus of an Interventional Cardiologist (MAM) and a GP (UTK) based on the following criteria:

- The likelihood of being recorded in primary care EHR, and
- The likelihood of predicting bleeding events post-hospital discharge

The twelve potential risk factors that were excluded were baseline anaemia, coronary angiography, gastroduodenal ulcer, systolic blood pressure, diastolic blood pressure, baseline haemoglobin, white cell count, use of Glycoprotein IIb/IIIa inhibitors, use of intra-aortic balloon pump, access site used (whether femoral or radial), sheath size, and timing of sheath removal. The reasons for exclusion were: 1) anaemia was included in the definition for history of bleeding complications, 2) all patients managed with PCI also have coronary angiography prior to the procedure, 3) only 0.6% (n = 171) of the study population had a history of gastroduodenal ulcer, 4) more than 30% of the study population had missing data on each of the following: baseline haemoglobin, white cell count, systolic and diastolic blood pressure. Also, the potential for collinearity between baseline haemoglobin and history of bleeding, and between hypertension and systolic and diastolic blood pressure resulted in the exclusion of these variables, 5) use of Glycoprotein IIb/IIIa inhibitors, use of intra-aortic balloon pump, access site used (whether femoral or radial), sheath size, and timing of sheath removal will not be recorded in primary care EHR. Three more potential risk factors (namely: COPD, prescription of NSAIDs and SSRIs) not identified in the three stages described above were adjudged relevant for inclusion based on the clinical judgement of UTK.

Overall, nineteen candidate risk factors were selected. **Table 8.1** presents these potential risk factors separated into socio-demographic, comorbidities, pharmacological and in-hospital procedural characteristics. For the risk factor of body weight, it was decided by consensus of KPJ and MAM to use BMI, since BMI will more accurately give a holistic estimate of an individual's weight than weight alone. The definitions and baseline measurement for each of these potential risk factors are described in detail in Chapter 5, section 5.4.2. But briefly, baseline for socio-demographic characteristics and

comorbidities was defined as the last recorded measurement in the patient's primary care record within 2 years before the index hospital discharge date, except for BMI which was defined as last record until 30 days after hospital discharge (to more accurately capture the most recent BMI for a patient). Procedural characteristics were defined based on the procedure recorded during the ACS hospitalisation stay. Pharmacological characteristics were defined as having a recorded prescription for any of the antithrombotic medications listed in Chapter 5, section 5.4.2.4, within 90 days after hospital discharge from the ACS event, except for NSAIDs and SSRIs, which were defined based on the 6 months prior to hospital discharge. Patients with a record for a risk factor in CPRD (as defined in Chapter 5) were classified as exposed, and those without as unexposed for that factor.

Table 8.1: Risk factors selected for inclusion in the current study

*Socio-demographic characteristics	*Comorbidities and procedural characteristics	Pharmacological characteristics
Advanced age	History of COPD	$Discharge antithrombotic therapy (whether SAPT, DAPT or oral anticoagulant)
Female gender	History of cancer	NSAID prescription within 6 months prior to hospital discharge
†BMI	History of diabetes	SSRI prescription within 6 months prior to hospital discharge
History of smoking	History of hypertension	
	History of renal insufficiency	
	History of heart failure	
	History of peripheral vascular disease	
	History of bleeding	
	Hyperlipidaemia	
	STEMI at presentation	
	NSTEMI at presentation	
	#Coronary revascularisation at index ACS hospitalisation	

** recorded within 2 years prior to hospital discharge, † historical record until 30 days after discharge, # recorded during the index ACS hospitalisation, $ recorded within 90 days after hospital discharge,* ***COPD;*** *Chronic obstructive pulmonary disease,* ***ACS;*** *Acute coronary syndrome,* ***STEMI;*** *ST-elevation myocardial infarction,* ***NSTEMI;*** *Non ST-elevation myocardial infarction,* ***SAPT;*** *Single antiplatelet therapy,* ***DAPT;*** *Dual antiplatelet therapy,* ***NSAID;*** *Non-steroidal anti-inflammatory drug,* ***SSRI;*** *Selective serotonin re-uptake inhibitor.*

8.3.1.4 Follow up

The study population were followed longitudinally for records of bleeding events post-hospital discharge for ACS. Follow up started from the index date of hospital discharge until date of first bleeding event within 12 months, or the date patient ceased contributing to CPRD due to death or leaving practice or practice leaving CPRD or the end of 12 months from the index date of hospital discharge or the date of last data collection at the time of data request. Patients with a record for each of the baseline characteristics listed in **table 8.1** were compared with those without in relation to the outcome of any bleed (within 12 months) following hospital discharge. Associations between the outcome

of any first bleed (within 12 months) post-hospital discharge with baseline socio-demographic, comorbidities, pharmacological, and in-hospital procedural characteristics (as risk factors) were determined. For the secondary objectives of the study, patients with a record for these baseline characteristics were compared with those without in relation to the outcomes of serious bleeds, non-serious bleeds, early bleeds, and site-specific bleeding events.

8.3.2 Sample size estimation

In cohort studies of risk factor analysis, the required sample size is often dictated by the number of events per variable (EPV), which is the ratio of the number of individuals with the outcome event to the number of risk factors (or the number of levels of a risk factors in the case of categorical variables) to be considered in the analysis. There is no consensus regarding what an optimal EPV should be, but some studies have recommended an EPV between 5 and 10 (Harrell et al., 1985; Peduzzi et al., 1996), while others postulated at least 20 and above in the presence of low prevalent risk factors (Ogundimu et al., 2016). Assuming 50 candidate risk factors were selected for inclusion in this study, there will be more than 70 EPVs (3,620/50) based on the 3,620 patients with the outcome of bleeding within the first 12 months of hospital discharge. This sample size should be sufficient for the primary analysis in this study.

8.3.3 Missing data

Sixty percent of the study population had complete data on all variables, and 40 percent had missing data on smoking and BMI status. Little's MCAR test was carried out to determine whether smoking and BMI were MCAR. A statistically significant result

indicated that both smoking and BMI were not MCAR. Multiple imputations by chained equation was then carried out to address data missingness. 10 imputations were carried out. Following White *et al's* recommendation, variables that were predictive of smoking and BMI were included as predictors in the imputation model. Variables which predicted whether smoking and BMI were missing (determined using standard logistic regression model where both smoking and BMI were treated as the outcome variables (in separate models), and dichotomised as 1 = missing and 0 = not missing) were also included. This approach makes the MAR assumption of the multiple imputation more plausible (Sterne et al., 2009; White et al., 2011). The distributions of smoking and BMI before and after the imputations were compared (see Chapter 5, section 5.6, for a detailed description of the imputation process).

8.3.4 Analysis

All the analyses in this study were based on a first bleeding event for a patient, and were carried out on the imputed datasets. To examine whether those who completed the study (i.e. those that had full 12 months of follow up or were censored at the time of first bleed) had the same baseline characteristics as those lost to follow up (i.e. those that did not have a bleed and did not have the full 12 months of follow up), the baseline characteristics of those who completed the study were descriptively compared to those who did not.

8.3.4.1 Univariable analysis

Crude associations between the outcome of bleeding (any bleed) within 12 months after hospital discharge and each risk factor (as the exposure) were determined using a

competing risk regression model, accounting for death as a competing event (for a detailed description of the competing risk model, the reader is referred to Chapter 5, section 5.5). Unadjusted associations between serious bleeds, non-serious bleeds, early bleeds, and of each type of bleeding event with each risk factor (as the exposure) were likewise determined. Robust variance estimators were used to account for clustering within GP practice. The magnitude of each association was quantified by sub-hazard ratio and associated 95% confidence intervals.

8.3.4.2 Multivariable analysis

Adjusted associations between the outcomes of bleeding and each risk factor (as the exposure) were determined using a competing risk regression model. Following Sun *et al's* recommendation (Sun et al., 1996), a full model approach was adopted where all candidate risk factors were included in the model regardless of whether they showed a statistically significant association (at the conventional 5 percent threshold) with bleeding or not in the univariable analysis. Robust variance estimators were used to account for clustering within GP practice. All associations were adjusted for year of index hospital discharge, geographic region and all other variables included in the models.

Overall, ten final models were created: the first model examined risk factors independently associated with the outcome of bleeding (any bleed) within the first 12 months of hospital discharge. The second and third models examined these associations with serious and non-serious bleeding events (based on first bleeds). The fourth model examined risk factors independently associated with early bleeding events (any first bleed within 30 days after hospital discharge). The remaining models examined the independent risk factors associated with each site-specific bleeding event (based on first

bleeds) within the first 12 months of hospital discharge. All analyses were carried out using Stata version 14.2, and the magnitude of all associations were quantified by adjusted sub-hazard ratios and associated 95% confidence intervals.

8.3.4.3 Checking the linearity assumption of the competing risk model

Age was the only continuous variable in the analyses. Thus, for each fitted model, Fractional Polynomials (Royston and Sauerbrei, 2008) were used to assess the functional form of age on the continuous scale. Fractional Polynomials assess the scale of continuous variables on whether they should be modelled linearly or transformed if the linearity assumption is violated.

8.3.4.4 Checking the proportional hazard assumption of the competing risk model

For each of the final models, risk factor by time (in days) interactions were included in the models to assess whether the relative hazard of bleeding remained constant over the duration of the follow-up period. A statistically significant interaction indicates a violation of the proportional hazard assumption, whereas a non-statistically significant interaction implies that the relative hazard of bleeding between the groups being compared was constant over the whole duration of follow up.

8.3.4.5 Subgroup analyses

Previous studies have shown that the risk of bleeding may increase with age (Moscucci et al., 2003; Raposeiras-Roubín, Faxén, et al., 2018), and may be higher among women than men (Moscucci et al., 2003; Subherwal et al., 2009). To explore whether the risk factors for bleeding differ by age and by gender, the multivariable analysis described above for

any bleed was repeated stratified by age categories (≤ 65 years old, 66 to 80 years old, and > 80 years old), and gender (men, women). Separately, the same analysis was repeated stratified by in-hospital management strategy (whether medically managed or with PCI). This was based on the hypothesis that the predictors for bleeding may differ depending on the in-hospital management strategy employed (which is often influenced by baseline patient characteristics).

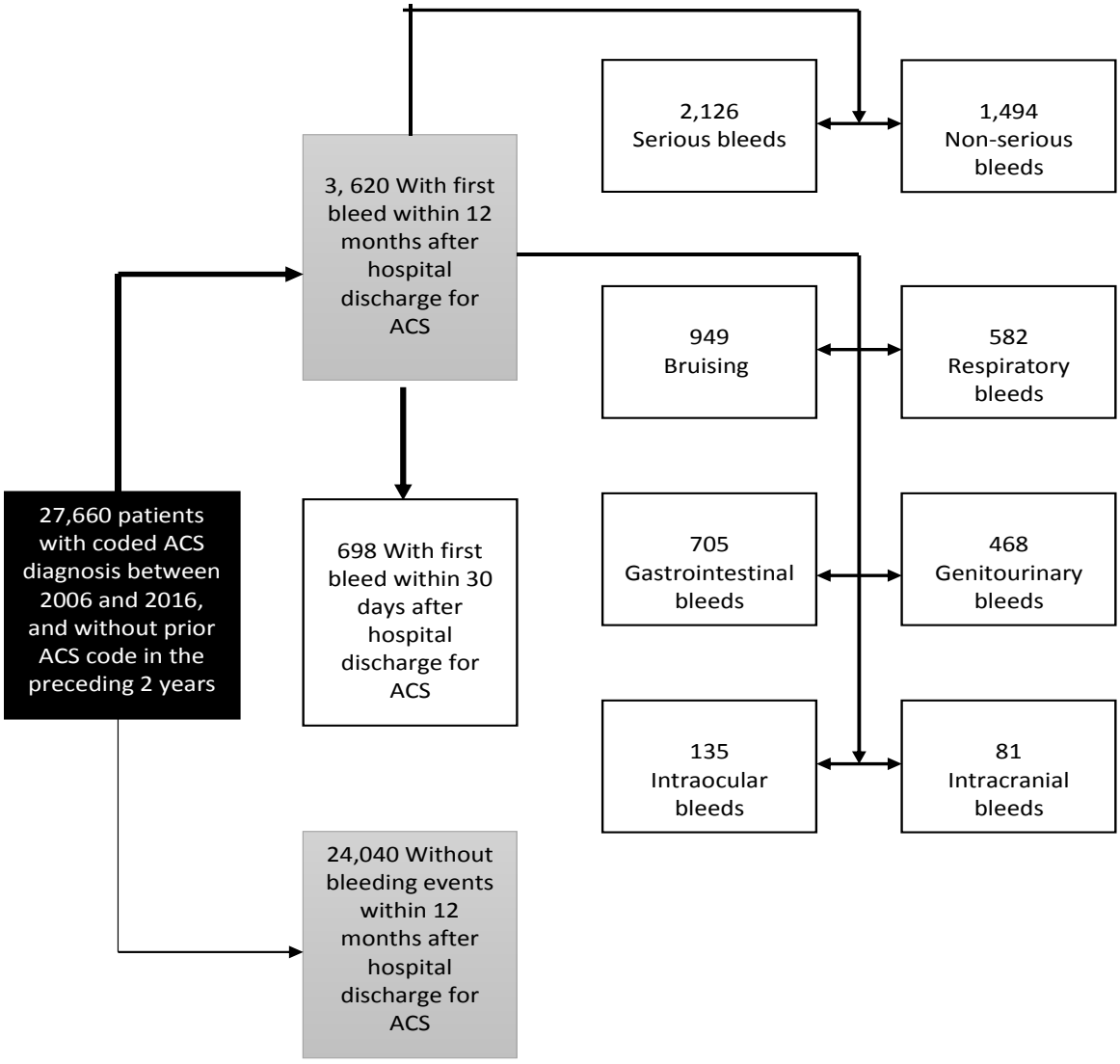
8.3.4.6 Sensitivity analyses

The multivariable analysis described above for any bleed was repeated: 1) on patients with complete data on all variables (complete case analysis); 2) using a standard Cox regression model (that is, not within a competing risk framework); and 3) censoring patients that had subsequent ACS events at the time of first ACS post-hospital discharge. All sensitivity analyses except for the analysis using the Cox model were carried out using a competing risk model, and results compared with those from the main analysis.

8.4 Results

The baseline characteristics of the study population dichotomised into those who experienced any bleeding and those who did not within the first 12 months after hospital discharge are presented in Chapter 7 table 7.2. **Figure 8.1** summarises the number of patients with and without the outcome of bleeding within the first 12 months after hospital discharge for ACS. Thirteen percent (3,620) of the study population experienced their first bleeding events over a follow-up period of 12 months following hospital discharge for ACS.

Figure 8.1: A flowchart depicting the number of patients with and without the outcome of bleeding within the first 12 months after hospital discharge for ACS



8.4.1 Distribution of smoking and BMI before and after multiple imputation

Table 8.2 shows the prevalence of smoking and BMI status before and after multiple imputation. Overall, the distribution of both smoking and BMI status did not overly differ before and after the imputation.

Table 8.2: Prevalence of smoking and BMI before and after multiple imputation

Variables	Prevalence (%) before imputation	Prevalence (%) after imputation
Smoking status	Prevalence (95% CI)	Prevalence (95% CI)
Non-smoker	33.2 (32.6, 33.8)	32.9 (32.2, 33.6)
Ex-smoker	38.7 (38.1, 39.4)	38.6 (38.0, 39.2)
Current smoker	28.1 (27.5, 28.7)	28.5 (27.9, 29.1)
BMI status	Prevalence (95% CI)	Prevalence (95% CI)
Normal weight	30.4 (29.7, 31.0)	30.8 (30.1, 31.5)
Underweight	2.00 (1.80, 2.20)	2.00 (1.80, 2.20)
Overweight	40.1 (39.4, 40.8)	40.1 (39.4, 40.9)
Obese	27.5 (26.9, 28.1)	27.0 (26.4, 27.7)

8.4.2 Baseline characteristics of those lost to follow-up

Table 8.3 descriptively summarises the baseline characteristics of those lost to follow up and those that completed the study (i.e. those that had full 12 months of follow up). Those lost to follow up as a result of transferring out of their GP practice or practice leaving CPRD or the end of the study period were generally similar to those that completed the study. But those that died in the course of the study were on average older, with higher prevalence of comorbidities.

Table 8.3: Baseline characteristics of those lost to follow up and those that completed the study

Risk factors	Not lost to follow up (n = 22227)	Lost to follow up (n = 5433)	Reasons for non-completion			
			Patient left practice (n = 1156)	Practice left CPRD (n = 1817)	Death (n = 2293)	End of study period (n = 167)
Demographics						
Age (years) (Mean ± SD)	68.8 ± 13.4	74.7 ± 14.0	72.7 ± 16.2	68.8 ± 13.5	80.9 ± 10.3	67.5 ± 13.3
Age (years) (n, %)						
≤ 65	8962 (40.3)	1426 (26.2)	402 (34.8)	750 (41.3)	198 (8.6)	76 (45.5)
66 - 80	8318 (37.4)	1729 (31.8)	271 (23.4)	664 (36.5)	734 (32.0)	60 (35.9)
> 80	4947 (22.3)	2278 (41.9)	483 (41.8)	403 (22.2)	1361 (59.4)	31 (18.6)
Male (n, %)	14643 (65.9)	3212 (59.1)	668 (57.8)	1202 (66.2)	1240 (54.1)	102 (61.1)
Female (n, %)	7584 (34.1)	2221 (40.9)	488 (42.2)	615 (33.8)	1053 (45.9)	65 (38.9)
BMI (kg/m^2) (n, %)						
Normal weight (BMI 18.50 to < 25)	4529 (29.4)	1395 (34.2)	255 (34.3)	489 (28.7)	639 (40.0)	12 (36.4)
Underweight (BMI < 18.50)	251 (1.6)	136 (3.3)	29 (3.9)	24 (1.4)	83 (5.2)	***
Overweight (BMI 25 to < 30)	6298 (40.8)	1531 (37.6)	274 (36.9)	697 (40.9)	548 (34.3)	12 (36.4)
Obese (BMI ≥ 30)	4352 (28.2)	1015 (24.9)	185 (24.9)	493 (28.9)	328 (20.5)	9 (27.3)
Smoking Status (n, %)						
Non-smoker	5978 (33.0)	1482 (34.2)	290 (33.4)	501 (34.0)	647 (34.9)	44 (31.2)
Ex-smoker	6956 (38.4)	1745 (40.3)	303 (34.9)	530 (36.0)	869 (46.9)	43 (30.5)
Current smoker	5203 (28.7)	1108 (25.6)	274 (31.6)	442 (30.0)	338 (18.2)	54 (38.3)
Comorbidities						
Diabetes (n, %)	4465 (20.1)	1351 (24.9)	252 (21.8)	415 (22.8)	646 (28.2)	38 (22.8)
Hypertension (n, %)	5661 (25.5)	1442 (26.5)	293 (25.3)	467 (25.7)	643 (28.0)	39 (23.4)

Continuation	Not lost to follow up (n = 22227)	Lost to follow up (n = 5433)	Reasons for non-completion			
			Patient left practice (n = 1156)	Practice left CPRD (n = 1817)	Death (n = 2293)	End of study period (n = 167)
Heart failure (n, %)	1813 (8.2)	708 (13.0)	95 (8.2)	162 (8.9)	437 (19.1)	14 (8.4)
Cancer (n, %)	2256 (10.1)	701 (12.9)	105 (9.1)	199 (11.0)	387 (16.9)	10 (6.0)
PVD (n, %)	725 (3.3)	225 (4.1)	32 (2.8)	51 (2.8)	139 (6.1)	***
COPD (n, %)	4269 (19.2)	1291 (23.8)	221 (19.1)	350 (19.3)	697 (30.4)	23 (13.8)
CKD (eGFR < 60 mL/min/1.73 m^2) (n, %)	6215 (28.0)	2192 (40.3)	413 (35.7)	459 (25.3)	1289 (56.2)	31 (18.6)
Hyperlipidaemia (n, %)	14296 (64.3)	3512 (64.6)	684 (59.2)	1194 (65.7)	1542 (67.2)	92 (55.1)
History of bleeding (n, %)	2561 (11.5)	761 (14.0)	136 (11.8)	185 (10.2)	423 (18.4)	17 (10.2)
ACS presentation (n, %)						
STEMI	2927 (13.2)	705 (13.0)	145 (12.5)	311 (17.1)	213 (9.3)	36 (21.6)
NSTEMI	8016 (36.1)	2399 (44.2)	445 (38.5)	821 (45.2)	1059 (46.2)	74 (44.3)
Not otherwise specified	11284 (50.8)	2329 (42.9)	566 (49.0)	685 (37.7)	1021 (44.5)	57 (34.1)
In-hospital procedure (n, %)						
PCI	8165 (36.7)	1520 (28.0)	309 (26.7)	833 (45.8)	280 (12.2)	98 (58.7)
Drug Therapy (n, %)						
Baseline NSAIDs	2940 (13.2)	543 (10.0)	132 (11.4)	192 (10.6)	203 (8.9)	16 (9.6)
Baseline SSRIs	1572 (7.1)	519 (9.6)	126 (10.9)	153 (8.4)	226 (9.9)	14 (8.4)
Discharge antithrombotic						
Single antiplatelet	5644 (25.4)	1310 (24.1)	240 (20.8)	374 (20.6)	665 (29.0)	31 (18.6)
Dual antiplatelet	13817 (62.2)	2653 (48.8)	541 (46.8)	1180 (64.9)	819 (35.7)	113 (67.7)
Oral anticoagulant	1242 (5.6)	317 (5.8)	42 (3.6)	116 (6.4)	144 (6.3)	15 (9.0)
No record	1524 (6.9)	1153 (21.2)	333 (28.8)	147 (8.1)	665 (29.0)	8 (4.8)

*** *frequency count is < 5,* ***eGFR:*** *estimated glomerular filtration rate,* ***ACS:*** *acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***CPRD:*** *clinical practice research datalink*

8.4.3 Linearity assumption for age

Fractional Polynomial analysis indicated that the functional form of age was not linear. That is to say, the relation between the outcome of bleeding and age (on a continuous scale) did not follow a linear trajectory but rather a sigmoidal pattern. Therefore, a plot of age against rates of bleeding (per 1000 person-years) was used to create cut points to categorise age (Mathews et al., 2011; Raposeiras-Roubín, Faxén, et al., 2018). Age was categorised into ≤ 65 years, 66 to 80 years and > 80 years based on the distribution of bleeding events.

8.4.4 Proportional hazard assumption of the competing risk model

Baseline characteristics/risk factors that violated the proportional hazard assumption of the competing risk model were included in the relevant models as time-dependent coefficients. These risk factors are denoted by asterisks in **tables 8.4**, **8.5**, **8.6**, and **8.7**.

8.4.5 Characteristics associated with bleeding after hospital discharge for ACS

The results of all univariable analyses are presented in **table 8.4** (for any bleed in the first 12 months) and **appendix table 8.1** (for all other analyses). All the multivariable models presented in this section represents the main effect models (but models included interactions with time for risk factors that violated the proportional hazard assumption of the competing risk model). The direction of the effect of each risk factor that interacted with time is signified by an asterisk. A single asterisk indicates that the risk of bleeding with that risk factor decreases with time, whereas two asterisks indicate that the risk of bleeding increases with time post-hospital discharge. The risk estimates of bleeding for each (statistically significant) risk factor that interacted with time are reported at two time-points (at 30 days and 365 days post-discharge) in **appendix table 8.2.**

8.4.5.1 Risk factors for any bleed in the first 12 months

Table 8.4 presents crude and adjusted associations between any bleed (within 12 months) and baseline patient characteristics. After multivariable adjustment, age greater than 65 years, female gender, history of PVD, COPD or bleeding complications, management with PCI during the ACS hospitalisation stay, and treatment with single antiplatelet or oral anticoagulants post-hospital discharge were independently associated with increased risk of bleeding in the first 12 months after hospital discharge for ACS. The increased risk of bleeding in those managed with PCI or those aged 80 years and over (compared to those aged 65 years and under) was highest on the day of hospital discharge, but then decreased with time. There was also a modest increased risk of bleeding with history of hypertension, prescription of NSAIDs, and in those without a history of heart failure. The most significant predictors of bleeding complications in the

first 12 months after hospital discharge were; history of bleeding within 2 years prior to hospital discharge (sHR 1.88, 95% CI: 1.73, 2.04), advanced age > 80 years vs age ≤ 65 years (sHR 1.42, 95% CI: 1.22, 1.66), and treatment with oral anticoagulants vs single antiplatelet post-hospital discharge (sHR 1.35, 95% CI: 1.17, 1.55). For those aged 80 years and over (compared to those aged 65 years and under), the increased risk of bleeding was sHR 1.39 (95% CI: 1.16, 1.67) at 30 days and sHR 1.06 (95% CI: 0.67, 1.68) at 365 days post-hospital discharge (see **appendix table 8.2**). Risk factors independently associated with bleeding in the first 12 months after hospital discharge for ACS are shown in **table 8.4**

Table 8.4: Characteristics associated with any bleed in the first 12 months after hospital discharge for ACS

Characteristics	Unadjusted associations		Adjusted associations	
Demographics	sHR (95% CI)	P-value	sHR (95% CI)	P-value
Age (years)				
≤ 65	1.00		1.00	
66 - 80	1.39 (1.28, 1.51)	P<0.001	**1.20 (1.10, 1.31)**	P<0.001
> 80	1.55 (1.43, 1.69)	P<0.001	**1.42[*] (1.22, 1.66)**	P<0.001
Female	1.32 (1.23, 1.40)	P<0.001	**1.19 (1.11, 1.28)**	P<0.001
BMI (kg/m^2)				
Normal weight *(18.50 to < 25)*	1.00		1.00	
Underweight *(< 18.50)*	1.09 (0.81, 1.45)	0.571	1.01 (0.76, 1.34)	0.963
Overweight *(25 to < 30)*	0.92 (0.84, 1.02)	0.104	0.96 (0.87, 1.06)	0.410
Obese *(≥ 30)*	0.93 (0.84, 1.03)	0.182	0.95 (0.85, 1.06)	0.354
Smoking Status				
Non-smoker	1.00		1.00	
Ex-smoker	1.02 (0.94, 1.12)	0.584	1.05 (0.96, 1.14)	0.329
Current smoker	0.82 (0.75, 0.91)	P<0.001	0.96 (0.87, 1.07)	0.486
Comorbidities				
Diabetes	1.10 (1.02, 1.18)	0.013	0.99 (0.91, 1.07)	0.812
Hypertension	1.24 (1.15, 1.34)	P<0.001	**1.13 (1.05, 1.21)**	0.001
Heart failure	1.02 (0.91, 1.14)	0.703	**0.87 (0.78, 0.97)**	0.016
Cancer	1.14 (1.04, 1.26)	0.006	1.06 (0.96, 1.17)	0.232
PVD	1.46 (1.25, 1.71)	P<0.001	**1.28 (1.09, 1.50)**	0.003
COPD	1.44 (1.34, 1.55)	P<0.001	**1.29 (1.20, 1.39)**	P<0.001
CKD (eGFR < 60 mL/min/1.73 m^2)	1.34 (1.25, 1.43)	P<0.001	1.07 (0.99, 1.16)	0.107
Hyperlipidaemia	1.24 (1.16, 1.33)	P<0.001	0.97[**] (0.86, 1.09)	0.641
History of bleeding	2.08 (1.92, 2.25)	P<0.001	**1.88 (1.73, 2.04)**	P<0.001
ACS presentation				
STEMI	1.00		1.00	
NSTEMI	1.17 (1.06, 1.30)	0.002	1.06 (0.95, 1.18)	0.292
ACS not otherwise specified	1.04 (0.94, 1.16)	0.466	1.00 (0.89, 1.12)	0.978
In-hospital procedure				
PCI	0.92 (0.86, 0.99)	0.019	**1.26[*] (1.11, 1.43)**	P<0.001
Drug therapy				
Baseline NSAIDs	1.11 (1.00, 1.22)	0.042	**1.13 (1.02, 1.25)**	0.017
Baseline SSRIs	1.22 (1.09, 1.37)	P<0.001	1.09 (0.97, 1.22)	0.142
Discharge antithrombotic				
Single antiplatelet	1.00		1.00	
Dual antiplatelet	1.00 (0.92, 1.08)	0.962	**0.81[**] (0.72, 0.93)**	0.002
Oral anticoagulant	1.39 (1.21, 1.60)	P<0.001	**1.35 (1.17, 1.55)**	P<0.001
No record	0.90 (0.80, 1.03)	0.117	1.07[*] (0.88, 1.30)	0.469

sHR: *subhazard ratio,* ***CI:*** *confidence interval,* [**] *included as time-dependent coefficient – estimated sHR at day of hospital discharge but increases with time post-discharge,* [*] *included as time-dependent coefficient –*

estimated sHR at day of hospital discharge but decreases with time post-discharge, ***eGFR:*** *estimated glomerular filtration rate,* ***ACS****: acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***1.00:*** *reference category,* ***Bold text:*** *indicates statistically significant predictors of bleeding at the 5% threshold.*

8.4.5.2 Risk factors for serious and non-serious bleeding events

Table 8.5 presents characteristics that are independently associated with serious and non-serious first bleeding events post-hospital discharge for ACS. After multivariable adjustment, the majority of the risk factors for any bleed were likewise found to be associated with increased risk of serious bleeding events, except female gender. There were some differences observed between the risk factors for serious and non-serious bleeding events. Advanced age > 65 years, history of hypertension, prescription of NSAIDs, and treatment with dual antiplatelets post-hospital discharge were not significantly associated with non-serious bleeding events, whereas female gender and having no record of diabetes were associated with increased risk of non-serious bleeds but not serious bleeding events. The most significant risk factors for non-serious bleeding events post-hospital discharge were: female gender (sHR 1.58, 95% CI: 1.42, 1.76), history of bleeding complications (sHR 1.58, 95% CI: 1.38, 1.80), and treatment with oral anticoagulants vs single antiplatelet post-hospital discharge (sHR 1.42, 95% CI: 1.15, 1.76).

8.4.5.3 Risk factors for early bleeding events

There were some differences in risk factors between any bleed within 12 months and early bleeding events (any bleed within 30 days) post-hospital discharge. History of smoking (current smoking) – recorded before hospital discharge and cancer were significantly associated with increased risk of early bleeding events but not any bleed (within 12 months). **Table 8.5** presents the independent risk factors for early bleeding events post-hospital discharge. The most significant predictors of early bleeds included history of bleeding in the 2 years before hospital discharge (sHR 1.83, 95% CI: 1.52, 2.20), hypertension (sHR 1.69, 95% CI: 1.27, 2.24), advanced age > 80 years vs age ≤ 65 years

(sHR 1.57, 95% CI: 1.23, 2.01), and history of smoking (current smoking) vs non-smoking - recorded before hospital discharge (sHR 1.54, 95% CI: 1.04, 2.27). The increased risk of an early bleed in patients with a history of hypertension or current smoking was highest on the day of hospital discharge, but these risks decreased with time (**table 8.5**). In patients with a history of smoking (current smoking) vs non-smoking - recorded before hospital discharge, the increased risk of an early bleed was sHR 1.25 (95% CI: 0.72, 2.19) at 7 days and sHR 0.64 (95% CI: 0.21, 2.01) at 30 days post-hospital discharge (see **appendix table 8.2**).

8.4.5.4 Risk factors for site-specific bleeding events

Baseline characteristics which were independently associated with each site-specific bleeding event (based on first bleeds) following hospital discharge are summarised in detail in **table 8.5**. Characteristics independently associated with increased risk of gastrointestinal bleeding events included history of bleeding complications before hospital discharge (sHR 2.22, 95% CI: 1.87 to 2.64), advanced age > 80 years vs age ≤ 65 years (sHR 1.29, 95% CI: 1.01 to 1.65), history of COPD (sHR 1.29, 95% CI: 1.08 to 1.55) and treatment with single antiplatelet vs dual antiplatelet post-hospital discharge. When considering intracranial bleeds, history of bleeding complications before hospital discharge (sHR 1.91, 95% CI: 1.05 to 3.45), and diabetes (sHR 1.77, 95% CI: 1.08 to 2.89) were the main risk factors for this type of bleeding complication following hospital discharge. There was also a non-significant increased risk of intracranial bleeds with oral anticoagulants, prescription of NSAIDs, history of PVD, and age > 65 years post-hospital discharge.

History of bleeding complications within 2 years before hospital discharge (sHR 2.06, 95% CI: 1.70, 2.49), management with PCI during the ACS hospitalisation stay (sHR 1.87, 95% CI: 1.37, 2.54), history of cancer (sHR 1.86, 95% CI: 1.26, 2.74), COPD (sHR 1.66, 95% CI: 1.36, 2.01), advanced age > 80 years vs age ≤ 65 years (sHR 1.60, 95% CI: 1.21, 2.12), and treatment with oral anticoagulant vs single antiplatelet post-hospital discharge (sHR 1.61, 95% CI: 1.15, 2.25) were the main risk factors for respiratory bleeding events post-hospital discharge. The increased risk of respiratory bleeding events in patients with a history of cancer or in those managed with PCI was highest on the day of hospital discharge, but these risks decreased with time (the risk estimate for PCI and history of cancer presented above represent the increased risk of respiratory bleed on the day of hospital discharge, see appendix **table 8.2** for these increased risks at 30 days and 365 days post discharge). There was also a significant increased risk of respiratory bleed with prior hypertension, prescription of NSAIDs, and in those aged 66 to 80 years old. Risk factors independently associated with each site-specific bleeding event are presented in **table 8.5**.

Table 8.5: Risk factors independently associated with serious bleeds, non-serious bleeds, early bleeds and each site-specific bleeding event post-hospital discharge for ACS

Risk factors	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Bruising** (n = 949)	**Respiratory bleeds** (n = 582)	**Gastrointestinal bleeds** (n = 705)	**Genitourinary bleeds** (n = 468)	**Intraocular bleeds** (n = 135)	**Intracranial bleeds** (n = 81)
Demographics	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
Age (years)									
≤ 65	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
66 - 80	**1.29 (1.14, 1.45)**	1.09 (0.96, 1.24)	**1.33 (1.09, 1.62)**	0.98 (0.84, 1.14)	**1.27 (1.01, 1.60)**	1.05 (0.86, 1.29)	**1.37 (1.05, 1.79)**	**2.02 (1.26, 3.25)**	1.81 (0.86, 3.83)
> 80	**1.43 (1.23, 1.67)**	1.08 (0.91, 1.29)	**1.57 (1.23, 2.01)**	0.81 (0.65, 1.03)	**1.60 (1.21, 2.12)**	**1.29 (1.01, 1.65)**	**1.65 (1.21, 2.24)**	1.49 (0.81, 2.75)	2.31 (0.92, 5.79)
Female	0.99 (0.90, 1.09)	**1.58 (1.42, 1.76)**	1.16 (0.98, 1.37)	**2.11 (1.85, 2.41)**	0.94 (0.79, 1.12)	0.97 (0.82, 1.13)	0.84 (0.67, 1.06)	0.78 (0.55, 1.11)	1.13 (0.74, 1.73)
BMI (kg/m^2)									
Normal weight *(18.50 to < 25)*	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Underweight *(< 18.50)*	0.92 (0.64, 1.32)	1.14 (0.76, 1.71)	0.94 (0.53, 1.66)	1.16 (0.73, 1.87)	2.02* (0.89, 4.58)	0.94 (0.49, 1.79)	0.73 (0.26, 2.04)	0.93 (0.23, 3.70)	1.14 (0.34, 3.80)
Overweight *(25 to < 30)*	0.91 (0.80, 1.04)	1.04 (0.90, 1.19)	0.96 (0.77, 1.18)	1.10 (0.93, 1.31)	0.93 (0.75, 1.16)	1.23* (0.84, 1.81)	0.95 (0.74, 1.22)	0.74 (0.45, 1.21)	0.59 (0.34, 1.02)
Obese *(≥ 30)*	0.96 (0.83, 1.10)	0.94 (0.81, 1.10)	0.96 (0.74, 1.25)	0.99 (0.81, 1.21)	0.91 (0.71, 1.17)	1.03 (0.82, 1.31)	1.12 (0.82, 1.51)	0.81 (0.49, 1.33)	**0.42 (0.20, 0.88)**
Smoking Status									
Non-smoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ex-smoker	1.06 (0.94, 1.18)	1.03 (0.89, 1.20)	1.01 (0.84, 1.23)	0.97 (0.80, 1.17)	1.13 (0.90, 1.43)	0.95 (0.77, 1.17)	1.10 (0.88, 1.38)	1.07 (0.71, 1.61)	1.15 (0.69, 1.92)

Continuation	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Bruising** (n = 949)	**Respiratory bleeds** (n = 582)	**Gastrointestinal bleeds** (n = 705)	**Genitourinary bleeds** (n = 468)	**Intraocular bleeds** (n = 135)	**Intracranial bleeds** (n = 81)
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
Smoking Status									
Current smoker	1.04 (0.90, 1.19)	0.86 (0.72, 1.01)	**1.54*** **(1.04, 2.27)**	0.87 (0.71, 1.07)	0.96 (0.74, 1.24)	0.99 (0.79, 1.25)	0.97 (0.72, 1.30)	0.94 (0.52, 1.68)	0.79 (0.37, 1.68)
Comorbidities									
Diabetes	0.98** (0.81, 1.18)	**0.79 (0.69, 0.91)**	0.96 (0.79, 1.16)	**0.73 (0.61, 0.88)**	0.91 (0.73, 1.13)	0.92 (0.77, 1.10)	0.96 (0.76, 1.19)	1.10 (0.73, 1.65)	**1.77 (1.08, 2.89)**
Hypertension	**1.15 (1.05, 1.26)**	1.11 (0.98, 1.25)	**1.69*** **(1.27, 2.24)**	1.02 (0.88, 1.18)	**1.43 (1.20, 1.72)**	1.11 (0.94, 1.31)	0.98 (0.79, 1.22)	**1.43 (1.02, 2.02)**	1.01 (0.62, 1.66)
Heart failure	0.90 (0.79, 1.04)	1.09* (0.81, 1.46)	0.90 (0.71, 1.14)	**0.75 (0.59, 0.96)**	1.09 (0.82, 1.43)	0.87 (0.67, 1.13)	0.80 (0.57, 1.11)	1.10* (0.42, 2.91)	**0.36 (0.13, 0.97)**
Cancer	1.10 (0.96, 1.25)	1.00 (0.86, 1.16)	**1.36 (1.13, 1.64)**	0.97 (0.79, 1.19)	**1.86*** **(1.26, 2.74)**	1.17 (0.94, 1.46)	1.10 (0.84, 1.45)	0.77 (0.43, 1.37)	0.78 (0.38, 1.63)
PVD	**1.29 (1.05, 1.58)**	1.29 (0.98, 1.70)	1.00 (0.69, 1.44)	1.20 (0.82, 1.76)	1.30 (0.90, 1.87)	1.06 (0.72, 1.54)	1.33 (0.85, 2.08)	1.03 (0.46, 2.30)	1.31 (0.49, 3.55)
COPD	**1.32 (1.20, 1.45)**	**1.28 (1.14, 1.44)**	1.18 (0.99, 1.42)	**1.21 (1.04, 1.40)**	**1.66 (1.36, 2.01)**	**1.29 (1.08, 1.55)**	**1.26 (1.01, 1.58)**	1.02 (0.64, 1.63)	1.11 (0.64, 1.93)
CKD (eGFR < 60 mL/min/1.73 m^2)	1.10 (1.00, 1.22)	1.02 (0.89, 1.17)	1.15 (0.96, 1.36)	1.10 (0.93, 1.31)	0.81 (0.66, 1.00)	1.12 (0.95, 1.33)	0.93 (0.73, 1.18)	**1.71 (1.11, 2.65)**	1.06 (0.61, 1.84)
Hyperlipidaemia	0.97** (0.83, 1.12)	1.12 (0.99, 1.27)	0.95 (0.80, 1.12)	1.09 (0.93, 1.26)	1.15 (0.94, 1.40)	0.94** (0.73, 1.22)	1.00 (0.83, 1.20)	1.32 (0.88, 1.95)	0.74 (0.45, 1.23)
History of bleeding	**2.17 (1.94, 2.42)**	**1.58 (1.38, 1.80)**	**1.83 (1.52, 2.20)**	1.11** (0.79, 1.56)	**2.06 (1.70, 2.49)**	**2.22 (1.87, 2.64)**	**2.79 (2.26, 3.44)**	**2.11 (1.34, 3.34)**	**1.91 (1.05, 3.45)**
ACS presentation									
STEMI	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00

Continuation	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Bruising** (n = 949)	**Respiratory bleeds** (n = 582)	**Gastrointestinal bleeds** (n = 705)	**Genitourinary bleeds** (n = 468)	**Intraocular bleeds** (n = 135)	**Intracranial bleeds** (n = 81)
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
ACS presentation									
NSTEMI	1.11 (0.96, 1.29)	1.00 (0.84, 1.19)	1.27 (0.95, 1.70)	1.13 (0.92, 1.39)	0.89 (0.69, 1.15)	0.82 (0.65, 1.04)	1.18 (0.85, 1.64)	1.07 (0.59, 1.93)	0.75 (0.40, 1.42)
Not otherwise specified	1.05 (0.91, 1.22)	0.93 (0.79, 1.10)	1.15 (0.87, 1.52)	1.01 (0.83, 1.22)	0.85 (0.65, 1.11)	0.83 (0.65, 1.05)	1.21 (0.89, 1.63)	1.09 (0.62, 1.94)	0.69 (0.37, 1.30)
In-hospital procedure									
PCI	**1.19*** **(1.01, 1.40)**	**1.23 (1.09, 1.39)**	**1.32 (1.10, 1.58)**	**1.24 (1.06, 1.44)**	**1.87*** **(1.37, 2.54)**	1.04 (0.87, 1.26)	1.03 (0.81, 1.30)	1.20 (0.77, 1.86)	1.01 (0.58, 1.77)
Drug Therapy									
Baseline NSAIDs	**1.15 (1.01, 1.31)**	1.12 (0.97, 1.29)	0.95 (0.76, 1.20)	1.06 (0.89, 1.27)	**1.29 (1.04, 1.59)**	1.12 (0.89, 1.42)	1.26 (0.95, 1.66)	0.96 (0.58, 1.59)	1.95* (0.71, 5.32)
Baseline SSRIs	1.07 (0.92, 1.24)	1.13 (0.95, 1.34)	1.08 (0.83, 1.40)	**1.23 (1.00, 1.50)**	0.93 (0.68, 1.28)	1.12 (0.88, 1.42)	1.23 (0.90, 1.68)	1.64 (0.97, 2.77)	1.03 (0.48, 2.19)
Discharge antithrombotic									
Single antiplatelet	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Dual antiplatelet	**0.73**** **(0.61, 0.86)**	0.99** (0.79, 1.22)	**0.72 (0.60, 0.86)**	**1.34 (1.14, 1.57)**	0.75** (0.54, 1.04)	**0.67**** **(0.49, 0.91)**	1.17 (0.93, 1.48)	**2.10 (1.27, 3.45)**	1.03 (0.62, 1.72)
Oral anticoagulant	**1.34 (1.12, 1.61)**	**1.42 (1.15, 1.76)**	1.19 (0.88, 1.61)	1.18 (0.90, 1.56)	**1.61 (1.15, 2.25)**	1.15 (0.83, 1.59)	**1.61 (1.11, 2.34)**	**3.64 (1.90, 6.98)**	1.45* (0.25, 8.46)
No record	**1.34*** **(1.06, 1.69)**	**0.60 (0.47, 0.76)**	**1.93*** **(1.27, 2.93)**	**0.49 (0.34, 0.68)**	**0.60 (0.43, 0.85)**	1.26 (0.98, 1.60)	0.96 (0.66, 1.39)	1.33 (0.63, 2.82)	6.53* (2.35, 18.12)

sHR: *subhazard ratio,* ***CI:*** *confidence interval,* ** *included as time-dependent coefficient – estimated sHR at day of hospital discharge but increases with time post-discharge,* * *included as time-dependent coefficient – estimated sHR at day of hospital discharge but decreases with time post-discharge,* ***eGFR:*** *estimated glomerular filtration rate,* ***ACS****: acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***1.00:*** *reference category,* ***Bold text****: indicates statistically significant risk factors for bleeding at the 5% threshold,* ***Early bleeds:*** *defined as first bleeds within the first 30 days after hospital discharge.*

8.4.6 Subgroup analyses

The independent risk factors for any bleed within 12 months stratified by age, gender, and in-hospital management strategy are presented in **table 8.6**. The risk estimates of bleeding for each (statistically significant) risk factor that interacted with time are reported at two time-points (at 30 days and 365 days post-discharge) in **appendix table 8.3.**

8.4.6.1 Age

Risk factors independently associated with any bleeding for each age band are summarised in detail in **table 8.6**. After multivariable adjustment, history of hypertension, and COPD mainly increased the risk of bleeding in those over 65 years old. While history of CKD, prescription of NSAIDs, and management with PCI during the ACS hospitalisation stay were mostly associated with increased risk of bleeding in those under 65 years. There was also a gradual decline in the increased risk of bleeding for women with age.

8.4.6.2 Gender

History of hypertension, PVD, COPD, and bleeding complication were associated with increased risk of bleeding in both men and women. However, advanced age > 65 years and history of smoking (current smoking) – recorded before hospital discharge were mainly associated with increased risk of bleeding in men (see **table 8.6)**.

8.4.6.3 In-hospital management strategy

Advanced age > 80 years, female gender, history of COPD, and bleeding complications prior to hospital discharge were associated with increased risk of bleeding regardless of

the in-hospital management strategy. Whilst there were similarities in risk factors for both management strategies, history of cancer, PVD, and prescription of NSAIDs were mainly associated with increased risk of bleeding in those managed invasively with PCI (see **table 8.6**).

Table 8.6: Independent risk factors for any bleed within 12 months after hospital discharge by age, gender, and in-hospital management strategy

Characteristics	**≤ 65 years** (n = 10388)	**66 - 80 years** (n = 10047)	**> 80 years** (n = 7225)	**Men** (n = 17855)	**Women** (n = 9805)	**PCI** (n = 9685)	**Medically managed** (n = 17611)
Demographics	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
Age (years)							
≤ 65				1.00	1.00	1.00	1.00
66 - 80				**1.31 (1.17, 1.46)**	0.95 (0.83, 1.09)	1.14 (0.99, 1.32)	**1.43*** **(1.18, 1.73)**
> 80				**1.77*** **(1.42, 2.20)**	0.96 (0.81, 1.13)	**1.27 (1.04, 1.56)**	**1.56*** **(1.27, 1.91)**
Female	**1.51 (1.31, 1.73)**	**1.14 (1.02, 1.27)**	1.01 (0.89, 1.15)			**1.30 (1.15, 1.46)**	**1.13 (1.04, 1.23)**
BMI (kg/m^2)							
Normal weight (BMI 18.50 to < 25)	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Underweight (BMI < 18.50)	0.86 (0.37, 1.97)	0.99 (0.65, 1.49)	1.10 (0.74, 1.63)	0.95 (0.54, 1.69)	1.06 (0.78, 1.43)	0.72 (0.34, 1.51)	1.10 (0.82, 1.48)
Overweight (BMI 25 to < 30)	0.86 (0.70, 1.05)	0.92 (0.79, 1.08)	1.08 (0.94, 1.26)	0.94 (0.83, 1.07)	1.00 (0.88, 1.14)	0.89 (0.75, 1.05)	0.99 (0.88, 1.11)
Obese (BMI ≥ 30)	0.86 (0.71, 1.04)	0.88 (0.76, 1.03)	1.13 (0.91, 1.39)	0.95 (0.84, 1.09)	0.94 (0.80, 1.11)	0.87 (0.70, 1.09)	0.98 (0.86, 1.12)
Smoking Status							
Non-smoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ex-smoker	0.96 (0.79, 1.16)	1.11 (0.96, 1.28)	0.98 (0.85, 1.13)	1.04 (0.93, 1.17)	1.02 (0.90, 1.16)	1.14 (0.97, 1.34)	1.03 (0.88, 1.21)
Current smoker	0.91 (0.78, 1.08)	0.91 (0.77, 1.08)	1.12 (0.89, 1.41)	**1.28*** **(1.03, 1.60)**	0.89 (0.77, 1.04)	1.01 (0.85, 1.20)	1.16* (0.96, 1.39)

Continuation	**≤ 65 years** (n = 10388)	**66 - 80 years** (n = 10047)	**> 80 years** (n = 7225)	**Men** (n = 17855)	**Women** (n = 9805)	**PCI** (n = 9685)	**Medically managed** (n = 17611)
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
Comorbidities							
Diabetes	0.89 (0.75, 1.06)	1.10 (0.96, 1.25)	0.90 (0.78, 1.05)	1.02 (0.92, 1.13)	0.92 (0.80, 1.06)	1.07 (0.92, 1.24)	0.96 (0.87, 1.05)
Hypertension	0.93 (0.79, 1.09)	**1.22 (1.09, 1.37)**	**1.16 (1.02, 1.32)**	**1.11 (1.01, 1.21)**	**1.16 (1.03, 1.30)**	1.12 (0.99, 1.27)	**1.13 (1.03, 1.23)**
Heart failure	1.08 (0.82, 1.42)	0.88 (0.74, 1.04)	**0.82 (0.68, 0.98)**	0.89 (0.77, 1.03)	**0.84 (0.72, 0.99)**	0.89 (0.69, 1.14)	0.88 (0.78, 1.00)
Cancer	1.12 (0.90, 1.40)	1.01 (0.88, 1.16)	1.09 (0.89, 1.32)	1.08 (0.96, 1.22)	0.98 (0.82, 1.18)	**1.30 (1.11, 1.52)**	0.95 (0.84, 1.08)
PVD	1.34 (0.93, 1.94)	1.12 (0.89, 1.42)	**1.41 (1.09, 1.82)**	**1.23 (1.01, 1.50)**	**1.31 (1.04, 1.64)**	**1.60 (1.20, 2.15)**	1.19 (0.98, 1.44)
COPD	1.03** (0.77, 1.38)	**1.32 (1.18, 1.47)**	**1.23 (1.07, 1.42)**	**1.31 (1.19, 1.44)**	**1.25 (1.12, 1.40)**	**1.41 (1.23, 1.62)**	**1.25 (1.14, 1.36)**
CKD (eGFR < 60 mL/min/1.73 m^2)	**1.46 (1.19, 1.79)**	0.99 (0.88, 1.12)	1.06 (0.93, 1.20)	1.08 (0.96, 1.21)	1.06 (0.95, 1.19)	1.10 (0.93, 1.31)	1.07 (0.97, 1.17)
Hyperlipidaemia	**1.17 (1.03, 1.33)**	**0.80** ** **(0.66, 0.97)**	1.08 (0.94, 1.24)	**1.13 (1.02, 1.25)**	1.05 (0.93, 1.18)	1.11 (0.98, 1.25)	1.09 (0.99, 1.20)
History of bleeding	**2.28 (1.93, 2.70)**	**1.81 (1.60, 2.04)**	**1.70 (1.48, 1.95)**	**2.03 (1.79, 2.29)**	**1.67 (1.48, 1.88)**	**2.01 (1.69, 2.38)**	**1.83 (1.67, 2.01)**
ACS presentation							
STEMI	1.00	1.00	1.00	1.00	1.00	1.00	1.00
NSTEMI	1.03 (0.86, 1.24)	1.02 (0.86, 1.22)	1.13 (0.91, 1.39)	1.05 (0.92, 1.20)	1.06 (0.89, 1.25)	1.00 (0.85, 1.19)	1.15 (0.97, 1.37)
Not otherwise specified	1.06 (0.89, 1.26)	1.00 (0.84, 1.18)	0.95 (0.76, 1.19)	1.04 (0.90, 1.19)	0.94 (0.79, 1.12)	0.98 (0.85, 1.13)	1.07 (0.89, 1.28)

Continuation	**≤ 65 years** (n = 10388)	**66 - 80 years** (n = 10047)	**> 80 years** (n = 7225)	**Men** (n = 17855)	**Women** (n = 9805)	**PCI** (n = 9685)	**Medically managed** (n = 17611)
	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)	sHR (95% CI)
In-hospital procedure							
PCI	**1.26*** **(1.01, 1.57)**	1.11 (0.97, 1.28)	1.16 (0.98, 1.37)	1.10 (0.99, 1.21)	1.12 (0.99, 1.26)		
Drug Therapy							
Baseline NSAIDs	**1.23** **(1.06, 1.42)**	1.11 (0.94, 1.30)	0.97 (0.78, 1.20)	**1.16** **(1.02, 1.33)**	1.05 (0.90, 1.23)	**1.24** **(1.05, 1.47)**	1.06 (0.94, 1.20)
Baseline SSRIs	1.07 (0.88, 1.30)	**1.28** **(1.08, 1.52)**	0.86 (0.68, 1.08)	1.06 (0.88, 1.28)	1.09 (0.94, 1.28)	0.93 (0.74, 1.16)	1.15 (0.99, 1.31)
Discharge antithrombotic							
Single antiplatelet	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Dual antiplatelet	0.87** (0.67, 1.13)	0.87** (0.70, 1.06)	**0.74**** **(0.60, 0.92)**	**0.74**** **(0.62, 0.87)**	1.11 (0.97, 1.26)	**0.74**** **(0.59, 0.94)**	**0.85**** **(0.73, 0.99)**
Oral anticoagulant	1.32 (0.96, 1.83)	**1.43** **(1.16, 1.75)**	1.20 (0.97, 1.48)	0.94** (0.69, 1.29)	**1.29** **(1.03, 1.60)**	1.22 (0.92, 1.63)	1.06** (0.80, 1.41)
No record	0.94 (0.70, 1.25)	0.82 (0.66, 1.01)	1.17* (0.87, 1.58)	0.95 (0.80, 1.12)	1.25* (0.90, 1.73)	0.80 (0.59, 1.10)	1.21* (0.97, 1.50)

sHR: *subhazard ratio,* ***CI:*** *confidence interval,* ** *included as time-dependent coefficient – estimated sHR at day of hospital discharge but increases with time post-discharge,* * *included as time-dependent coefficient – estimated sHR at day of hospital discharge but decreases with time post-discharge,* ***eGFR:*** *estimated glomerular filtration rate,* ***ACS****: acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***1.00:*** *reference category,* ***Bold text****: indicates statistically significant risk factors for bleeding at the 5% threshold.*

8.4.7 Sensitivity analyses

Table 8.7 summarises the baseline characteristics that were independently associated with any bleeding event from the full competing risk model, and the three sensitivity analyses: the complete case analysis, the analysis using a standard Cox model (that is, not using a competing risk framework), and the analysis where patients with subsequent ACS were censored at the time of first ACS event post-discharge. Generally, the important risk factors identified in the sensitivity analyses did not differ to those from the main analysis.

Table 8.7: Comparison between the results of the imputed data analysis (main analysis), the complete case analysis, the Cox regression analysis, and the analysis where patients with subsequent ACS post-hospital discharge were censored at the time of the subsequent ACS event (for the outcome of any bleed within 12 months after hospital discharge)

Characteristics	**Main (Imputed data) analysis** (n = 27660)		**Complete case analysis** (n = 16273)		**Imputed data analysis where patients with subsequent ACS were censored at the time of second ACS event** (n = 27660)		**Imputed data analysis using Cox model** (n = 27660)	
	Bleeding events (n = 3620)		Bleeding events (n = 2259)		Bleeding events (n = 3112)		Bleeding events (n = 3620)	
Demographics	sHR (95% CI)	P-value	sHR (95% CI)	P-value	sHR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)								
≤ 65	1.00		1.00		1.00		1.00	
66 - 80	1.20 (1.10, 1.31)	P<0.001	1.14 (1.02, 1.27)	0.019	1.22 (1.11, 1.34)	P<0.001	1.22 (1.12, 1.33)	P<0.001
> 80	1.42* (1.22, 1.66)	P<0.001	1.50* (1.22, 1.84)	P<0.001	1.48* (1.25, 1.75)	P<0.001	1.41* (1.21, 1.65)	P<0.001
Female	1.19 (1.11, 1.28)	P<0.001	1.14 (1.05, 1.25)	0.003	1.18 (1.10, 1.28)	P<0.001	1.19 (1.11, 1.27)	P<0.001
BMI (kg/m^2)								
Normal weight (BMI 18.50 to < 25)	1.00		1.00		1.00		1.00	
Underweight (BMI < 18.50)	1.01 (0.76, 1.34)	0.963	1.09 (0.81, 1.47)	0.579	1.05 (0.79, 1.39)	0.73	1.05 (0.79, 1.40)	0.721
Overweight (BMI 25 to < 30)	0.96 (0.87, 1.06)	0.41	0.99 (0.90, 1.10)	0.907	0.99 (0.90, 1.09)	0.794	0.94 (0.86, 1.04)	0.244
Obese (BMI ≥ 30)	0.95 (0.85, 1.06)	0.354	0.98 (0.88, 1.09)	0.674	0.99 (0.88, 1.11)	0.838	0.94 (0.84, 1.04)	0.223
Smoking Status								
Non smoker	1.00		1.00		1.00		1.00	

Continuation	**Main (Imputed data) analysis** (n = 27660)		**Complete case analysis** (n = 16273)		**Imputed data analysis where patients with subsequent ACS were censored at the time of second ACS event** (n = 27660)		**Imputed data analysis using Cox model** (n = 27660)	
	Bleeding events (n = 3620)		Bleeding events (n = 2259)		Bleeding events (n = 3112)		Bleeding events (n = 3620)	
Smoking Status								
Ex-smoker	1.05 (0.96, 1.14)	0.329	1.03 (0.92, 1.15)	0.609	1.01 (0.92, 1.12)	0.773	1.05 (0.96, 1.15)	0.250
Current smoker	0.96 (0.87, 1.07)	0.486	0.92 (0.80, 1.05)	0.194	0.98 (0.87, 1.10)	0.724	0.97 (0.87, 1.08)	0.581
Comorbidities								
Diabetes	0.99 (0.91, 1.07)	0.812	1.04 (0.96, 1.14)	0.341	0.99 (0.90, 1.08)	0.772	1.00 (0.92, 1.08)	0.981
Hypertension	1.13 (1.05, 1.21)	0.001	1.11 (1.02, 1.22)	0.02	1.14 (1.05, 1.23)	0.001	1.12 (1.04, 1.20)	0.003
Heart failure	0.87 (0.78, 0.97)	0.016	0.85 (0.75, 0.98)	0.024	0.86 (0.76, 0.97)	0.015	0.90 (0.81, 1.01)	0.084
Cancer	1.06 (0.96, 1.17)	0.232	1.10 (0.97, 1.24)	0.126	1.07 (0.96, 1.19)	0.213	1.09 (0.99, 1.20)	0.077
PVD	1.28 (1.09, 1.50)	0.003	1.33 (1.10, 1.61)	0.003	1.28 (1.07, 1.53)	0.006	1.29 (1.10, 1.52)	0.002
COPD	1.29 (1.20, 1.39)	P<0.001	1.24 (1.14, 1.36)	P<0.001	1.27 (1.18, 1.37)	P<0.001	1.32 (1.22, 1.42)	P<0.001
CKD (eGFR < 60 mL/min/1.73 m^2)	1.07 (0.99, 1.16)	0.107	1.06 (0.96, 1.18)	0.231	1.10 (1.01, 1.20)	0.034	1.09 (1.01, 1.18)	0.035
Hyperlipidaemia	0.97** (0.86, 1.09)	0.641	0.98** (0.84, 1.15)	0.843	0.94** (0.83, 1.07)	0.344	0.96** (0.85, 1.08)	0.498
History of bleeding	1.88 (1.73, 2.04)	P<0.001	1.85 (1.67, 2.06)	P<0.001	1.87 (1.71, 2.05)	P<0.001	1.89 (1.73, 2.05)	P<0.001
ACS presentation								
STEMI	1.00		1.00		1.00		1.00	
NSTEMI	1.06 (0.95, 1.18)	0.292	1.14 (0.99, 1.31)	0.063	1.05 (0.94, 1.19)	0.379	1.06 (0.95, 1.18)	0.320
Not otherwise specified	1.00 (0.89, 1.12)	0.978	1.03 (0.90, 1.18)	0.64	1.00 (0.88, 1.12)	0.943	0.99 (0.89, 1.11)	0.866

Continuation	**Main (Imputed data) analysis** (n = 27660)		**Complete case analysis** (n = 16273)		**Imputed data analysis where patients with subsequent ACS were censored at the time of second ACS event** (n = 27660)		**Imputed data analysis using Cox model** (n = 27660)	
	Bleeding events (n = 3620)		Bleeding events (n = 2259)		Bleeding events (n = 3112)		Bleeding events (n = 3620)	
In-hospital procedure								
PCI	1.26* (1.11, 1.43)	P<0.001	1.30* (1.10, 1.53)	0.002	1.24* (1.09, 1.41)	0.001	1.26* (1.11, 1.43)	P<0.001
Drug Therapy								
Baseline NSAIDs	1.13 (1.02, 1.25)	0.017	1.13 (1.00, 1.28)	0.057	1.10 (0.99, 1.23)	0.089	1.12 (1.01, 1.24)	0.027
Baseline SSRIs	1.09 (0.97, 1.22)	0.142	1.11 (0.96, 1.29)	0.146	1.10 (0.98, 1.25)	0.11	1.10 (0.98, 1.24)	0.090
Discharge antithrombotic								
Single antiplatelet	1.00		1.00		1.00		1.00	
Dual antiplatelet	0.81** (0.72, 0.93)	0.002	0.85** (0.71, 1.00)	0.056	0.81** (0.71, 0.94)	0.004	0.81** (0.71, 0.93)	0.002
Oral anticoagulant	1.35 (1.17, 1.55)	P<0.001	1.38 (1.16, 1.65)	P<0.001	1.33 (1.15, 1.54)	P<0.001	1.34 (1.16, 1.54)	P<0.001
No record	1.07* (0.88, 1.30)	0.469	1.12* (0.88, 1.42)	0.366	1.06* (0.87, 1.30)	0.551	1.19* (0.98, 1.44)	0.077

sHR: *subhazard ratio,* ***CI:*** *confidence interval,* ** *included as time-dependent coefficient – estimated sHR at day of hospital discharge but increases with time post-discharge,* * *included as time-dependent coefficient – estimated sHR at day of hospital discharge but decreases with time post-discharge,* ***eGFR:*** *estimated glomerular filtration rate,* ***ACS****: acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***1.00:*** *reference category.*

8.5 Discussion

8.5.1 Summary of findings

This study reports that age greater than 65 years, female gender, management with PCI during the ACS hospitalisation stay, treatment with single antiplatelet or oral anticoagulant post-hospital discharge, prescription of NSAIDs within 6 months prior to hospital discharge, history of bleeding, hypertension, PVD, COPD, and not having a record for heart failure within 2 years prior to hospital discharge were independently associated with increased risk of bleeding complications in the first 12 months after hospital discharge for ACS. These characteristics were also predictors across different types of bleeding events, with some variation by time, severity, and anatomic site of the bleeding event. **Table 8.8** summarises the baseline characteristics that were significantly associated with any bleed, serious bleeds, non-serious bleeds, early bleeds, and each site-specific bleeding event post-hospital discharge for ACS.

Table 8.8: Summary of risk factors significantly associated with any bleed, serious bleeds, non-serious bleeds, early bleeds and each site-specific bleeding event post-hospital discharge for ACS

Risk factors	Any bleed	Serious bleeds	Non-serious bleeds	Early bleeds	Bruising	Respiratory bleeds	Gastrointestinal bleeds	Genitourinary bleeds	Intraocular bleeds	Intracranial bleeds
Demographics										
Age (years)										
66 - 80	✓	✓		✓		✓		✓	✓	
> 80	✓	✓		✓		✓	✓	✓		
Female	✓		✓		✓					
Obesity (BMI ≥ 30)										✓
Current smoking				✓						
Comorbidities										
Diabetes			✓		✓					✓
Hypertension	✓	✓		✓		✓			✓	
Heart failure	✓				✓					✓
Cancer				✓		✓				
PVD	✓	✓								
COPD	✓	✓	✓		✓	✓	✓	✓		
CKD									✓	
Hyperlipidaemia										
History of bleeding	✓	✓	✓	✓		✓	✓	✓	✓	✓
NSTEMI										

Continuation	Any bleed	Serious bleeds	Non-serious bleeds	Early bleeds	Bruising	Respiratory bleeds	Gastrointestinal bleeds	Genitourinary bleeds	Intraocular bleeds	Intracranial bleeds
ACS not otherwise specified										
In-hospital procedure										
PCI	✓	✓	✓	✓	✓	✓				
Drug Therapy										
Baseline NSAIDs	✓	✓				✓				
Baseline SSRIs					✓					
Discharge antithrombotic										
Dual antiplatelet	✓	✓		✓	✓		✓		✓	
Oral anticoagulant	✓	✓	✓			✓		✓	✓	

ACS: *acute coronary syndrome,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index, tick mark: indicates statistically significant association in the multivariable analysis.*

8.5.2 Comparison of the risk factors identified in the present study with those for in-hospital and post-discharge bleeding events from previous studies.

The primary objective of the current study was to identify the independent risk factors for any bleeding event within the first 12 months after hospital discharge. But the emphasis in the majority of previous studies has been on major bleeding events. Because the majority of the predictors for any bleeding event (with the exception of female gender) were also predictive of serious bleeds in the current study, comparison with previous studies will be based on any bleed.

8.5.2.1 Comparison of the risk factors for any bleed identified in the present study with those for in-hospital bleeding events.

Table 8.9 shows the comparison of risk factors for any bleed identified in the present study with those for in-hospital bleeding events. Characteristics such as advanced age, female gender, history of bleeding, hypertension, PVD, and management with PCI during the ACS hospitalisation stay which were identified as predictors of any bleed in the present study have some overlap with the risk factors reported for in-hospital bleeding events (**table 8.9**). However, some characteristics that have been reported to increase the risk of in-hospital bleeds did not increase the risk of any bleed in the present study. Diabetes which increased the risk of major in-hospital bleeding events in both CRUSADE and ACTION studies (Mathews et al., 2011; Subherwal et al., 2009) was not found to be associated with an increased risk of any bleed in the present study. In previous studies (Mathews et al., 2011; Subherwal et al., 2009), history of congestive heart failure was shown to increase the risk of major in-hospital bleeding events (**table 8.9**). The present study found a decreased risk of post-discharge bleed in patients with a history of heart

failure. The reason for the decreased risk of bleeding with heart failure in the present study is unclear, but the role of chance cannot be excluded, which also represent an avenue for further research.

History of CKD has consistently been shown to increase the risk of major in-hospital bleeding events (**table 8.9**) (Mathews et al., 2011; Mehran et al., 2010; Moscucci et al., 2003; Subherwal et al., 2009). However, in the present study, history of CKD was not associated with an increased risk of any bleed. The lack of an association between CKD and bleeding in the present study may be due to differences in the methods used in ascertaining CKD status between the present study and previous in-hospital studies. In some studies of in-hospital bleeds, serum creatinine was used as a surrogate for CKD (Mathews et al., 2011; Mehran et al., 2010), while in others, creatinine clearance estimated by the Cockcroft Gault equation was used to ascertain kidney function (Subherwal et al., 2009). Serum creatinine alone is a poor measure of kidney function because the level of creatinine in blood depends on other factors such as age, gender and ethnicity. In the present study, CKD was ascertained based on the presence of diagnostic Read codes in patients primary care record or eGFR estimated using the kidney disease improving global outcome guideline equation, which has been shown to be more robust (Levey et al., 2009). Nevertheless, there was a strong unadjusted increased risk of any bleed in patients with a history of CKD in the present study, but this increased risk of bleeding disappeared after multivariable adjustment. Therefore, it may be possible that residual confounding may explain the increased risk of major in-hospital bleeding event seen in previous studies.

History of COPD and prescription of NSAIDs within 6 months prior to hospital discharge for ACS increased the risk of any bleed in the present study. Previous contemporary

studies of bleeding in the in-hospital setting have not examined the impact of these characteristics on major in-hospital bleeding events. In contrast to previous studies of in-hospital bleeds (Mathews et al., 2011; Mehran et al., 2010), the present study did not find type of ACS indication to increase the risk of any bleed after hospital discharge.

Other characteristics such as Glycoprotein IIb/IIIa inhibitors (Moscucci et al., 2003), use of intra-aortic balloon pump (Nikolsky et al., 2007), access site used (whether femoral or radial), sheath size, and time of sheath removal (Cantor et al., 2007) have been shown to influence in-hospital bleeding events in the PCI setting. But these characteristics are generally not recorded in primary care databases, hence were not examined in the present study. Therefore, assessing the impact of these characteristics on the risk of longer-term bleeding events has not been possible in the present study.

Table 8.9: Comparison between the findings of the current study with those of previous studies for in-hospital bleeding events

Risk factors	Current study	CRUSADE	ACUITY/ HORIZON	ACTION	GRACE
Demographics					
Age	↑	✗	↑	↑	↑
Female	↑	↑	↑	↑	↑
BMI (kg/m2)	✗	●	●	✗	●
Smoking Status	✗	✗	✗	✗	●
Comorbidities					
Diabetes	✗	↑	✗	↑	●
Hypertension	↑	↑	✗	↑	●
Heart failure	↓	↑	●	↑	●
Cancer	✗	●	●	●	●
PVD	↑	↑	●	↑	●
COPD	↑	●	●	●	●
CKD	✗	↑	↑	↑	↑
Hyperlipidaemia	✗	✗	●	✗	●
History of bleeding	↑	●	●	●	↑
ACS presentation					
NSTEMI	✗	●	↑	↑	●
In-hospital procedure					
PCI	↑	✗	✗	✗	↑
Drug Therapy					
Baseline NSAID's	↑	●	●	●	●
Baseline SSRI's	✗	●	●	●	●
Discharge antithrombotic					
Dual antiplatelet	↓	●	●	●	●
Oral anticoagulant	↑	●	●	↑	●

↑	Increased risk of bleeding
✗	No association with bleeding
↓	Decreased risk of bleeding
●	Not studied

CRUSADE; can rapid risk stratification of unstable angina patients suppress adverse outcomes with early implementation of the ACC/AHA guidelines quality improvement initiative, **ACUITY;** acute catheterisation and urgent intervention triage strategy, **HORIZON;** harmonizing outcomes with revascularisation and stents, **ACTION;** acute coronary treatment and intervention outcomes network registry, **GRACE;** global registry of acute coronary events, **BMI;** body mass index, **PVD;** peripheral vascular disease, **COPD;** chronic obstructive pulmonary disease, **CKD;** chronic kidney disease, **ACS;** acute coronary syndrome, **NSTEMI;** non ST-elevation myocardial infarction, **PCI;** percutaneous coronary intervention, **NSAID;** non-steroidal anti-inflammatory drugs, **SSRI;** selective serotonin re-uptake inhibitors.

8.5.2.2 Comparison of the risk factors for any bleed identified in the present study with those of previous studies of bleeding in the post-discharge setting.

Although an attempt will be made in comparing the risk factors identified for any bleed in the present study with those from previous studies, it is important to note that the majority of the previous studies were either carried out in the PCI setting in clinical trials, or only considered major bleeding events, or the majority of patients enrolled in the study were low-risk patients with stable coronary artery disease or other unspecified cardiovascular diseases. Notwithstanding these differences, table 8.10 shows the comparison of risk factors identified for any bleed in the present study with those identified in previous studies in the post-discharge setting. Advanced age, history of bleeding, and management with oral anticoagulant post-hospital discharge that were identified as important risk factors for any bleed in the present study have also been reported to be important predictors of bleeding in previous studies (**table 8.10**). The present study found an increased risk of bleeding in women compared to men, which is in contrast to the majority of previous studies of bleeding in the post-discharge setting (**table 8.10**) (Baber et al., 2016; Buresly et al., 2005; Khan et al., 2015; Raposeiras-Roubín, Faxén, et al., 2018; Yeh et al., 2016). The lack of an association between female gender and bleeding in the previous studies may be due to the definition of bleeding used, as the majority of the previous studies only considered major bleeding events, and the analysis in this chapter has shown that female gender was only associated with increased risk of non-serious bleeding events following hospital discharge.

Some of the characteristics identified as predictors for any bleed in the present study (such as COPD and prescription of NSAIDs) have not been examined in previous studies, whereas some characteristics which have been reported to increase the risk of bleeding

in previous studies within the post-discharge setting (such as BMI, current smoking, cancer, CKD, and type of ACS presentation) have not been found to increase the risk of any bleed in the present study (**table 8.10**). Also, across previous studies within the post-discharge setting, there were conflicting findings on risk factors of bleeding events. That is to say, characteristics that increased the risk of bleeding in some studies were not shown to increase the risk of bleeding in others. These disparities across studies may be due to the lower number of events and the population studied. The present study is the largest to identify and report on the risk factors for bleeding in an ACS cohort within the "real-world" setting.

Table 8.10: Comparison between the findings of the current study with those of previous studies of post-discharge bleeding events

Risk factors	Current study	DAPT	Precise-DAPT	Trilogy-ACS	BleeMACs	PARIS	BRIC-ACS	Genereux et al	Valle et al	Khan et al	Buresly et al	Lattuca et al
Demographics												
Age	⇧	⇧	⇧	⇧	⇧	⇧	✕	⇧	⇧	⇧	⇧	✕
Female	⇧	✕	●	⇩	✕	✕	⇧	●	●	✕	✕	⇧
BMI (kg/m2)	✕	✕	●	●	●	⇧	⇩	●	●	●	●	●
Smoking Status	✕	✕	✕	●	●	⇧	●	●	●	⇧	●	●
Comorbidities												
Diabetes	✕	✕	✕	●	✕	✕	●	✕	⇧	✕	⇧	✕
Hypertension	⇧	⇧	●	●	⇧	●	⇧	✕	✕	⇧	✕	●
Heart failure	⇩	✕	●	●	✕	●	●	✕	⇧	✕	●	●
Cancer	✕	✕	●	●	⇧	●	●	●	●	●	●	✕
PVD	⇧	⇧	●	✕	⇧	✕	●	⇧	⇧	✕	●	●
COPD	⇧	●	●	●	●	●	●	●	●	●	●	●
CKD	✕	⇧	●	⇧	⇧	⇧	✕	●	⇧	⇧	⇧	✕
Hyperlipidaemia	✕	●	●	●	●	●	●	✕	⇩	⇧	●	●
History of bleeding	⇧	✕	⇧	●	⇧	●	●	✕	⇧	⇧	⇧	✕
ACS presentation												
NSTEMI	✕	✕	●	⇧	●	✕	✕	●	✕	✕	●	●
In-hospital procedure												
PCI	⇧	●	●	●	●	●	●	●	●	⇧	●	●
Drug Therapy												
Baseline NSAID's	⇧	●	●	●	●	●	●	●	●	●	●	●
Baseline SSRI's	✕	●	●	●	●	●	●	●	●	●	●	●
Discharge antithrombotic												
Dual antiplatelet	⇩	⇧	●	●	●	●	⇧	●	⇧	⇧	⇧	●
Oral anticoagulant	⇧	●	●	●	●	⇧	●	⇧	⇧	●	⇧	●

⇧	Increased risk of bleeding
✕	No association with bleeding
⇩	Decreased risk of bleeding
●	Not studied

DAPT; dual antiplatelet therapy study, **Precise-DAPT;** predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy, **Trilogy-ACS;** targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes, **BleeMACs;** bleeding complications in a Multicenter registry of patients discharged with diagnosis of Acute Coronary Syndrome, **PARIS;** patterns of Non-Adherence to Anti-Platelet Regimen in Stented Patients, **BRIC-ACS;** bleeding risk in real world chinese acute coronary syndrome patients, **BMI;** body mass index, **PVD;** peripheral vascular disease, **COPD;** chronic obstructive pulmonary disease, **CKD;** chronic kidney disease, **ACS;** acute coronary syndrome, **NSTEMI;** non ST-elevation myocardial infarction, **PCI;** percutaneous coronary intervention, **NSAID;** non-steroidal anti-inflammatory drugs, **SSRI;** selective serotonin re-uptake inhibitors.

8.5.3 Interpretation of the findings for the secondary objectives

Whilst the present study has shown that there was some overlap of predictors between the in-hospital and post-discharge settings, the predictors identified for early bleeding events in this study showed some differences to those for any bleed post-hospital discharge.

History of smoking (current smoking) - recorded before hospital discharge increased the risk of early bleeding events but not any bleed over 12 months, and this increased risk of bleeding was highest immediately after hospital discharge but decreased with time. Smoking may increase early bleeding events (30-days bleeds) by induction of cytochrome p450 hepatic enzymes. These enzymes may increase the conversion of antiplatelet drugs into their active metabolites, leading to greater platelet inhibition (Bliden et al., 2008, 2013). The gradual decline in risk of bleeding among smokers and the lack of an association between smoking and longer-term bleeds may in fact be due to cessation of smoking post ACS. One study report nearly 55% of patients diagnosed with ACS quit smoking within the initial 30 days of ACS (Yudi et al., 2017). Smoking cessation significantly increases platelet reactivity (Bliden et al., 2013; Park et al., 2012).

History of cancer in the two years prior to hospital discharge likewise increased the risk of early bleeding events only. Cancers which are systemic, such as those emanating from the lungs or gastro-oesophageal tract may likely increase bleeding more than skin cancers (Potts et al., 2018; Shivaraju et al., 2011). It can be speculated that patients experiencing early bleeding events represented those with higher prevalence of cancers, which were systemic in nature. This was evidently reflected by the fact that, upon stratifying bleeding by sites, patients with a history of cancer mostly had significant increase in risk of

respiratory bleeds, which was only present at 30 days after hospital discharge, and a modest albeit non-significant increased risk of gastrointestinal bleeds.

Another novel finding of this study was in the assessment of the predictors of site-specific bleeding events. The study found that advanced age > 80 years and prior history of bleeding were predictive of all site-specific bleeding events (except bruising). Increasing age may cause vessels to be brittle, leaky and less likely to constrict and more prone to bleed due to the deposition of amyloid and collagen in the ageing arterial tunica media (Steg et al., 2011). Whilst both advanced age > 80 years and history of bleeding were predictive of all site-specific bleeding events (except bruising), some predictors showed variation in the types of bleeding events they are associated with post-hospital discharge.

Female gender was only predictive of nuisance bruising, and not serious bleeds (such as intracranial and gastrointestinal bleeds) contrary to that reported by in-hospital studies (Mathews et al., 2011; Mehran et al., 2010; Moscucci et al., 2003; Nikolsky et al., 2007; Subherwal et al., 2009). This finding was consistent with the majority of studies in the post-discharge setting which also showed a lack of association between female gender and serious bleeding events (Baber et al., 2016; Buresly et al., 2005; Grodecki et al., 2018; Raposeiras-Roubín, Faxén, et al., 2018; Yeh et al., 2016). The higher risk of bruising observed among women may presumably stem from the fact that women in general (Campbell and Roland, 1996), and those with ACS (Hyun et al., 2016), consult their GPs more often than men post-hospital discharge. Therefore, they may be more likely to report bruising and have this recorded in their medical record (the prevalence of bruising was twice as high in women 5.0% than men 2.5%).

This study found COPD to be a strong risk factor for bruising, respiratory, gastrointestinal and genitourinary bleeding events post-hospital discharge. Most contemporary studies in

the ACS setting have either not examined the impact of COPD on bleeding or have not recorded its diagnosis. COPD is characterised by local and systemic inflammation (Moermans et al., 2011). Patients with COPD are exposed to oxidative stress via chronic hypoxia and increased release of reactive oxygen species by leukocytes (MacNee, 2000, 2005). This damages gastric mucosa (Kang et al., 2010), and may predispose to peptic ulcer bleeds (Huang et al., 2012). Patients with COPD are often treated with steroids to control lung inflammation. Steroids may delay peptic ulcer healing (Luo et al., 2004), thus increasing the risk of perforation and bleeding complications (Hernández-Díaz and Rodríguez, 2001; Narum et al., 2014).

History of CKD increased the risk of gastrointestinal, intraocular and intracranial bleeding events in the univariable analysis. However, after multivariable adjustment, CKD was only found to be predictive of intraocular bleeds. The reason for this finding remains difficult to explain, but in patients that have a history CKD, 17% of those that sustained intraocular bleeding events were discharged on oral anticoagulants, compared to only 8% in those that did not have CKD. Dual antiplatelet therapy decreased the risk of gastrointestinal bleeds in the immediate period following hospital discharge. The reason for the decreased risk of gastrointestinal bleeds with dual antiplatelet may presumably stem from the fact that patients with a history of this type of bleeding event, who were deemed to be at higher risk of bleeding may have been only prescribed single antiplatelet or not given any antithrombotic medication at the time of hospital discharge.

8.5.4 Interpretation of the subgroup analyses

When risk factors for bleeding (any bleed) were stratified by age in the subgroup analysis, CKD increased the risk of bleeding in those under 65 years, but not in those over 65 years

old. The lack of an association between CKD and bleeding in those over 65 years is difficult to explain. But there was an indication that before the age of 65 years, patients with CKD were more often discharged on anticoagulants than those without (7% vs 3%). But this difference in rate of prescribing became attenuated after the age of 65 years. Although discharge antithrombotic therapy has been accounted for in the analysis, the impact of residual confounding from other unmeasured factors such the indications for oral anticoagulant cannot be excluded.

This study did not find an association between age and bleeding among women in the subgroup analysis. This lack of an association between age and bleeding may in part be due to the natural decline in oestrogen seen in post-menopausal women (which constitute the majority of women in this study). This decline in oestrogen is associated with higher levels of fibrinogen, thus suggesting rapid clotting among women (The Writing Group for the Estradiol Clotting Factors Study, 1996). Women also have higher platelet count post menopause (Segal and Moliterno, 2006), with higher numbers of surface receptors to bind greater amounts of fibrinogen (Faraday et al., 1997; Johnson et al., 1975).

Smoking (current smoking – recorded before hospital discharge) increased the risk of bleeding among men but not women. The prevalence of smoking generally tends to be higher among men than women (ONS, 2017b), and smoking has been shown to increase the conversion of antiplatelets into their active metabolites leading to greater inhibition of platelet activities (Bliden et al., 2008, 2013). Besides, women generally have enhanced platelet reactivity than men (Haque et al., 2001), both with and without antiplatelet therapy (Bobbert et al., 2012).

Malignancy has been an exclusion criterion in previous studies like the CRUSADE, DAPT, and Trilogy-ACS (Alfredsson et al., 2017; Subherwal et al., 2009; Yeh et al., 2016). The sub-group analysis in the present study revealed that cancer is an important predictor of bleeding complications in patients managed with PCI. This finding was consistent with those of the BleeMACS study and the study by Potts and colleagues which reported an increased risk of serious bleeding events in cancer patients managed with PCI (Potts et al., 2018; Raposeiras-Roubín, Faxén, et al., 2018). This increased risk of bleeding with cancer may be due to the fact that patients managed with PCI often continue dual antiplatelet therapy for up to 12 months following hospital discharge. Prolonged exposure to antiplatelet drugs may irritate pre-existing systemic malignancies in mucosal linings (such as gastric cancers), resulting in bleeding complications. Nausea and vomiting, which is common among cancer patients undergoing chemotherapy (Sun et al., 2005) may result in haematemesis from Mallory-Weiss tears. Radiotherapy and chemotherapy often result in mucosal erosion and ulceration, which may also predispose to bleeding complications (Shadad et al., 2013). Thus, this finding supported by the BleeMACS study and the study by Potts and colleagues suggests that cancer should be taken into account when assessing the future risk of bleeding in patients managed with PCI.

8.5.5 Strengths and limitations

This is the first large scale primary care consultation based study to examine the independent risk factors for bleeding complications following hospital discharge for ACS. It is also the first to examine the independent risk factors for site-specific bleeding events. The study goes beyond the traditional risk factors identified from studies of in-hospital bleeding events by further exploring the independent effects of cancer, COPD, and

NSAIDs on risk of future bleeding complications. The study included ACS patients with indications for oral anticoagulation which were excluded in the majority of previous studies (Costa et al., 2017; Subherwal et al., 2009; Yeh et al., 2016).

The findings from this study should be interpreted in light of some limitations. First, the observational design of the study does not preclude residual confounding from unmeasured patient factors such as frailty, dosing and duration of discharge antithrombotic drugs, gastroduodenal ulcer, and genetic factors. The study was not adequately powered to examine the independent risk factors for some site-specific bleeding events such as intracranial and intraocular bleeds. Thus, findings in relation to these bleeding events should be viewed as exploratory. Each site-specific bleeding event (such as gastrointestinal and respiratory) will consist of both serious and non-serious bleeds. However, due to limited number of events, risk factors for site-specific bleeds were not stratified by severity. Defining each patient discharge antithrombotic medication was based on a 3 months follow-up from the date of hospital discharge. It was therefore unclear whether or not patients remained and adhered to the same treatment regimen beyond this period. Multiple statistical tests of associations were carried out, and the possibility that some findings may be due to chance cannot be excluded. Finally, the elderly and comorbid nature of the study population mean that over-adjustment bias may have attenuated some associations between risk factors and bleeding events.

8.5.6 Conclusion

Using a large primary care consultation database with linkage to hospital episode statistics and mortality data, this study has identified baseline characteristics that are associated with increased risk of bleeding complications in the first 12 months after

hospital discharge. These characteristics (such as age, female gender, history of bleeding, hypertension, PVD, and management with PCI during the ACS hospitalisation stay) have some overlap with those reported for in-hospital bleeding events, and whilst there were some similarities in predictors, the present study did not find history of diabetes, heart failure, CKD, and type of ACS presentation to be associated with an increased risk of any bleed following hospital discharge for ACS. The characteristics identified that increased the risk of any bleed were also predictors across different types of bleeding events, with some variation by time, severity, and anatomic site of the bleeding event.

The next chapter (Chapter 9) will determine the independent effect of these bleeding events on all-cause mortality. That is to say, whether patients who sustain these bleeding complications have a higher risk of mortality than those who did not.

Chapter 9.0: **Prognostic impact of bleeding complications on all-cause mortality**

9.1 Introduction

This chapter examines the association of bleeding following hospital discharge after ACS with all-cause mortality (objective 5). The motivation for the present study has been described in detail in Chapters 1 and 3 of this thesis, but briefly, these are summarised as follows:

- The emphasis in the majority of previous studies has been on the prognostic impact of in-hospital or bleeding events within the first 30-days of ACS (a composite of in-hospital and post-discharge bleeds), with little consideration for longer-term (post-discharge) bleeds.
- Previous studies within the in-hospital setting have shown an increased risk of mortality in patients that experienced in-hospital bleeding events (Eikelboom et al., 2006; Kinnaird et al., 2003; Manoukian et al., 2007; Rao et al., 2005, 2006). There is limited evidence on whether post-discharge bleeding events are also associated with an increased risk of mortality. The finding of an association between in-hospital bleeds and mortality strengthens the need to determine whether post-discharge bleeding events also convey greater risk of mortality.
- The majority of the previous studies within the post-discharge setting have excluded non-serious bleeding events, and it is unclear whether these types of bleeding events are associated with all-cause mortality post-hospital discharge.
- There is uncertainty on whether any adverse impact of post-discharge bleeding on mortality may depend on the anatomic site of the bleed. This is important for bleeding following hospital discharge since the site of bleeding may differ from the in-hospital setting.

- There is uncertainty on whether the risk factors for post-discharge bleeding will also be predictive of mortality in patients that experienced bleeding events. If this is true, this subgroup of patients may benefit from an individualised management strategy.

Accordingly, this chapter addresses these gaps in knowledge by determining independent associations between bleeding events within the first 12 months following hospital discharge and all-cause mortality also occurring within a year after discharge. The independent risk factors for all-cause mortality in patients that experienced bleeding complications were also explored.

9.2 Aim and objectives

9.2.1 Aim

The overall aim was to determine the independent association of post-discharge bleeding with all-cause mortality within the first 12 months after hospital discharge for ACS.

9.2.2 Specific objectives

Primary objective:

To determine the independent association of any post-discharge bleeding event with all-cause mortality within the first 12 months after hospital discharge for ACS.

Secondary objectives:

The secondary objectives were to determine the independent associations of:

- Serious and non-serious bleeding events with all-cause mortality within the first 12 months after hospital discharge for ACS.
- Site-specific bleeding events with all-cause mortality within the first 12 months after hospital discharge for ACS.
- Whether early bleeding events (compared to late bleeding events) are associated with a higher risk of mortality (within the first 30 days after the bleeding event).
- Whether the risk factors identified for bleeding are also associated with mortality in patients that experienced bleeding complications in the first 12 months after hospital discharge.

9.3 Methods

The data source, exposures, covariates, and outcome definitions, as well as the baseline characteristics of the study population are described in Chapters 5, 6 and 7.

9.3.1 Study design

This was a cohort study set within CPRD with linkage to HES and ONS mortality data.

9.3.1.1 Study population

The steps involved in identifying the study population were described in Chapter 6, section 6.3.1. Briefly, the study population comprised 27,660 patients with a coded ACS diagnosis between 2006 and 2016.

9.3.1.2 The outcome of all-cause mortality

For the primary objective of the analysis described in this chapter, the outcome of all-cause mortality was defined as having a death record in the ONS mortality data within the first 12 months after hospital discharge for ACS. The motivation for selecting the first 12 months after hospital discharge (as opposed to the first 12 months after the bleeding event) was to avoid immortal time bias which may occur when the patients who experienced a bleeding event are followed from the time of the bleeding event (thus ignoring time contributed from hospital discharge to time of bleeding post-discharge) and those who did not are followed from the date of hospital discharge. This time frame (the first 12 months) was selected based on the findings of a previous review which indicated that the prognostic impact of in-hospital bleeding events on mortality was maintained for up to 12 months following hospital discharge (Kwok et al., 2014), and the fact that the

descriptive analysis in Chapter 7 showed that 53% of all first bleeds that occurred during follow up happened in the first 12 months after discharge.

For the secondary objectives of this analysis, the definition for the outcome of all-cause mortality remained the same except for the comparison between early bleeds (bleeds within the first 30 days) and late (bleeds between 31 – 335 days) bleeding events where the outcome of all-cause mortality was defined as having a death record in the ONS mortality data within the first 30 days after the bleeding event. The motivation for selecting the first 30 days after the bleeding event was based on the hypothesis that deaths occurring within this period are more likely to be due to the bleeding event.

9.3.1.3 The exposure (bleeding)

For the primary objective of the analysis described in this chapter, the exposure was defined as having a coded consultation record for any first bleeding event in the patient's primary care record within the first 12 months after hospital discharge for ACS or a death record in the ONS mortality data with bleeding as the primary underlying cause post-hospital discharge. Patients with consultation records for bleeding within the first 12 months after hospital discharge or a death record in the ONS mortality data with bleeding as the primary underlying cause were classified as exposed from the time of first bleeding event (and unexposed prior to that) and those without any bleeding event as unexposed for the entire duration of follow up.

For the secondary objectives, the definition for the exposure of bleeding remained the same, but was categorised (based on first bleeds) by severity (serious and non-serious), site (such as gastrointestinal), and timing of the bleeding event (early: within the first 30 days, and late: between 31 – 335 days post-discharge). The reason for categorising

bleeding by severity and anatomic site was based on previous literature which showed that the prognostic impact of in-hospital bleeding events on mortality varied by severity and anatomic site of the bleed (Kwok et al., 2015; Rao et al., 2005, 2006). While the motivation for grouping bleeding based on the timing of the event was to explore whether patients who experienced early bleeding events have a higher risk of mortality than those experiencing these bleeding complications at a later time-point post-hospital discharge. This was mainly to expand on the findings from the descriptive analysis in Chapter 7, which indicated that within the first 12 months following hospital discharge, bleeding events occurred more frequently in the first 30 days. Also, the cut-off of 335 days was selected for late bleeding events because patients who experienced bleeding complications after day 335 will not have the complete 30-days of follow up post bleed (time period for outcome for this secondary analysis) within the 12 months after discharge.

9.3.1.4 Covariates

All the baseline socio-demographic characteristics, comorbidities, in-hospital procedures, and pharmacological characteristics considered as potential risk factors for bleeding in Chapter 8 table 8.1, were considered as potential confounders of the association between bleeding and all-cause mortality. The motivation for selecting these characteristics as potential confounders was based on those which previous studies of in-hospital and post-discharge bleeding had considered and adjusted for in their analyses (Caneiro-Queija et al., 2018; Eikelboom et al., 2006; Généreux et al., 2015; Kinnaird et al., 2003; Rao et al., 2005; Valgimigli et al., 2016; Valle et al., 2016), and the fact that these characteristics are also associated with mortality (Généreux et al., 2015; Valle et al.,

2016). The definitions for these characteristics are described in detail in Chapter 5, section 5.4.

9.3.1.5 Follow up

The study population were followed from the date of hospital discharge until date of death or date patient ceased contributing to CPRD due to the patient leaving practice or practice leaving CPRD or the end of 12 months from the index date of hospital discharge or the date of last data collection at the time of data request. Patients with a record for any first bleeding event post-hospital discharge (the exposed group) were compared with those without bleeding events (the unexposed group) in relation to all-cause mortality. Associations between the outcome of all-cause mortality (within the first 12 months after hospital discharge) with bleeding events also within 12 months after hospital discharge were determined. For the secondary objectives of the study (examining the prognostic impact of bleeding by severity and site), patients who had a record for the relevant bleeding event (based on first bleed) were compared to those without any bleeding event in relation to all-cause mortality. When comparing early bleeds (bleeds within the first 30 days) to late (bleeds between 31 – 335 days) bleeding events, patients that did not experience any bleeding event within the first 12 months following hospital discharge were excluded.

9.3.2 Sample size

Assuming 50 covariates were selected for adjustment in the current study, there will be more than 50 EPVs (2,657/50) based on the 2,657 patients with the outcome of all-cause

mortality within the first 12 months of hospital discharge. This sample size should be sufficient for the primary analysis in this study (Ogundimu et al., 2016).

9.3.3 Missing data

The description of the variables that were imputed, the number of imputations, and the imputation process were described in Chapter 8.0, section 8.3.3. The same imputed datasets that were used for the analyses in the previous chapter (Chapter 8.0) were also used for all analyses in this study.

9.3.4 Analysis

All the analyses in this study were based on a first bleeding event for a patient and were carried out on the imputed datasets. Mortality rates (per 1000 person-years) within the first 12 months following hospital discharge were determined among those that experienced bleeding complications and those that did not, following the same procedure described in Chapter 7, section 7.2.2.1.

9.3.4.1 Univariable analysis

The crude association between the outcome of all-cause mortality and any bleeding event (as the exposure) within the first 12 months after hospital discharge was determined using a Cox proportional hazard regression model. Bleeding was incorporated into the model as a time-varying exposure. A time-varying exposure allows patients to be classified as unexposed before experiencing a bleeding event and then as exposed thereafter. For the outcome of mortality that occurred on the same day as the exposure (bleeding event), half a day (0.5) was subtracted from the timing of bleeding so that these

deaths could be included in the analysis. Similarly, for deaths that occurred on the last day of the study (day 365), half a day was subtracted from the timing of death. Robust variance estimators were used to take into account clustering within GP practices. The magnitude of each association was quantified by hazard ratio and associated 95% confidence intervals.

9.3.4.2 Multivariable analysis

Adjusted association between the outcome of all-cause mortality with any bleeding event as a time-varying exposure was determined using a Cox proportional hazard regression model. The association was adjusted for year of index hospital discharge, geographic region and all the baseline characteristics considered as risk factors for bleeding in Chapter 8 table 8.1. Adjustment was carried out in three stages. First, the association of bleeding events with all-cause mortality was determined adjusting for socio-demographic characteristics. Second, this association was re-examined adjusting for socio-demographic characteristics, comorbidities and in-hospital procedures. Finally, the association of bleeding events with all-cause mortality adjusting for socio-demographic characteristics, comorbidities, in-hospital procedures, and pharmacological characteristics was determined. Robust variance estimators were used to take into account clustering within GP practices.

For the secondary objectives of the analyses, the univariable and multivariable analyses described above for the primary objective were repeated with the exposure of any first bleeding event (within 12 months) categorised by severity and site of the bleeding event. All bleeding events were incorporated into the relevant Cox models as time-varying

exposures. The magnitudes of all associations were quantified by adjusted hazard ratios and associated 95% confidence intervals.

Separately, for the comparison between early and late bleeding events in relation to the outcome of mortality within 30 days after the bleeding event, the univariable and multivariable analyses described above were repeated, this time using a standard logistic regression model. The magnitude of this comparison was quantified by odds ratio and associated 95% confidence intervals. All analyses were carried out in Stata version 14.2.

9.3.4.3 Checking the proportional hazard assumption of the Cox model

For each of the final models, exposure or covariate by time (in days) interactions were included in the models to assess whether the relative hazard of all-cause mortality between the groups being compared remained the same over the duration of the study follow-up period. A statistically significant interaction indicates a violation of the proportional hazard assumption, whereas a non-statistically significant interaction implies that the relative hazard of all-cause mortality between the groups being compared was constant over the whole duration of follow up. That is to say, the relative hazard of all-cause mortality between the exposed (those with any first bleeding event post-discharge) and the unexposed (those without any bleeding event post-discharge) group is approximately constant over the whole duration of follow up.

9.3.4.4 Subgroup analyses

To explore whether the association of bleeding with all-cause mortality varies by baseline patient characteristics, the multivariable analysis described above for any bleed was repeated including interaction terms between any first bleed and age, gender, in-hospital

management strategy, and discharge antithrombotic therapy. Separately, the univariable and multivariable analyses described above for any bleed were repeated stratified by age categories (≤ 65 years old, 66 to 80 years old, and > 80 years old), gender (men, women), in-hospital management strategy (whether medically managed or with PCI), and discharge antithrombotic drugs combinations (single antiplatelet, dual antiplatelet, and receipt of oral anticoagulants). The motivation for the gender stratification was based on previous studies of in-hospital bleeding events which indicated that the risk of mortality from major in-hospital bleeding may be higher among men than women (Holm et al., 2016; Kaul et al., 2013; Mehta et al., 2012). While in regards to age, in-hospital management strategy, and discharge antithrombotic therapy, the stratification was based on the hypothesis that the risk of mortality from bleeding may increase with age, number of discharge antithrombotic drugs, or differ based on the in-hospital management strategy employed. For each stratified category, patients who experienced bleeding were compared to those who did not within that category. For example, for the male gender, men that experienced bleeding within the first 12 months following hospital discharge were compared to men that did not in relation to the outcome of all-cause mortality also within 12 months after discharge.

9.3.4.5 Sensitivity analyses

The multivariable analysis described above for any first bleed within 12 months following hospital discharge was repeated on patients with complete data on all variables (complete case analysis). Results of the complete case analysis were then compared with those from the imputed dataset. Separately, the multivariable analysis described above for any bleed was repeated taking account of multiple bleeding events (that is to say, not

only first bleeds, but all bleeding events that occurred in the first 12 months after hospital discharge) with the exposure of bleeding treated as a 3 category time-varying variable (no bleed, non-serious bleed, and serious bleed) so that patients can move up the ladder from no bleed to non-serious bleed to serious bleed over time, but not down the ladder.

9.3.4.6 Risk factors for mortality analysis

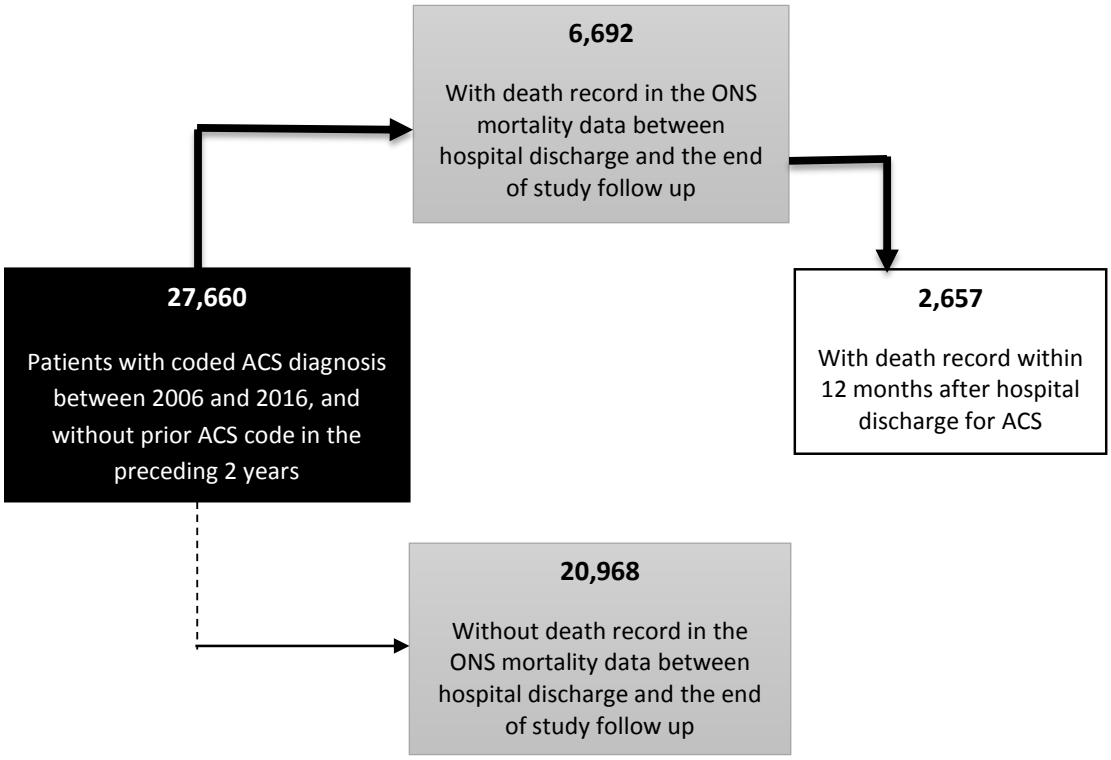
To explore whether the baseline characteristics that increased the risk of bleeding also increase the risk of mortality in patients that sustained bleeding events, univariable and multivariable Cox models were used to examine the association of all-cause mortality (within the first 12 months after the bleeding event) with all the baseline characteristics considered as potential risk factors for bleeding in Chapter 8 table 8.1. Analysis was restricted to patients with a bleeding event and patients were followed from date of first bleeding event following hospital discharge for ACS until death or date patient ceased contributing to CPRD due to the patient leaving practice or practice leaving CPRD or the end of 12 months from the date of first bleeding event post-hospital discharge or the date of last data collection at the time of data request. Patients with a record for each of the baseline characteristics listed in table 8.1 were compared to those without in relation to the outcome of all-cause mortality within 12 months post-bleed. Associations between the outcome of all-cause mortality with baseline socio-demographic, comorbidities, pharmacological, and in-hospital procedural characteristics (as risk factors) were determined. These associations were only examined in patients who did experience a bleeding event within the first 12 months after hospital discharge, and those that did not were excluded from the analysis. All multivariable associations were adjusted for year of index hospital discharge, geographic region, and the anatomic site of bleeding. Robust

variance estimators were used to account for clustering within GP practice. All modelling assumptions were examined as described above for the primary objective of the study.

9.4 Results

The incidence and timing of mortality by bleeding within the first 12 months after hospital discharge for ACS are summarised in Chapter 7, section 7.2. The number of patients with the exposure of bleeding are summarised in Chapter 8, figure 8.1. Thirteen percent (3,620) of the study population experienced first bleeding events over a follow-up period of 12 months post-hospital discharge. **Figure 9.1** summarises the number of patients with and without the outcome of all-cause mortality within the first 12 months after hospital discharge for ACS. Overall, 9.6% (2,657) of the study population died within a year after discharge.

Figure 9.1: Flowchart describing the number of patients with and without the outcome of all-cause mortality within the first 12 months after hospital discharge for ACS



9.4.1 Proportional hazard assumption of the Cox model

The covariates that did not satisfy the proportional hazard assumption of the Cox model were included in the relevant models as time-dependent coefficients. All (bleeding) exposures satisfied the proportional hazard assumption of the Cox model.

9.4.2 Associations of bleeding events with all-cause mortality

9.4.2.1 Association of any bleeding event with all-cause mortality

Table 9.1 presents crude and adjusted associations between any bleeding event and all-cause mortality within the first 12 months following hospital discharge for ACS. Generally, adjusting for socio-demographic characteristics had some effect on the risk of mortality, while further adjusting for the other characteristics had little effect. After full multivariable adjustment, any first bleeding was independently associated with all-cause mortality. Those that experienced bleeding complications in the first 12 months after hospital discharge had 70 percent (HR 1.70, 95% CI: 1.50, 1.92) increased likelihood of mortality in this period than those who did not experience bleeding events.

Table 9.1: Crude and adjusted associations between any first bleeding event and all-cause mortality within the first 12 months following hospital discharge

Exposure	No: of deaths	Mortality rate per 1000 person-years (95% CI)	Unadjusted association		Adjusted for socio-demographic characteristics		Adjusted for socio-demographics, comorbidities and in-hospital procedures		Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics	
	(n/N)		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
No bleed (within 12 months)	2,295/24,040	103 (99, 107)	1.00		1.00		1.00		1.00	
Any bleed (within 12 months)	362/3,620	184 (166, 204)	2.23 (1.99, 2.50)	p<0.001	1.89 (1.69, 2.12)	p<0.001	1.80 (1.59, 2.03)	p<0.001	1.70 (1.50, 1.92)	p<0.001

HR: *Hazard ratio,* ***CI:*** *Confidence interval,* ***1.00:*** *reference category****, No:*** *Number.*

9.4.2.2 Association of serious and non-serious bleeding events with all-cause mortality

Table 9.2 presents crude and adjusted associations of serious and non-serious first bleeding events with all-cause mortality in the first 12 months following hospital discharge. After full multivariable adjustment, patients who experienced serious (HR 1.89, 95% CI: 1.64, 2.18) and non-serious (HR 1.32, 95% CI: 1.06, 1.63) bleeds as their first bleeding events following hospital discharge both had a higher risk of mortality than those who did not experience any bleeding event. This increased risk of mortality from bleeding was nearly three times higher (89% vs 32%) in those that experienced serious bleeding events than in those experiencing non-serious bleeds following hospital discharge (**table 9.2**). Non-serious bleeds comprised bruising, nose bleeds and sub-conjunctival bleeds, and upon stratifying the association of non-serious bleeds with all-cause mortality by type, bruising (HR 0.94, 95% CI: 0.68, 1.30) and sub-conjunctival bleeds (HR 0.55, 95% CI: 0.17, 1.77) did not increase the risk of mortality, whereas those that sustained nose bleeds (HR 1.82, 95% CI: 1.35, 2.46) had a higher risk of mortality than those who did not experience any bleeding event following hospital discharge.

9.4.2.3 Associations of site-specific bleeding events with all-cause mortality

The crude and adjusted associations of each site-specific bleeding event with all-cause mortality are summarised in detail in **table 9.2.** After full multivariable adjustment, an intracranial first bleed (HR 7.52, 95% CI: 4.41, 12.81, (compared to those with no bleed)), gastrointestinal first bleed (HR 2.07, 95% CI: 1.66, 2.58), and respiratory first bleeding events (HR 2.02, 95% CI: 1.56, 2.60) remained independently associated with increased risk of all-cause mortality in the first 12 months following hospital discharge. The increased risk of mortality from bleeding (compared to those with no bleed) was highest

(sevenfold) in patients that experienced intracranial bleeds following hospital discharge. There was a modest increased risk of mortality with genitourinary bleeding events (HR 1.26, 95% CI: 0.88, 1.79), but this association did not reach statistical significance. Bruising (HR 0.94, 95% CI: 0.68, 1.30) and intraocular (HR 0.75, 95% CI: 0.33, 1.71) first bleeding events did not increase the risk of mortality post-hospital discharge (**table 9.2**).

Table 9.2: Crude and adjusted associations between any first bleeding events (by severity and site) and all-cause mortality within the first 12 months following hospital discharge

Exposures	No: of deaths	Mortality rate per 1000 person-years (95% CI)	Unadjusted associations		Adjusted for socio-demographic characteristics		Adjusted for socio-demographics, comorbidities and in-hospital procedures		Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics	
	(n/N)		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
No bleed (within 12 months)	2,295/24,040	103 (99, 107)	1.00		1.00		1.00		1.00	
By severity										
Serious	266/2,126	234 (207, 264)	2.81 (2.47, 3.20)	p<0.001	2.33 (2.06, 2.65)	p<0.001	2.09 (1.82, 2.39)	p<0.001	**1.89 (1.64, 2.18)**	p<0.001
Non-serious	96/1,494	116 (95, 141)	1.42 (1.14, 1.76)	0.002	1.24 (1.00, 1.55)	0.052	1.31 (1.06, 1.62)	0.014	**1.32 (1.06, 1.63)**	0.012
By type/site										
Bruising	42/949	78 (57, 105)	0.90 (0.66, 1.23)	0.517	0.84 (0.61, 1.16)	0.297	0.91 (0.66, 1.26)	0.580	0.94 (0.68, 1.30)	0.706
Respiratory	68/582	218 (172, 277)	2.56 (2.00, 3.29)	p<0.001	2.12 (1.64, 2.73)	p<0.001	2.07 (1.60, 2.67)	p<0.001	**2.02 (1.56, 2.60)**	p<0.001
Gastrointestinal	92/705	250 (204, 306)	2.99 (2.45, 3.66)	p<0.001	2.62 (2.15, 3.20)	p<0.001	2.39 (1.94, 2.94)	p<0.001	**2.07 (1.66, 2.58)**	p<0.001
Genitourinary	37/468	142 (103, 196)	1.71 (1.23, 2.39)	0.002	1.46 (1.04, 2.06)	0.028	1.39 (0.99, 1.96)	0.058	1.26 (0.88, 1.79)	0.201
Intraocular	6/135	85 (38, 189)	1.00 (0.46, 2.20)	0.895	0.79 (0.35, 1.76)	0.562	0.74 (0.32, 1.70)	0.478	0.75 (0.33, 1.71)	0.496

Continuation	No: of deaths	Mortality rate per 1000 person-years (95% CI)	Unadjusted associations		Adjusted for socio-demographic characteristics		Adjusted for socio-demographics, comorbidities and in-hospital procedures		Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics	
	(n/N)		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Intracranial	37/81	1292 (936, 1784)	15.49 (10.09, 23.77)	p<0.001	11.6 (7.2, 18.68)	p<0.001	10.96 (6.80, 17.66)	p<0.001	**7.52 (4.41, 12.81)**	p<0.001

HR: *Hazard ratio,* ***CI:*** *Confidence interval,* ***No:*** *Number,* ***1.00:*** *reference category****, Bold text:*** *indicates statistically significant associations at the 5% threshold.*

9.4.2.4 Comparison between early and late bleeding events in relation to mortality within 30 days after the bleeding event

Figure 9.2 summarises the types of early and late bleeding events after hospital discharge for ACS, and **table 9.3** presents the crude and adjusted associations of early bleeding events (compared to late bleeds) with all-cause mortality within 30 days following the bleeding event. Generally, there was no difference in the risk of mortality between those that experienced early and those experiencing late bleeding events following hospital discharge (OR 0.66, 95% CI: 0.42, 1.03). Among those that experienced early bleeding events and died within 30 days after the bleed (n that died = 20), 25% of all deaths were due to bleeding, 45% to cardiovascular causes, and 30% to non-cardiovascular and non-bleeding causes. Whereas in patients that experienced late bleeding events and died within 30 days of the bleed (n that died = 99), 56% of all deaths were bleeding related, 23% were cardiovascular, and 21% were non-cardiovascular and non-bleeding related.

Figure 9.2: Percentage of patients with first type of each bleeding event within 12 months following hospital discharge stratified by timing of bleed (early/late)

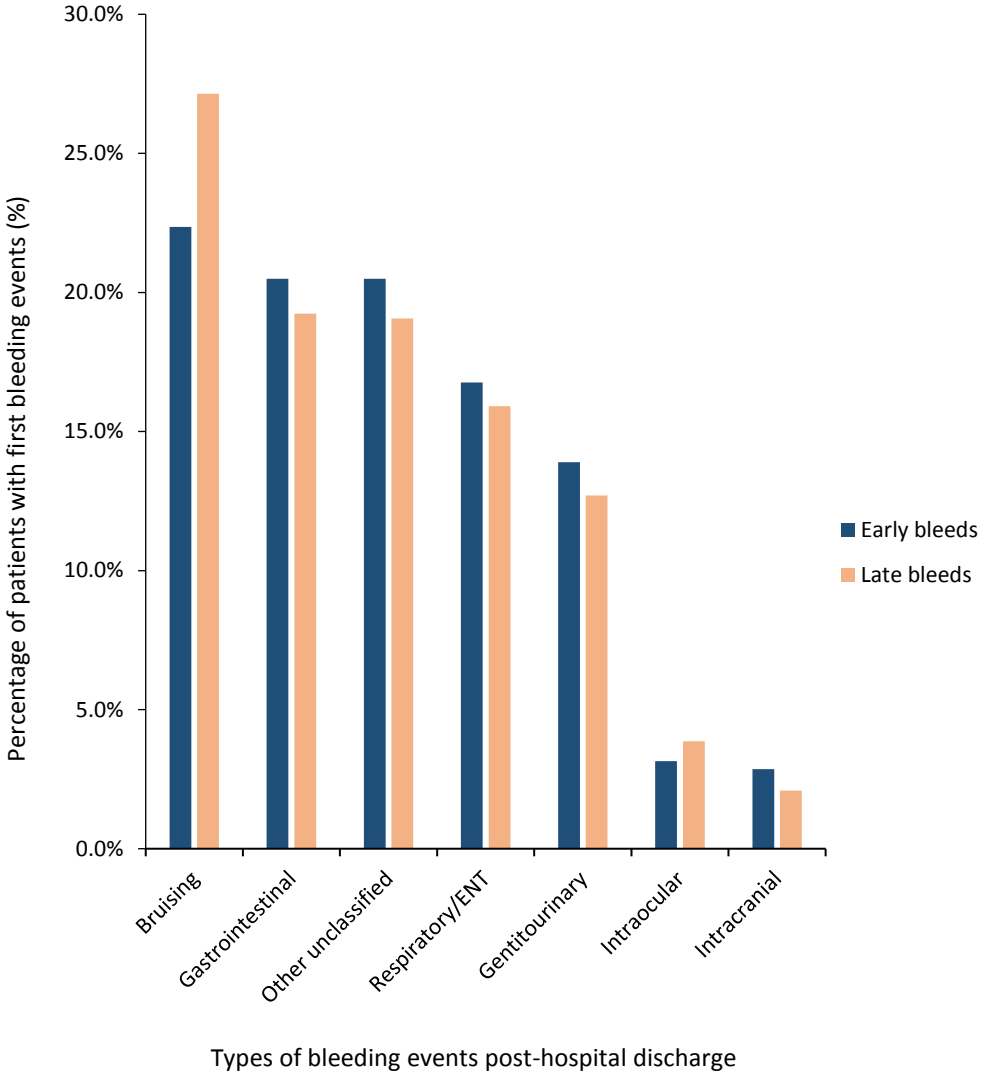


Table 9.3: Crude and adjusted associations between early bleed (compared to late bleed) and all-cause mortality within 30 days after the bleeding event

Exposure	No: of deaths	Unadjusted association		Adjusted for socio-demographic characteristics		Adjusted for socio-demographics, comorbidities and in-hospital procedures		Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics	
	% (n/N)	*OR (95% CI)*	*P-value*	*OR (95% CI)*	*P-value*	*OR (95% CI)*	*P-value*	*OR (95% CI)*	*P-value*
#late bleeds	3.6% (99/2,755)	1.00		1.00		1.00		1.00	
***Early bleeds**	2.9% (20/698)	0.79 (0.50, 1.26)	0.323	0.73 (0.45, 1.16)	0.182	0.74 (0.46, 1.19)	0.215	0.66 (0.42, 1.03)	0.067

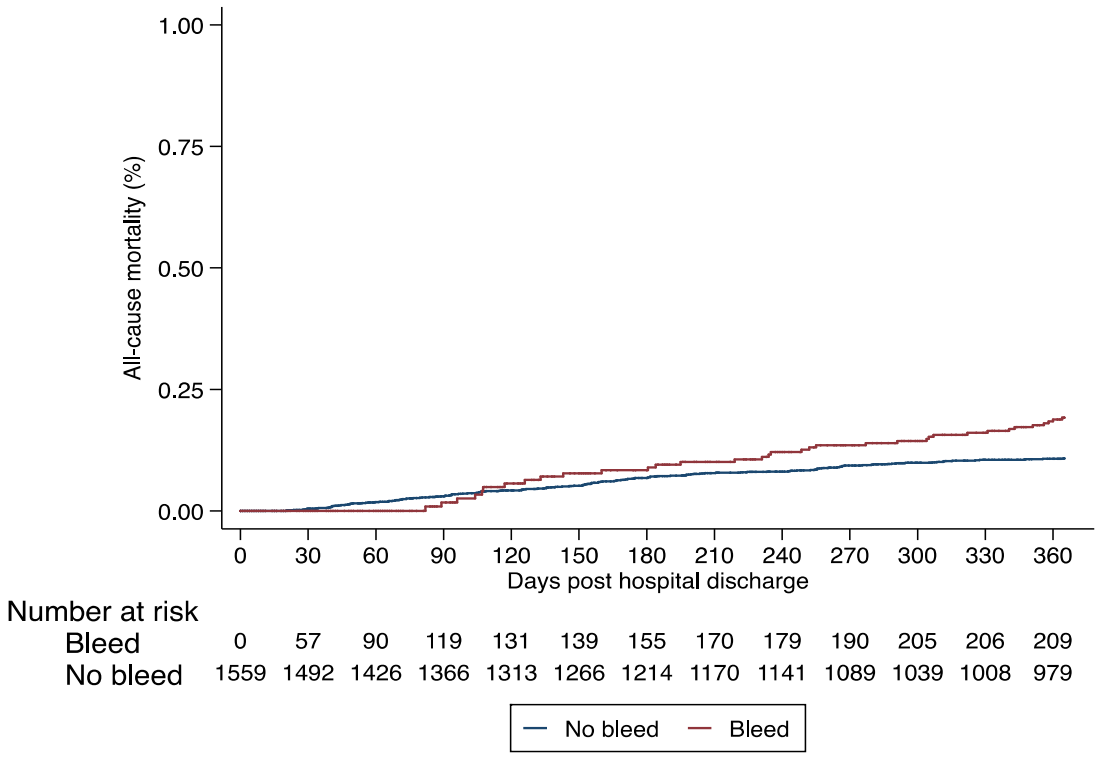
***OR:** Odds ratio, **CI:** Confidence interval, **1.00:** reference category, **No:** Number, #**Late bleeds**: defined as first bleeding events between 31 and 335 days following hospital discharge for ACS, *__Early bleeds__: defined as first bleeding events within the first 30 days following hospital discharge for ACS.*

9.4.3 Subgroup analyses

None of the interaction terms between any bleeding event with age, gender, in-hospital management strategy, and discharge antithrombotic therapy was statistically significant.

Table 9.4 presents the crude and adjusted associations between any bleeding event and all-cause mortality within the first 12 months after hospital discharge for ACS, stratified by age, gender, in-hospital management strategy, and discharge antithrombotic drugs combinations. The exposure of bleeding for the subgroup analysis based on discharge antithrombotic therapy did not satisfy the proportional hazard assumption of the Cox model. For the subgroup of patients on oral anticoagulants, the Kaplan Meier plot in **figure 9.3** reveals that the risk of mortality in the first 100 days after hospital discharge was approximately similar between those that experienced bleeding complications and those that did not, but this risk was higher after the first 100 days in those who experienced bleeding complications post-hospital discharge. Thus, the analysis time for this subgroup of patients was split into the first 100 days and between 101 – 365 days post-hospital discharge.

Figure 9.3: Mortality rate within the first 12 months following hospital discharge among patients discharged on oral anticoagulants stratified by bleeding



9.4.3.1 Age

There was an increased risk of mortality from bleeding in the first 12 months after hospital discharge, regardless of age category. This increased risk of mortality from bleeding was higher in those below the age of 65 years (HR 2.97, 95% CI: 1.94, 4.55) which then decreased slightly with increasing age (66 to 80 years - (HR 1.77, 95% CI: 1.39, 2.24), 80 years and over - (HR 1.61, 95% CI: 1.38, 1.86)).

9.4.3.2 Gender

The increased risk of mortality from bleeding was similar in men (HR 1.77, 95% CI: 1.49, 2.10) and women (HR 1.63, 95% CI: 1.38, 1.93) (**table 9.4**).

9.4.3.3 In-hospital management strategy

There was no difference in the increased risk of mortality from bleeding complications following hospital discharge between those managed with PCI (HR 1.73, 95% CI: 1.19, 2.51) and those who were medically managed (HR 1.67, 95% CI: 1.46, 1.90) during the index ACS hospitalisation stay.

9.4.3.4 Discharge antithrombotic drugs

There may be an increased risk of mortality from bleeding as the number of discharged antithrombotic drugs increases (**table 9.4**). However, the interaction term for these differences in the risk of mortality across the different treatment groups was not statistically significant.

Table 9.4: Crude and adjusted associations between any first bleeding event (by age, gender, in-hospital management strategy, and discharge antithrombotic drug combinations) and all-cause mortality within the first 12 months following hospital discharge

Sub-groups	No: of deaths among those with bleeding events	Mortality rate per 1000 person-years in those with bleed (95% CI)	No: of deaths among those without any bleeding event (Reference group)	Mortality rate per 1000 person-years in those without any bleed (95% CI)	Unadjusted associations		Adjusted for socio-demographic characteristics		Adjusted for socio-demographics, comorbidities and in-hospital procedures		Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics	
	(n/N)		*(n/N)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
***Age**												
≤ 65 years	34/1,079	54 (38, 76)	198/9,309	22 (19, 25)	3.27 (2.27, 4.71)	p<0.001	3.24 (2.22, 4.74)	p<0.001	3.12 (2.10, 4.64)	p<0.001	2.97 (1.94, 4.55)	p<0.001
66 - 80 years	115/1,433	147 (122, 176)	735/8,614	89 (83, 96)	2.01 (1.62, 2.50)	p<0.001	2.04 (1.64, 2.53)	p<0.001	1.81 (1.44, 2.27)	p<0.001	1.77 (1.39, 2.24)	p<0.001
> 80 years	213/1,108	378 (331, 433)	1362/6,117	265 (251, 279)	1.71 (1.48, 1.98)	p<0.001	1.72 (1.49, 2.00)	p<0.001	1.70 (1.46, 1.97)	p<0.001	1.61 (1.38, 1.86)	p<0.001
***Gender**												
Men	196/2,126	170 (147, 195)	1,240/15,729	84 (80, 89)	2.53 (2.14, 2.98)	p<0.001	1.99 (1.69, 2.34)	p<0.001	1.84 (1.55, 2.18)	p<0.001	1.77 (1.49, 2.10)	p<0.001
Women	166/1,494	206 (177, 239)	1,055/8,311	139 (130, 147)	1.82 (1.54, 2.14)	p<0.001	1.77 (1.50, 2.08)	p<0.001	1.74 (1.48, 2.06)	p<0.001	1.63 (1.38, 1.93)	p<0.001

Continuation	No: of deaths among those with bleeding events	Mortality rate per 1000 person-years in those with bleed (95% CI)	No: of deaths among those without any bleeding event (Reference group)	Mortality rate per 1000 person-years in those without any bleed (95% CI)	Unadjusted associations		Adjusted for socio-demographic characteristics		Adjusted for socio-demographics, comorbidities and in-hospital procedures		Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics	
	(n/N)		*(n/N)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
In-hospital management strategy												
Medically Managed	313/2,381	249 (223, 278)	2,008/15,230	144 (138, 151)	2.11 (1.86, 2.40)	p<0.001	1.85 (1.63, 2.09)	p<0.001	1.76 (1.54, 2.00)	p<0.001	1.67 (1.46, 1.90)	p<0.001
PCI	47/1,201	69 (52, 92)	281/8,484	34 (31, 39)	2.62 (1.90, 3.61)	p<0.001	2.20 (1.58, 3.06)	p<0.001	1.84 (1.29, 2.63)	0.001	1.73 (1.19, 2.51)	0.004
Discharge antithrombotic medication												
Single antiplatelet	115/908	224 (186, 269)	665/6,046	117 (109, 127)	2.06 (1.68, 2.53)	p<0.001	1.71 (1.39, 2.11)	p<0.001	1.70 (1.37, 2.11)	p<0.001	1.71 (1.37, 2.12)	p<0.001
Dual antiplatelet	151/2,151	131 (112, 154)	820/14,319	59 (55, 63)	2.37 (1.97, 2.85)	p<0.001	2.03 (1.69, 2.45)	p<0.001	1.92 (1.59, 2.33)	p<0.001	1.91 (1.58, 2.32)	p<0.001
Oral anticoagulant	35/276	237 (170, 330)	145/1,283	117 (100, 138)	2.09 (1.41, 3.08)	p<0.001	2.09 (1.38, 3.17)	p<0.001	1.98 (1.29, 3.06)	0.002	2.00 (1.31, 3.07)	0.001

Continuation	No: of deaths among those with bleeding events	Mortality rate per 1000 person-years in those with bleed (95% CI)	No: of deaths among those without any bleeding event (Reference group)	Mortality rate per 1000 person-years in those without any bleed (95% CI)	Unadjusted associations		Adjusted for socio-demographic characteristics		Adjusted for socio-demographics, comorbidities and in-hospital procedures		Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics	
	(n/N)		*(n/N)*		*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Association of bleeding with all-cause mortality among patients discharged on oral anticoagulants stratified by follow-up time post-discharge												
within 100 days post-discharge	3/276	143 (46, 444)	52/1,283	131 (100, 172)	0.91 (0.29, 2.84)	0.867	0.98 (0.32, 3.01)	0.966	0.87 (0.27, 2.77)	0.817	0.88 (0.27, 2.89)	0.840
between 101 and 365 days post-discharge	32/276	200 (141, 282)	93/1,283	77 (62, 94)	2.43 (1.56, 3.78)	0.000	2.44 (1.51, 3.93)	0.000	2.41 (1.46, 3.97)	0.001	2.37 (1.44, 3.92)	0.001

[*] ***the reference group for each category comprised patients within that category that did not experience any bleeding event within 12 months following hospital discharge, HR:*** *Hazard ratio,* ***CI:*** *Confidence interval,* ***PCI:*** *Percutaneous coronary intervention.*

9.4.4 Sensitivity analyses

The sensitivity analysis revealed that the estimated increased risk of mortality from bleeding in the first 12 months after hospital discharge did not overly differ between the imputed data analysis (HR 1.70, 95% CI: 1.50, 1.92) and the complete case analysis (HR 1.57, 95% CI: 1.34, 1.85) **table 9.5**.

When the analysis was repeated so that patients with multiple bleeding events can move between categories of bleeding severity over time (i.e. from no bleed to non-serious bleed to serious bleed but not the reverse), the increased risk of mortality in patients whose first or only bleeding events post-hospital discharge were non-serious, and in those whose first bleeding events were serious, did not differ to those reported using first bleeding events above (in **table 9.2)**. But, the association of non-serious bleeding events with all-cause mortality did not reach statistical significance in the sensitivity analysis (**table 9.6**). For patients who first experienced a non-serious bleeding event and later sustained a serious bleeding complication, the risk of mortality within the first 12 months following hospital discharge (compared to those with no bleed) was nearly threefold (HR 2.85, 95% CI: 1.48, 5.49).

Table 9.5: Comparison between the result of the main imputed data analysis and those of the complete case analysis (for the outcome of all-cause mortality within the first 12 months following hospital discharge)

Unadjusted associations		**Adjusted for socio-demographic characteristics**		**Adjusted for socio-demographics, comorbidities and in-hospital procedures**		**Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics**	
HR (95% CI)	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
Main imputed data analysis							
2.23 (1.99, 2.50)	p<0.001	1.89 (1.69, 2.12)	p<0.001	1.80 (1.59, 2.03)	p<0.001	1.70 (1.50, 1.92)	p<0.001
Complete case analysis							
2.10 (1.81, 2.44)	p<0.001	1.81 (1.55, 2.10)	p<0.001	1.67 (1.43, 1.96)	p<0.001	1.57 (1.34, 1.85)	p<0.001

HR: *Hazard ratio,* ***CI:*** *Confidence interval.*

Table 9.6: Analysis where multiple bleeding events within the first 12 months following hospital discharge were categorised based on severity

Severity of bleeding event experienced	**Unadjusted association**		**Adjusted for socio-demographic characteristics**		**Adjusted for socio-demographics, comorbidities and in-hospital procedures**		**Adjusted for socio-demographics, comorbidities, in-hospital procedures and pharmacological characteristics**	
	HR (95% CI)	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*	*HR (95% CI)*	*P-value*
No bleed	1.00		1.00		1.00		1.00	
First or only experienced non-serious bleed	1.27 (1.01, 1.61)	0.043	1.13 (0.89, 1.43)	0.323	1.20 (0.95, 1.50)	0.126	1.20 (0.96, 1.51)	0.113
First experienced serious bleed	2.80 (2.46, 3.19)	p<0.001	2.32 (2.05, 2.63)	p<0.001	2.08 (1.81, 2.38)	p<0.001	**1.89 (1.64, 2.17)**	p<0.001
First experienced non-serious bleed followed by a serious bleed	4.71 (2.69, 8.23)	p<0.001	3.34 (1.84, 6.07)	p<0.001	2.88 (1.52, 5.46)	p<0.001	**2.85 (1.48, 5.49)**	p<0.001

HR: *Hazard ratio,* ***CI:*** *Confidence interval,* ***No:*** *Number,* ***1.00:*** *reference category,* ***Bold text:*** *indicates statistically significant associations at the 5% threshold.*

9.4.5 Risk factors for mortality in patients with bleeding complications

All the baseline characteristics included in the model satisfied the proportional hazard assumption. **Table 9.7** presents the crude and adjusted associations between all-cause mortality in the first 12 months (post bleed) and baseline patient characteristics (in patients with a bleed). Generally, after multivariable adjustment, age greater than 65 years, being underweight, history of diabetes, heart failure, cancer, PVD, COPD, and CKD within 2 years prior to hospital discharge were independently associated with an increased risk of mortality in the first 12 months following bleeding events in patients that experienced these bleeding complications post-hospital discharge for ACS. There was also an increased risk of mortality with NSTEMI, and smoking (current smoking) – recorded before hospital discharge in patients that experienced bleeding complications, but these associations did not reach statistical significance. History of hyperlipidaemia, PCI during the index ACS hospitalisation stay, and being overweight were associated with lower risk of mortality post-discharge. The most significant risk factors for all-cause mortality in patients that sustained bleeding complications within the first 12 months after hospital discharge were: advance age > 80 years vs age ≤ 65 years (HR 3.54, 95% CI: 2.42, 5.19), being underweight vs normal weight (HR 2.80, 95% CI: 1.70, 4.60), age 66 - 80 years vs age ≤ 65 years (HR 1.77, 95% CI: 1.22, 2.56), history of heart failure (HR 1.56, 95% CI: 1.20, 2.02), CKD (HR 1.50, 95% CI: 1.18, 1.89), cancer (HR 1.50, 95% CI: 1.16, 1.95), PVD (HR 1.48, 95% CI: 1.00, 2.18), COPD (HR 1.45, 95% CI: 1.20, 1.74), and diabetes (HR 1.39, 95% CI: 1.10, 1.76).

Table 9.7: Characteristics associated with all-cause mortality in the first 12 months post-bleed in patients that sustained bleeding complications following hospital discharge

Characteristics	Unadjusted Associations		Adjusted Associations	
Demographics	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)				
≤65	1.00		1.00	
66 - 80	2.58 (1.86, 3.56)	P<0.001	**1.77 (1.22, 2.56)**	0.002
> 80	6.98 (5.09, 9.55)	P<0.001	**3.54 (2.42, 5.19)**	P<0.001
Female	1.18 (0.98, 1.43)	0.084	0.96 (0.79, 1.17)	0.693
BMI (kg/m^2)				
Normal weight (BMI 18.50 to < 25)	1.00		1.00	
Underweight (BMI < 18.50)	2.45 (1.55, 3.87)	P<0.001	**2.80 (1.70, 4.60)**	P<0.001
Overweight (BMI 25 to < 30)	0.71 (0.57, 0.88)	0.002	**0.78 (0.62, 0.99)**	0.037
Obese (BMI > 30)	0.69 (0.54, 0.89)	0.005	0.87 (0.65, 1.15)	0.328
Smoking Status				
Non-smoker	1.00		1.00	
Ex-smoker	0.99 (0.79, 1.24)	0.93	1.00 (0.78, 1.28)	0.981
Current smoker	0.72 (0.53, 0.97)	0.033	1.23 (0.88, 1.73)	0.230
Comorbidities				
Diabetes	1.59 (1.30, 1.95)	P<0.001	**1.39 (1.10, 1.76)**	0.006
Hypertension	1.15 (0.96, 1.39)	0.123	0.99 (0.82, 1.20)	0.925
Heart failure	2.20 (1.75, 2.77)	P<0.001	**1.56 (1.20, 2.02)**	0.001
Cancer	1.50 (1.17, 1.92)	0.001	**1.50 (1.16, 1.95)**	0.002
PVD	2.07 (1.49, 2.88)	P<0.001	**1.48 (1.00, 2.18)**	0.047
COPD	1.81 (1.52, 2.16)	P<0.001	**1.45 (1.20, 1.74)**	P<0.001
CKD (eGFR < 60 mL/min/1.73 m^2)	2.85 (2.35, 3.46)	P<0.001	**1.50 (1.18, 1.89)**	0.001
Hyperlipidaemia	0.98 (0.82, 1.18)	0.832	**0.74 (0.60, 0.90)**	0.003
History of bleeding	1.62 (1.30, 2.01)	P<0.001	1.18 (0.93, 1.49)	0.170
ACS presentation				
STEMI	1.00		1.00	
NSTEMI	2.70 (1.87, 3.90)	P<0.001	1.37 (0.90, 2.10)	0.143
ACS not otherwise specified	1.67 (1.14, 2.43)	0.008	1.11 (0.72, 1.71)	0.647
In-hospital procedure				
PCI	0.25 (0.19, 0.34)	P<0.001	**0.47 (0.35, 0.63)**	P<0.001
Drug Therapy				
Baseline NSAIDs	0.56 (0.40, 0.77)	P<0.001	0.81 (0.57, 1.14)	0.223
Baseline SSRIs	1.14 (0.83, 1.56)	0.416	1.08 (0.77, 1.51)	0.656
Discharge antithrombotic				
Single antiplatelet	1.00		1.00	
Dual antiplatelet	0.54 (0.44, 0.67)	P<0.001	0.83 (0.66, 1.05)	0.116
Oral anticoagulant	1.02 (0.74, 1.41)	0.906	1.10 (0.79, 1.52)	0.578
No record	1.67 (1.25, 2.23)	0.001	1.25 (0.92, 1.69)	0.158

HR: *subhazard ratio,* ***CI:*** *confidence interval,* ***eGFR:*** *estimated glomerular filtration rate,* ***ACS****: acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,*

NSAID: *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***1.00:*** *reference category,* ***Bold text:*** *indicates statistically significant predictors of bleeding at the 5% threshold.*

9.5 Discussion

9.5.1 Summary of findings

This study reports that bleeding complications post ACS are associated with an increased risk of all-cause mortality in the first 12 months following hospital discharge. This increased risk of mortality depends on the severity and anatomic site of the bleeding event, with intracranial bleeds having the worst prognostic impact. There was an indication that there was no difference in the risk of mortality (within the first 30 days following the bleeding event) between patients who experienced early bleeding events (bleeds within 30 days after hospital discharge) and those experiencing these events at a later time-point post-hospital discharge (bleeds between 31 – 335 days post-hospital discharge). Age greater than 65 years, being underweight, history of cancer, CKD, PVD, COPD, heart failure, and diabetes (recorded in the 2 years prior to hospital discharge) were the most significant risk factors for all-cause mortality within the first 12 months following bleeding events in patients that experienced these bleeding complications post-hospital discharge for ACS.

9.5.2 Interpretation of the association between bleeding and all-cause mortality

The results of this study highlights that post-discharge bleeding events, which have not been given due consideration in the literature, have important prognostic impact on mortality. These bleeding events, as shown in Chapter 7, occur more frequently within the first 30 days after hospital discharge, with the rate of mortality being highest in the 30 days following the bleeding events. This finding of an association between bleeding and mortality in the present study was consistent with those of similar previous studies in the post-discharge setting (Brinkert et al., 2017; Valgimigli et al., 2016). As has been shown in

the descriptive analysis in Chapter 7, 17% of all deaths among patients that experienced bleeding complications in the present study were attributed to bleeding as the primary underlying cause, while in 38%, the underlying cause was recorded as cardiovascular. Thus, suggesting that bleeding complications following hospital discharge may both directly and indirectly impact on mortality (**figure 9.4**).

One of the novel findings of this study was that non-serious bleeding events, which have been ignored in the majority of previous studies, appeared to have important albeit modest prognostic impact on mortality. Although, this increased risk of mortality was only observed with nose bleeds and not bruising or sub-conjunctival bleeds. This type of bleeding event may not directly result in death, but the intervening events often employed to address the underlying root cause of these bleeds may themselves result in mortality. In patients with non-serious bleeds (and at times serious bleeds), antithrombotic medication is sometimes discontinued, or the patient may voluntarily discontinue medication (Armero et al., 2011; Jura-Szołtys and Chudek, 2011; Roy et al., 2008). Discontinuation of antiplatelet therapy results in rebound platelet reactivity which increases the risk of stent thrombosis in patients managed with PCI (due to incomplete stent endothelialisation) (Huczek et al., 2013; McFadden et al., 2004). Stent thrombosis is a strong predictor of MI and death in patients with ACS (Dangas et al., 2012; Sandhu et al., 2007). Patients that sustained bleeding complications and discontinued antiplatelet medication have been shown to have higher rates of mortality than those who bled but continued antiplatelet therapy (Spencer et al., 2007).

Another novel finding of this study was in the assessment of the prognostic impact of site-specific bleeding events on all-cause mortality. The study found that the greatest risk of mortality from bleeding was in patients that experienced intracranial bleeds following

hospital discharge. It is intuitive that these types of bleeding events are severe and often instantaneously result in death (Kwok et al., 2015), which highlights the importance of identifying patients who are vulnerable for this type of bleeding complications following hospital discharge. Gastrointestinal and respiratory bleeding events were the second most important predictors of mortality post-hospital discharge for ACS. As in the case of intracranial bleeding events, the more severe forms of these types of bleeding complications such as massive gastrointestinal bleeds are also likely to directly result in death (Kwok et al., 2015).

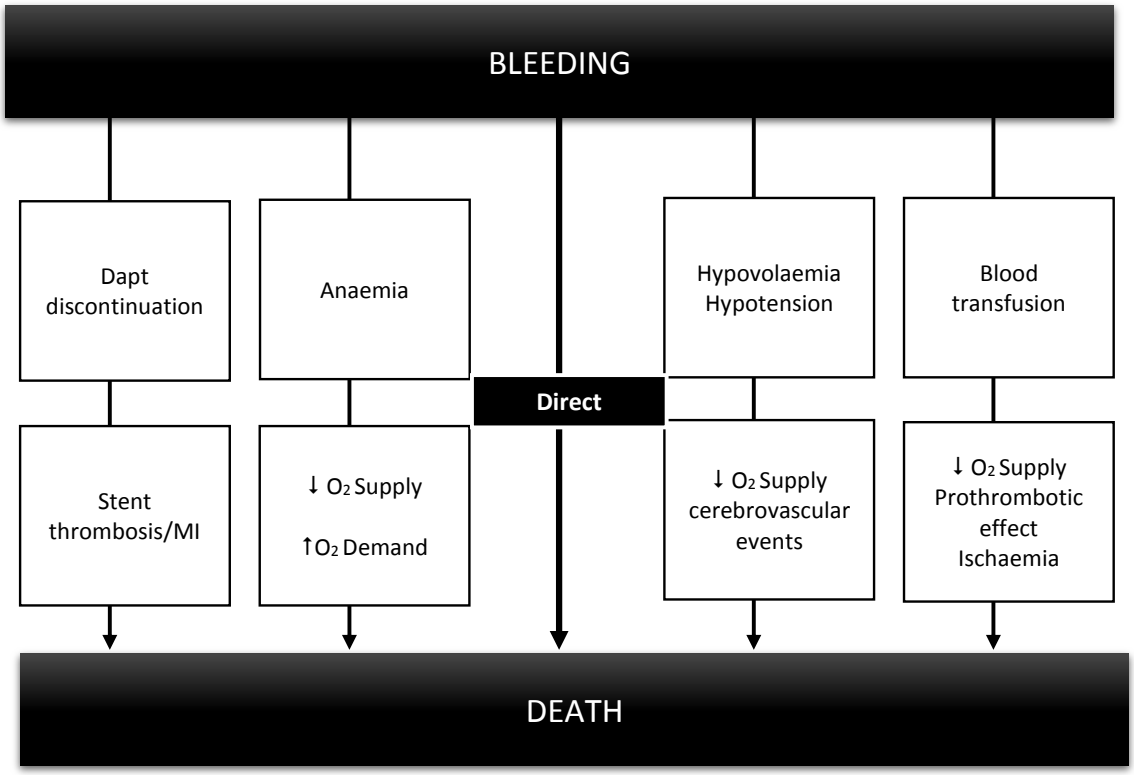
Besides the direct impact of bleeding on mortality, bleeding may also influence death via indirect pathways (Doyle et al., 2009; Fitchett, 2007; Rao, 2015). Bleeding may cause hypovolaemia, hypotension, and anaemia, which often results in reduced myocardial oxygen supply. In response, reflex tachycardia is initiated to maintain adequate systemic oxygenation, which simultaneously increases myocardial oxygen demand (Bassand, 2007). This causes an imbalance between myocardial oxygen demand and supply, which results in/or exacerbate pre-existing coronary ischaemia and increases the risk of mortality (Bassand, 2007). Anaemia secondary to bleeding influences the synthesis and release of erythropoietin. Erythropoietin contributes to a systemic prothrombotic state via platelet activation and induction of plasminogen activator inhibitor-1 (Doyle et al., 2009), which has been associated with increased risk of thrombosis, MI and death in patients with ACS (Najjar et al., 2011; Ott et al., 2010).

Another potential explanation for the bleeding-mortality association is blood transfusion. Bleeding causes haemodynamic compromise, and to maintain haemodynamic stability, transfusion of whole blood or packed red blood cells appears to be the most readily available solution. In the ACS setting, receipt of blood transfusion has been linked with

increased risk of mortality (Chatterjee et al., 2013; Rao et al., 2004). Mortality as a result of blood transfusion may occur via a number of mechanisms, including the prothrombotic effects mediated through platelet release of CD40 ligand and induction of plasminogen activator inhibitor-1 (a pro-coagulant protein) (Doyle et al., 2009; Twomley et al., 2006). Increasing haemoglobin via transfusion increases oxygen delivery, but the uptake of oxygen by tissues either decreases or does not change partly due to haematological alterations of red blood cells which causes plugging of transfused cells at the microvascular level, leading to ischaemia (Doyle et al., 2009). Nitric oxide produced by vascular endothelium and transported by red blood cells act as inhibitors of platelet activation (Twomley et al., 2006). Impaired nitric oxide delivery and release by transfused red blood cells may increase the risk of thrombosis at sites of endothelial dysfunction (Doyle et al., 2009).

Furthermore, the elderly nature of the present study population means that these cohorts of patients are likely frail, with higher prevalence of unmeasured comorbidities. Whilst these patients will be more prone to bleeding complications (as demonstrated in Chapter 8), they are also more likely to die from other causes, and bleeding may have been a marker for severe illness.

Figure 9.4: Potential mechanisms underlying the association between bleeding complications and all-cause mortality



Dapt; *dual antiplatelet,* ***O_2;*** *Oxygen,* ***MI;*** *myocardial infarction*

9.5.3 Early vs late bleeds

The comparison between early and late bleeding events showed that there was no significant difference in risk of 30-day mortality between the two groups. However, the effect estimate (HR: 0.66) suggests that those who experienced late bleeding events may have an increased risk of mortality than those experiencing these events earlier (within the first 30 days post-discharge). In patients that experienced late bleeding events, 56% of all deaths were bleeding related compared to only 25% in those experiencing early bleeds. It can be speculated that the (non-significant) difference in risk of mortality may have been due to differences in the severity of bleeding, with late bleeding events being

more likely serious than early bleeding events. However, due to small number of events, this finding will need to be further investigated in future studies.

9.5.4 Sensitivity analysis

The finding from the sensitivity analysis revealed that patients who first experience a non-serious bleed and later sustained a serious bleeding event had nearly threefold increased risk of mortality. The reason for this finding remain difficult to explain, but having more than one bleeding event is likely to be a marker for frailty and other severe illnesses which may not have been accounted for in the multivariable analysis.

9.5.5 Risk factors for all-cause mortality

Another novel finding of this study was in reviewing the risk factors for all-cause mortality in patients that experienced bleeding complications following hospital discharge, which indicated that the risk factors for all-cause mortality (such as age greater than 65 years, history of PVD, COPD, and cancer) have some overlap with those reported for bleeding complications (in Chapter 8). Thus suggesting that, for this patient population, the risk of mortality is even more amplified in the presence of both bleeding and these baseline characteristics. Using these baseline risk features, longer-term management strategy can be optimised based on individual patient risk profile so that the future risk of bleeding complications can be mitigated in this subgroup of patients.

9.5.6 Strengths and limitations

This is the first EHR-based study to examine the independent effect of different types of bleeding events on all-cause mortality within a primary care setting. The study is the first

to show that non-serious bleeding events (mainly nose bleeds), which have often been ignored in previous studies, have an important prognostic impact on mortality. The study goes beyond examining the associations of bleeding with mortality by further exploring the independent risk factors for mortality in patients that experienced bleeding complications.

The findings of this study ought to be interpreted in light of some limitations. First, the observational design of the study does not preclude residual confounding from unmeasured patient factors such as frailty. In patients with multiple types of bleeding events, the study assumed that the effect of a first bleed remained constant over the duration of follow up, regardless of whether the patient had subsequent bleeding events. However, a sensitivity analysis was carried out which allowed patients with multiple bleeding events to change status on bleeding severity over time. That is to say, a patient with multiple bleeds may change status from no bleed to non-serious bleed to serious bleed (or no bleed to serious bleed) but not in the opposite direction. This sensitivity analysis showed similar results to the analysis using first bleeding events for patients with a bleed. However, patients who first experienced a non-serious bleed and later develop a serious bleed had the greatest risk for mortality. The study was not adequately powered to detect the independent associations of intracranial and intraocular bleeding events with all-cause mortality. Although the study found an association between bleeding and all-cause mortality, this relationship is unlikely to be causal given the complex interplay between comorbidities, bleeding, and all-cause mortality. Due to immortal time bias, the prognostic impact of bleeding on all-cause mortality by time from the bleeding event was not assessed. Multiple statistical tests of associations were carried out, and the possibility that some findings may be due to chance cannot be excluded.

9.5.7 Conclusion

Using a large EHR database, this study found that longer-term bleeding events are associated with an increased risk of all-cause mortality in the first 12 months after hospital discharge for ACS. This increased risk of mortality was, however, greatest in patients that experienced intracranial bleeding events post-hospital discharge. Patients who experienced gastrointestinal and respiratory bleeding events are also at increased risk of mortality following hospital discharge. While some bleeding events (such as intracranial bleeds) may have direct impact on mortality, the link between other serious bleeding events and non-serious bleeds with mortality remain ambiguous. Future studies will need to explore this relationship further.

The next chapter summarises and discussed the overall findings of the thesis and their implications for clinical practice and research.

Chapter 10.0: **Discussion**

10.1 Introduction

This thesis investigated the incidence, timing, and types of bleeding complications following hospital discharge post ACS and identified the baseline patient characteristics that are associated with increased risk of these bleeding events. The association of these bleeding events with the adverse outcome of all-cause mortality was also examined. This chapter, therefore, reviews these overall findings, the strengths and limitations of the thesis, and the implications of these findings for clinical practice and future research.

10.2 Summary of key findings

10.2.1 *Systematic review of the incidence, timing, and types of bleeding complications after hospital discharge following ACS, and their prognostic impact on mortality, MACE, re-infarction, and rehospitalisation*

The overall findings from the systematic review are discussed in detail in Chapter 3. The review identified that bleeding complications following hospital discharge post ACS are common, but there was wide variation between the included studies in terms of length of follow up, the severity of the bleeding examined, type of bleeding examined, type of ACS presentation examined, patient characteristics, and discharge antithrombotic regimens. The majority of studies did not report on the incidence of bleeding, but rather episodes of bleeding had to be extracted from individual studies to calculate the incidence figures. In the majority of these studies that reported on the episodes of bleeding events, it was unclear whether patients were counted more than once if they had more than one episode of bleeding, and the calculated incidence figures did not take into account time at

risk. There was some limited evidence that bleeding events occurred more frequently in the first three months after hospital discharge, with bruising and gastrointestinal bleeds the most common, while intracranial bleeds were relatively rare. There was also an indication based on the calculated incidence figures that whilst bleeding may be common in the first three months after hospital discharge, these bleeding events might continue to occur for more than a year, with the majority of the bleeding events being more likely minor and nuisance bleeds, although, the evidence pool was very limited. There was some evidence that major bleeding may increase the risk of mortality following hospital discharge, but the strength of the evidence was weak. Nuisance bleeding events defined as BARC 1 bleeds did not increase the risk of mortality in one study. However, there was an indication that bleeding may increase the risk of MACE in two studies and re-hospitalisation in another study.

10.2.2 *Defining bleeding complications following ACS in primary care (a CiPCA pilot study)*

A comprehensive list of 380 Read codes was used to define bleeding in primary care, developed through the consensus of an Interventional Cardiologist and three GPs with experience of using Read codes in both the research and primary care consultation settings. This definition was subsequently used to address the main objectives of the thesis.

10.2.3 *Incidence, timing, and types of bleeding and mortality following hospital discharge for ACS*

The analysis of 27,660 patients with an ACS record between 2006 and 2016 within a large UK national primary care database, with linkage to secondary care and mortality records revealed that bleeding complications presented to primary care following ACS were common and occurred in more than 1 in 10 patients post-hospital discharge. These bleeding events were more frequent in the first 30 days following hospital discharge. Bruising and gastrointestinal bleeds were the more commonly reported types of bleeding events post-discharge, while intracranial bleeds were generally rare. Mortality rate was higher among patients that experienced bleeding complications (than in those who did not) within the first 12 months after hospital discharge and highest in those experiencing intracranial bleeds. Mortality in those that experienced bleeding complications occurred more frequently in the first 30 days following the bleeding event. Among those that died within the first 12 months after hospital discharge, bleeding was the primary cause of death in 2.4% of patients, while cardiovascular and non-cardiovascular/non-bleeding causes accounted for 54.5% and 43.1% respectively.

10.2.4 *Determining the independent risk factors for bleeding following hospital discharge post ACS*

The independent risk factors for bleeding within the first 12 months after hospital discharge for ACS are described in detail in Chapter 8. Generally, patients that had a history of bleeding complication in the 2 years prior to hospital discharge, those aged 80

years and over (compared to those ≤ 65 years old), and those discharged on oral anticoagulants were more likely to bleed in the first 12 months after hospital discharge for ACS. Women (compared to men), those between the ages of 66 and 80 years (compared to those ≤ 65 years old), those with a history of PVD, COPD or those managed with PCI during the index ACS hospitalisation stay were also more vulnerable to bleeding complications in the first 12 months after discharge. These characteristics were also independent risk factors across different severities and types of bleeding events, and in sub-groups of patients, but with some variations. For example, women were more likely to report bruising than men, while patients with a history of cancer (compared to those without) were more likely to experience respiratory and gastrointestinal bleeds following hospital discharge.

10.2.5 *Determining the prognostic impact of bleeding on all-cause mortality following hospital discharge post ACS*

The multivariable analysis in Chapter 9 indicated that the risk of mortality within the first 12 months following hospital discharge for ACS was significantly higher in patients that experienced bleeding complications than in those who did not experience any bleeding event within the same period, even after adjustment for multiple important confounders. This increased risk of mortality depends on the severity and anatomic site of the bleed, with the risk being greater in those that experienced intracranial bleeds. The risk of mortality within 12 months after discharge was also higher in patients that experienced gastrointestinal and respiratory bleeding events. There was no difference in risk of mortality (mortality measured within 30 days after the bleeding event) between patients

that sustained early bleeding events (bleeds within 30 days after hospital discharge) and those experiencing these events first at a later time-point post-hospital discharge for ACS (bleeds between 31 and 335 days post-hospital discharge).

10.3 Comparison with previous research

Comparison of the findings from this thesis to those of previous research need to be considered in the context of some differences in relation to the definition of bleeding used, length of follow up, patients characteristics, study design, and the ACS management strategies employed between the studies reported in this thesis and previous studies.

10.3.1 Incidence of bleeding

The finding from this thesis showed that bleeding complications were common and occurred with an incidence of 13% within the first 12 months following hospital discharge for ACS. As shown in the systematic review in Chapter 3, the incidence of bleeding within the first 12 months following hospital discharge in previous studies varied between 0.2% and 37.5%. The 13% reported in this thesis, although falling within the range reported in the systematic review, appears to be lower than what has been reported in some studies (identified in the review) with similar length of follow up (Amin et al., 2013; Lattuca et al., 2016). The reason for these differences in findings may be due to differences in the method used to ascertain bleeding events between the present study and these previous studies. In the study by Amin et al and Lattuca et al, bleeding events were ascertained based on patient self-reports during interviews. Patients that had experienced bleeding events in these studies may be more likely to recall previous events, and also report on minor and nuisance bleeds such as bruising and nose bleeds. In the present study,

bleeding was ascertained based on diagnostic records within primary care EHR. Thus, minor and nuisance bleeding events, which did not cause patients to seek medical advice, or those that resulted in death but were not recorded as the primary cause of death will not have been captured in patients' primary care records. This means that the true incidence of post-discharge bleeding may be higher than what has been reported in this thesis.

In secondary care (in-hospital setting), the reported incidence of major bleeding varied between 1% and 10% in RCTs (Rao et al., 2007; Stone et al., 2006; The PURSUIT Trial Investigators, 1998; Yusuf et al., 2006), and between 2.8% (Spencer et al., 2007) and 11% (Amlani et al., 2010) in observational studies. However, the emphasis in the majority of these studies has been on major bleeding events. In the PURSUIT and SYNERGY trials (The PURSUIT Trial Investigators, 1998; Vavalle et al., 2013) which incorporated minor/nuisance bleeds in the definition of bleeding used, the reported incidence of (in-hospital) bleeding were 26% and 37% respectively. These reported incidence for in-hospital bleeding alongside the results from this thesis highlights that bleeding complications are more common in the early phase of treatment (in the in-hospital setting), and these bleeding events continue to occur after discharge.

10.3.2 Types/sites of bleeding

In contrast to previous studies (Généreux et al., 2015; Moscucci et al., 2003; Valle et al., 2016) which highlighted the gastrointestinal tract as the most common site of bleeding in both the secondary and primary care settings, the present study found that bruising was the most common, followed by gastrointestinal bleeds. However, it should be noted that minor and nuisance bleeding events especially bruising have not been reported in

previous studies. The fact that both bruising and gastrointestinal bleeds were the more common types of bleeding events after hospital discharge reflects the likelihood that this patient population had to remain on guideline-recommended dual antiplatelet therapy with mostly aspirin and clopidogrel, thus, reflecting the adverse effect of longer-term exposure to these drugs.

10.3.3 Time of bleeding

Previous studies which combined ACS patients and those with stable coronary artery disease have highlighted the first 30 days following hospital discharge as the period for greater vulnerability for bleeding complications (Généreux et al., 2015; Valle et al., 2016). The finding from the present study add granularity and confirms the findings of these studies. However, the reason why bleeding may cluster in the early phase of hospital discharge warrants further investigation. It can be speculated that baseline patient characteristics may contribute to the clustering of bleeding in this period. For example, management with antithrombotic drugs may unmask undiagnosed conditions such as gastroduodenal ulcers and occult malignancy in gastrointestinal tract, which is likely to occur in the early phase of treatment. The characteristics of patients that increase the risk of bleeding in this period have been identified and discussed in Chapter 8. Individualising discharge antithrombotic therapy to fit individual patient risk profile may mitigate the increased risk of bleeding in this period.

10.3.4 Risk factors for bleeding

The independent risk factors for any bleeding event identified in the analysis in this thesis are reported and compared with those from previous studies of in-hospital and post-

discharge bleeding in Chapter 8 tables 8.9 and 8.10. The characteristics found to be strongly associated with any bleed are discussed herein.

The analysis in this thesis revealed that patients over the age of 65 years (compared to those aged 65 years and under) were more likely to experience bleeding complications in the first 12 months after hospital discharge. This finding was consistent with the results of previous studies in both the secondary and primary care settings which showed a similar trend with bleeding as age increases (Alfredsson et al., 2017; Costa et al., 2017; Moscucci et al., 2003; Raposeiras-Roubín, Faxén, et al., 2018; Yeh et al., 2016). This increased risk of bleeding with age is likely the synergistic effect of several factors such as frailty, anatomical changes in blood vessels and other comorbid conditions such as haemophilia and Von Willebrand disease which have not been accounted for in this thesis or in the previous studies. Therefore, based on the finding from this thesis and those of previous studies, closer monitoring of this elderly sub-group of patients is warranted.

Another important finding from the analysis in this thesis was that patients who had a history of bleeding complication within 2 years before hospital discharge were more likely to experience bleeding following hospital discharge. A similar finding has been reported in the GRACE registry (Moscucci et al., 2003) and from a previous study of patients managed with PCI during the index ACS hospitalisation stay (Valle et al., 2016). Among the 3,620 patients that experienced bleeding complications in the first 12 months after hospital discharge in this thesis, 21% had a history of bleeding within 2 years prior to hospital discharge, of which 8% consulted with the same type of bleeding event post discharge, while the remaining 13% consulted with a different type of bleed.

Having an indication for oral anticoagulant has been an exclusion criterion in most contemporary studies of bleeding in the in-hospital setting (Mehran et al., 2010;

Subherwal et al., 2009). However, the analysis in this thesis has shown that having an indication for oral anticoagulant need to be taking into account when assessing the risk of post-discharge bleeding events. Similar studies within the post-discharge setting (albeit with mixed cohort of patients with ACS and stable angina) have likewise highlighted oral anticoagulant as a strong predictor of bleeding complications (Baber et al., 2016; Buresly et al., 2005; Généreux et al., 2015; Valle et al., 2016). The analysis in this thesis has also shown that, history of COPD, which has not been examined in previous studies, is an important predictor of bleeding complications following hospital discharge. The potential mechanism underlying this association has been described in detail in Chapter 8. This important and novel finding suggests that COPD need to be included in future studies evaluating the risk of bleeding complications.

10.3.5 Prognostic impact of bleeding on all-cause mortality

The analysis reviewing the prognostic impact of bleeding on all-cause mortality showed that patients who sustained either serious or non-serious bleeding events have an increased risk of mortality following hospital discharge. Although, the increased risk of mortality with non-serious bleeds was only observed with nose bleeds and not bruising or sub-conjunctival bleeding events. As demonstrated in the systematic review in Chapter 3, there have not been many studies that have examined the prognostic impact of post-discharge bleeding events on mortality, and of the few that did, the emphasis has been on major bleeding events. Therefore, the finding in this thesis that non-serious bleeding events (mainly nose bleeds) may be associated with an increased risk of mortality following hospital discharge is novel but need confirmation in future studies.

In reviewing the prognostic impact of site-specific bleeding events, the analysis in this thesis revealed that the risk of mortality following hospital discharge was higher among patients that experienced gastrointestinal and respiratory bleeding events, and highest in those experiencing intracranial bleeds. This finding was consistent with the result of a systematic review of in-hospital bleeding events (Kwok et al., 2015), which similarly showed that the risk of mortality was much more pronounced in those experiencing intracranial bleeds. Thus, indicating that of all anatomic sites, bleeds emanating from the intracranial cavity have the worst prognostic impact on mortality, which also highlights the importance of identifying patients with high-risk features for these types of bleeding events at the time of hospital discharge. There have not been studies (to the author's knowledge) that have examined the prognostic impact of site-specific bleeding events in the post-discharge setting, which makes the finding in this analysis novel, and adds to the literature around bleeding complications in the post-discharge arena.

10.4 Strengths and limitations

Strengths and limitations pertinent to each objective of the thesis are described in the relevant chapters where these objectives were addressed. The overall strengths and limitations of the thesis are discussed herein.

10.4.1 Strengths

One of the strengths of this thesis was the definition of bleeding used, which included minor and nuisance bleeding events. Nuisance bleeds especially have been excluded in the majority of formal definitions (such as TIMI, GUSTO and GRACE) (Bovill et al., 1991; Moscucci et al., 2003; The GUSTO Investigators, 1993). Their inclusion in the definition

used in this thesis has made it possible to examine whether these types of bleeding events are also associated with adverse outcome events.

Another key strength of the analyses presented in this thesis relates to the use of the CPRD database, thus, allowing the analysis of a large cohort of ACS patients in primary care, with linked secondary care and mortality data. The CPRD is broadly representative of the UK population (Herrett, Thomas, et al., 2010), which implies that the findings from the analyses in this thesis are generalisable to the wider English ACS population in primary care. Previous contemporary studies have either excluded patients with indications for oral anticoagulants or were RCTs or have been carried out in the PCI setting where the majority of the patients were those with stable coronary artery disease and other unspecified cardiovascular diseases (Baber et al., 2016; Costa et al., 2017; Généreux et al., 2015; Subherwal et al., 2009; Valle et al., 2016; Yeh et al., 2016). The inclusion of only high-risk ACS patients in the analyses in this thesis irrespective of discharge antithrombotic medication, type of ACS presentation, and in-hospital management strategy further enhances the generalisability of the findings of this thesis to the wider post ACS population within primary care. The emphasis in the majority of previous studies has been on in-hospital or 30-days bleeding events. These studies only provided a snapshot of bleeding complications. The longer-term longitudinal follow up of patients in the analyses in this thesis gives more detailed information on the incidence and prognostic impact of bleeding on adverse outcomes within the real-world setting.

An additional key strength of this thesis lies in the study design used. The cohort design employed in addressing the objectives of the thesis has allowed temporality to be established between the exposures and outcomes investigated. The definitions for the majority of exposures, outcomes, and covariates in this thesis have been based on coded

diagnoses in patients primary care record (CPRD). Read code lists used for these definitions have been based on code lists used in previous studies and have been cross-validated by a GP within the Research Institute. Coding of diagnoses for morbidities and conditions within the CPRD database has been shown to have high validity (Herrett, Thomas, et al., 2010; Khan, Harrison, et al., 2010).

10.4.2 Limitations

The findings from the analyses in this thesis ought to be interpreted in light of some limitations. First, the definition of bleeding was based on clinical parameters, as opposed to both clinical and laboratory parameters, or receipt of blood transfusion. Therefore, bleeding events which have been recorded as a drop in haemoglobin or as a receipt of blood transfusion may not have been captured in the definition used. However, evidence has shown that bleeding events assessed based on clinical parameters are more robust than those assessed using laboratory parameters (Rao et al., 2006). Classifying bleeding by severity (serious and non-serious bleeds) was based on the typical nature of the bleeding event and the clinical judgement of a GP, as opposed to using both clinical and laboratory parameters, or receipt of blood transfusion data. It was therefore not possible to assess the magnitude of the severity of each bleeding event, and the results of analyses based on the severity of bleeding (serious and non-serious bleed) should be viewed as exploratory and hypothesis-generating.

Reporting bias is a likely cause for concern in this thesis as not all patients who experienced minor or nuisance bleeding events (such as nose bleeds and bruising) will seek medical advice or have this recorded in their medical records. Similarly, not all deaths as a result of bleeding will be recorded with bleeding as the primary underlying

cause. This may have resulted in the under-estimation of bleeding events and possibly the attenuation of associations between bleeding and all-cause mortality. There may also be confounding by indication, with patients deemed to be at higher risk of bleeding discharged on single antiplatelet or not given any antithrombotic medication at the time of hospital discharge. However, this may have represented situations where risk assessment (based on clinical judgement) may have been carried out prior to the initiation of antithrombotic therapy.

The impact of dosage and duration of discharge antithrombotic drugs on subsequent risk of bleeding has not been explored in the analyses in this thesis, and risk of bleeding may likely increase as the dosage and duration of discharge antithrombotic drugs increases. However, with any retrospective EHR analysis of medication use, there is uncertainty on whether patients with recorded prescriptions for these antithrombotic drugs are actually taking these medications or not. Similarly, the impact of factors such as frailty, history of gastroduodenal ulcer, and genetic factors such as haemophilia and Von Willebrand disease on the future risk of bleeding has not been assessed, and these factors are likely to increase a patient's risk of bleeding. The more potent antiplatelets namely, prasugrel and ticagrelor, and the newer oral anticoagulants such as dabigatran, rivaroxaban and apixaban became available during the study period. However, the majority of the patients (90%) in this thesis were treated with aspirin, clopidogrel or warfarin post-hospital discharge. Therefore, the generalisability of the findings in this thesis onto patients treated with the more potent antiplatelets or the newer oral anticoagulants is uncertain. The majority of the baseline patient characteristics in the analyses in this thesis were defined as last recorded measurement or status prior to the date of hospital discharge. However, these baseline characteristics (such as BMI) may vary or a patient status may

change over the course of the study follow up period, and this variation or change in status has not been accounted for in the analysis in this thesis.

Another limitation of this thesis lies in the fact that some patients had incomplete data on key variables such as smoking and BMI. However, multiple imputation has been carried out to address data missingness, and results of both the complete case analysis and the imputed data analysis have shown congruity. The absence of a relevant Read code for a condition or morbidity in patient primary care record was assumed to imply the absence of that condition/morbidity in this thesis. This may have resulted in the misclassification of some patients. Misclassification of patients may have also occurred as a result of variation in coding practices between GPs, as some GPs might record diagnosis and bleeding as free text and not necessarily using the relevant Read code during patient consultations, and CPRD does not provide free text data for research purposes due to patient confidentiality issues. Similarly, patient contacts with secondary care are manually entered into patient's primary care record. Some of these information such as diagnoses may have been recorded very infrequently or not at all. Likewise, secondary care prescriptions and over the counter medication use (such as aspirin) may not have been recorded at all in patients primary care record.

10.5 Clinical implications of research findings

The findings in this thesis have some important messages for clinicians who are the main point of contact for patients with ACS, and who have been entrusted with the responsibility of making key decisions in selecting the most optimal management strategy for individual patients post ACS.

One of the key findings in this thesis was that bleeding complications following hospital discharge were common, with bruising and gastrointestinal bleeds the most common. In the context of bruising, these types of events are unlikely to be serious or directly result in adverse outcomes such as mortality (as demonstrated in Chapter 9). Therefore, the discontinuation of guideline-recommended antithrombotic therapy in the presence of bruising events should be avoided. In the case of gastrointestinal bleeds, predisposing risk factors for these types of bleeding events are reported in Chapter 8 table 8.5. For patients presenting with these risk features such as those over the age of 80 years, with a history of bleeding, and COPD, selecting an antithrombotic regimen which has less gastrointestinal toxicity (such as clopidogrel as opposed to aspirin) may mitigate the excess risk of these types of bleeding events following hospital discharge. For those who are managed with PCI, who do not have an indication for oral anticoagulants, and are at lower risk for ischaemic events, restricting dual antiplatelet therapy to a maximum period of 1 month after hospital discharge followed by single antiplatelet therapy with clopidogrel may further reduce the incidence of these types of bleeding events. This management strategy has been shown to have a more favourable safety profile in the [20]STOPDAPT-2 trial with the caveat that only 38% of the study population were ACS patients (Watanabe et al., 2019).

Proton pump inhibitors have been shown to effectively reduce upper gastrointestinal bleeding events and have been advocated by ESC guidelines for the management of patients with ACS who have a history of these types of bleeding events and in whom dual antiplatelet therapy is indicated (Ibanez et al., 2017; Roffi et al., 2016). However, in the

[20] Short and optimal duration of dual antiplatelet therapy after everolimus-eluting cobalt chromium stent

analysis in this thesis, 40% of patients with high-risk features for these types of bleeding events had not been prescribed proton pump inhibitors upon hospital discharge. Similar evidence has shown that more than half of ACS patients who have an indication for proton pump inhibitors are not prescribed such prophylaxis at the time of hospital discharge (Badar et al., 2013). Therefore, greater awareness among clinicians regarding the appropriate use of gastrointestinal prophylaxis in this patient population may reduce the incidence of these types of bleeding events following hospital discharge.

The first 30 days following hospital discharge for ACS was identified as the period for greater vulnerability for bleeding complications, which has resulted in identifying the independent risk factors for bleeding in this period (risk factors reported in Chapter 8 table 8.5). However, this period also represents the time when the risk of adverse ischaemic events will likely be higher among patients (Crimi et al., 2019; Giustino et al., 2017). Therefore, striking the right balance between safety and efficacy in relation to discharge antithrombotic regimen in this period is a very important yet complex issue. Notwithstanding this complexity, in patients presenting with high-risk features for bleeding within this period, who are at lower risk for ischaemic events, management with a less potent antiplatelet such as clopidogrel which have a more favourable safety profile than prasugrel or ticagrelor may reduce the risk of bleeding events (Wallentin et al., 2009; Wiviott et al., 2007). Likewise, the use of the lowest most effective dosage of antithrombotic drugs for the secondary prevention of ischaemic events may also reduce the frequency of bleeding in this period. But overall, given the complexity of balancing the risk of bleeding and ischaemic events in this period, deciding on the most optimal antithrombotic course for individual patients should always be accompanied by clinical judgement.

A key finding from reviewing the risk factors for bleeding in this thesis was that patients aged 80 years and over, and those who had a history of bleeding in the 2 years prior to hospital discharge were more vulnerable to all types of bleeding events (except bruising) following hospital discharge. In the context of those aged 80 years and over, this sub-group of patients represents the frailest individuals who are more likely to also have a higher prevalence of comorbidities (resulting in polypharmacy) or receive excessive doses of antithrombotic drugs (Alexander et al., 2005). The baseline characteristics of this patient population which increase their risk of bleeding following hospital discharge has been described in Chapter 8 table 8.6. Hence, for patients presenting with these risk features, emphasis on selecting the most appropriate dosage, combination, and duration of antithrombotic drugs are paramount in reducing the risk of bleeding complications. Co-prescribing of drugs that increases the risk of bleeding (such as NSAIDs and steroids) should be limited or completely avoided in this patient population.

Patients with an indication for oral anticoagulant following hospital discharge had an increased risk of respiratory, genitourinary, intraocular, and intracranial bleeding events. The majority (92%) of the patients with an indication for oral anticoagulants in this thesis were managed with warfarin. Newer oral anticoagulants such as dabigatran and apixaban have a more favourable safety profile than warfarin (Connolly et al., 2009; Granger et al., 2011). Replacing warfarin with the newer oral anticoagulants in this patient population may reduce the risk of bleeding following hospital discharge. Vessel endothelialisation has been shown to be more rapid with second generation drug-eluting stents such as everolimus-eluting stents (Joner et al., 2008). For patients who have an indication for oral anticoagulants, who also require coronary artery stenting, management with these types of stents or the newer third generation stents (such as Bio Freedom biolimus stent) may

shorten the prolonged exposure to multiple antithrombotic drugs usually mandated for this patient population following hospital discharge (Naber et al., 2016). Secondary management for this subset of patients may then include dual therapy with clopidogrel and a newer oral anticoagulant (such as rivaroxaban, dabigatran, or apixaban) as opposed to warfarin or triple antithrombotic therapy. This has been shown to have more favourable safety profile in recent trials such as the [21]RE-DUAL PCI, [22]PIONEER AF-PCI and [23]AUGUSTUS (Cannon et al., 2017; Gibson et al., 2016; Lopes et al., 2019).

Patients that had a history of COPD within two years prior to hospital discharge had an increased risk of respiratory, gastrointestinal, and genitourinary bleeding events. This patient population often require management with steroids to control lung inflammation, which are themselves associated with an increased risk of bleeding (Hernández-Díaz and Rodríguez, 2001; Narum et al., 2014). Management of this patient population should, therefore, have a multi-disciplinary team approach involving both Cardiologist and Pulmonologist so that the best strategy to control COPD combined with the most optimal antithrombotic regimen that shows greater efficacy, but lower risk of bleeding is selected.

Patients that had a history of cancer prior to hospital discharge had an increased risk of respiratory bleeding following hospital discharge. Cancers that are systemic in nature, such as lung cancers, are likely to themselves cause bleeding complications. Therefore,

[21] Randomized evaluation of dual antithrombotic therapy with dabigatran versus triple therapy with warfarin in patients with nonvalvular atrial fibrillation undergoing percutaneous coronary intervention

[22] Open-label randomized controlled multi-centre study exploring two treatment strategies of rivaroxaban and a dose-adjusted oral vitamin k antagonist treatment strategy in subjects with atrial fibrillation who undergo percutaneous coronary intervention

[23] A Study of apixaban in patients with atrial fibrillation not caused by a heart valve problem, who are at risk for thrombosis (blood clots) due to having had a recent coronary event such as a heart attack or a procedure to open the vessels of the heart

thoughtful consideration should be given to this group of patients upon deciding on secondary management strategy post ACS.

Another key finding in this thesis was that patients who experienced bleeding, especially intracranial bleeding events, were more likely to die within 12 months after hospital discharge than those who did not. Previous risk stratification tools developed to identify those vulnerable to bleeding complications have mainly focused on major bleeding events, or were either developed in the clinical trial or PCI setting, or have excluded important predictors such as cancer, or the majority of the study population were patients with stable coronary artery disease. This thesis, therefore, proposes a more generalisable and comprehensive list of risk factors which readily identify those at risk of bleeding and of site-specific bleeding events so that bleeding avoidance strategies can be implemented.

For patients where discharge antithrombotic therapy needed to be discontinued due to planned surgical interventions or to control bleeding events, resumption of antithrombotic therapy as soon as it is deemed safe may reduce the risk of adverse ischaemic events and mortality. However, in situations where discontinuation of antithrombotic therapy was voluntary, better education for this subset of patients may improve compliance. In the context of blood transfusion, receipt of blood products should be reserved for patients who are haemodynamically compromised with a haemoglobin of less than 7 g/dL or haematocrit of less than 25%, as advocated by the ESC guideline for the management of patients with NSTEMI (Roffi et al., 2016).

10.6 Research implications

The findings in this thesis warrant replication in future prospective cohort studies. As highlighted in Chapter 7, the study population in the analysis in this thesis comprised patients who were mostly elderly with higher prevalence of comorbidities, and may, therefore, have a higher propensity for bleeding. The extent to which the bleeding events in this study can be attributed to ACS and its management is therefore unclear. Future prospective studies should incorporate a "control" cohort of patients without ACS matched for age, gender and comorbidity, so that comparison on the incidence of bleeding between an ACS population and the general population can be made, and the excess risk of bleeding attributed to ACS and its management can be determined. Prospective studies replicating the findings of this thesis should ideally use a formal definition for bleeding (such as the preferred BARC criteria), so that classifying bleeding based on severity will integrate both clinical and laboratory parameters or receipt of blood transfusion. There was an indication that the incidence of bleeding reported in this thesis may have been underestimated as not all patients who sustained minor and nuisance bleeding events will seek medical care. Therefore, prospective studies replicating the finding of this thesis should attempt to capture these minor and nuisance bleeding events by means of questionnaires or structured interviews or telephone follow-ups.

The impact of factors such as frailty, gastroduodenal ulcer, genetic factors (such as haemophilia, Von Willebrand disease), dosage and duration of discharge antithrombotic drugs warrants investigation in future studies assessing the risk factors for bleeding complications. These future studies should also take into account variations in patient characteristics such as changes in BMI, smoking status, and discontinuation or switching

between antithrombotic drugs over the course of the study follow up period. Previous contemporary studies of bleeding have not considered patients with significant COPD or malignancy. The finding in this thesis suggest that both COPD and malignancy should be taken into account when assessing the future risk of bleeding complications, but this finding will need further confirmation in subsequent studies.

There were patients that experienced multiple episodes of bleeding events in the course of the study follow up period (although, the majority of patients only had one bleeding event (74% of patients with a bleed)). These subsets of patients are likely to have a distinct risk profile. Examining their risk profile in detail may inform longer-term management strategy, which also represents an avenue for further research. For the future, the risk factors for bleeding identified in this thesis will need combining into a risk scoring algorithm. This risk scoring algorithm will simplify the stratification of patients based on the future risk of bleeding and assist in guiding longer-term management for individual patients. However, this risk score will also need to be cross-validated within a primary care setting before being routinely applied in clinical practice. Future studies should also build upon the findings of this study by developing a risk score that specifically predict the risk of ischaemic events, so that deciding on the most appropriate antithrombotic management for individual patients can be based upon combined assessment of the patient's ischaemic and bleeding risk profile.

The analysis in this thesis found an association between bleeding and all-cause mortality, but the evidence pool around the mechanisms of this association is limited. Understanding these mechanisms may result in the development of strategies that will improve patient outcomes. Therefore, future studies ought to first establish whether the relation between bleeding and mortality is causal, and if so, what are the mechanisms

underlying this potentially causal association. There was evidence in this thesis that the impact of bleeding on mortality depends on the anatomic site of the bleeding event. However, each site-specific bleed may comprise both serious and non-serious bleeding events. Future prospective studies using formal definitions for bleeding should build upon the findings of this analysis by exploring whether the association of site-specific bleeding events with all-cause mortality varies by severity. In the future, studies replicating the finding of this thesis should also investigate whether the prognostic impact of bleeding on all-cause mortality varies by time from the bleeding event. These future prospective studies should also expand on the findings of the systematic review by exploring whether post-discharge bleeding is an independent predictor of MACE, re-infarction and rehospitalisation.

10.7 Conclusion

Bleeding complications following ACS are common and occur in more than 1 in 10 patients within the first 12 months after hospital discharge. Bleeding occurs more frequently in the first 30 days after discharge, with bruising and gastrointestinal bleeds the most common types. Patients who experience bleeding complications following hospital discharge have a higher risk of mortality than those who do not. The risk of mortality from bleeding varies by severity and anatomic site of the bleeding event, with intracranial bleeds having the worst prognostic impact. Patients who experience bleeding complications post-hospital discharge have distinct baseline characteristics. These characteristics were also predictors across different types and severities of bleeding, and in subgroups of patients, although, with some variations. These characteristics can assist clinicians in identifying patients at risk of bleeding complications following hospital

discharge so that longer-term antithrombotic therapy can be tailored to fit an individual patient's risk profile. Utilising such a patient-centred approach rather than the present "one size fits all" strategy might reduce bleeding events and their associated adverse effects such as mortality. However, further work is required to combine these characteristics to develop and validate a risk score for bleeding complications following hospital discharge for use in the primary care setting.

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List of appendices

Chapter 3.0 appendices

Appendix 3.1: Published systematic review paper

Open access Research

BMJ Open

Incidence and prognostic impact of post discharge bleeding post acute coronary syndrome within an outpatient setting: a systematic review

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ABSTRACT

Objective The primary objective was to determine the incidence of bleeding events post acute coronary syndrome (ACS) following hospital discharge. The secondary objective was to determine the prognostic impact of bleeding on mortality, major adverse cardiovascular events (MACE), myocardial re-infarction and rehospitalisation in the postdischarge setting.

Design A narrative systematic review.

Data source Medline, Embase, Amed and Central (Cochrane) were searched up to August 2018.

Study selection For the primary objective, randomised controlled trials (RCT) and observational studies reporting on the incidence of bleeding post hospital discharge were included. For the secondary objective, RCTs and observational studies that compared patients with bleeding versus those without bleeding post hospital discharge vis-à-vis mortality, MACE, myocardial re-infarction and rehospitalisation were included.

Results 53 studies (36 observational studies and 17 RCTs) with a combined cohort of 714 458 participants for the primary objectives and 187 317 for the secondary objectives were included. Follow-up ranged from 1 month to just over 4 years. The incidence of bleeding within 12 months post hospital discharge ranged from 0.20% to 37.5% in observational studies and between 0.96% and 39.4% in RCTs. The majority of bleeds occurred in the initial 3 months after hospital discharge with bruising the most commonly reported event. Major bleeding increased the risk of mortality by nearly threefold in two studies. One study showed an increased risk of MACE (HR 3.00,95% CI 2.75 to 3.27; p<0.0001) with bleeding and another study showed a non-significant association with rehospitalisation (HR 1.20,95% CI 0.95 to 1.52; p=0.13).

Conclusion Bleeding complications following ACS management are common and continue to occur in the long term after hospital discharge. These bleeding complications may increase the risk of mortality and MACE, but greater evidence is needed to assess their long-term effects.

PROSPERO registration number CRD42017062378.

Strengths and limitations of this study

- This is the first systematic review that has examined the incidence and prognostic impacts of bleeding complications post acute coronary syndrome (ACS) within the outpatient setting.
- The review combined evidence from observational studies and randomised controlled trials involving a total of 714 458 participants for the primary objectives and 187 317 for the secondary objectives.
- The studies included in the review were heterogeneous in regard to bleeding definition, the ACS presentation, demographic characteristics of the study participants, severity and type of bleeding examined, length of follow-up, discharged antiplatelet and anticoagulant regimens, therefore we were unable to pool data quantitatively.
- The findings in relation to major adverse cardiovascular events and rehospitalisation should serve as hypothesis generating due to limited data.

INTRODUCTION

The management of acute coronary syndrome (ACS) depends on the clinical presentation, with an overall aim of reducing myocardial ischaemia and adverse ischaemic events.[1] This goal is fundamentally achieved via therapy with a combination of antithrombotic and invasive strategies. Paradoxically, these management strategies while achieving the desired goal of reducing ischaemic events increases the risk of bleeding complications.[2–4] In the clinical trial setting, the incidence of major bleeding is reported to be between 1% and 10% depending on the bleeding definition used,[5–7] with observational studies reporting incidences of between 2.8%[8] and 11%.[9] However, the emphasis in the majority of these studies has been on major in-hospital or 30-day bleeding events (a composite of in-hospital and postdischarge events), with little consideration for events in the long term after hospital discharge. Post hospital discharge, patients with ACS may remain on dual antiplatelet therapy for up to a year, and

aspirin indefinitely, so their risk of bleeding complications persist in the long term.

Major bleeding is an independent predictor of adverse outcomes, including mortality, recurrent myocardial infarction (MI), stroke, and stent thrombosis in patients with ACS.[5 10–13] The association between major in-hospital bleeding events and adverse outcomes (most notably mortality) appeared to be maintained regardless of the definition of bleeding used.[5 10–12 14] These adverse events do, however, appear to depend on the anatomic site of the bleed,[15] and the site of bleeding may vary between the in-hospital and the postdischarge settings. While the nature of in-hospital bleeds and their association with adverse events has been well described, the timing, types and association of bleeding events that occur late after hospital discharge with clinical outcomes such as mortality is unclear.

To date, there has not been a systematic review of the incidence, types, and prognostic impact of bleeding events post hospital discharge for ACS. The primary objective of this systematic review was therefore to determine the incidence, timing, and types of post hospital discharge bleeds within the adult post-ACS population. The secondary objective was to determine the association of postdischarge bleeds with mortality, major adverse cardiovascular events (MACE), rehospitalisation and re-infarction in the outpatient setting.

METHODS

Eligibility criteria

There were two linked objectives for the systematic review. For the primary objective, we selected studies that reported on the incidence, timing, and types of bleeding post-ACS post hospital discharge. For the secondary objective, we included studies that compared patients with versus those without bleeding post-ACS post hospital discharge in relation to mortality, MACE, myocardial re-infarction and rehospitalisation. We only included randomised controlled trials (RCTs) where bleeding events were reported as secondary or safety outcomes, and observational studies which were published in English. Studies where the intervention was coronary artery bypass graft surgery or elective percutaneous coronary intervention (PCI) were excluded. We also excluded studies where the study population comprised patients with stable angina or other coronary artery disease. See table 1 for detailed inclusion and exclusion criteria for the review. For studies using the same data source, only one was included in the review, based on: (1) quality, and then by (2) sample size, followed by (3) length of follow-up, unless the studies reported on different outcomes.

Search strategy

Medline (Healthcare Databases Advanced Search (HDAS); 1946–August 2018), Embase (Ovid SP; 1974–August 2018), Amed (Ovid SP; 1985–August 2018) and Central (Cochrane central register of controlled trials) were searched up to August 2018 using a search strategy which combined keywords and related database-specific subject headings for both primary and secondary objectives (see online supplementary table 1 for the full search strategy used on the Embase database). The *Journal of the American College of Cardiology (JACC)*, the *European Heart Journal*, *Heart*, and *Circulation* were electronically searched for relevant articles and grey literature. The bibliographies of included studies and relevant review articles identified from each database were scrutinised for additional relevant articles. Citation tracking of included studies via Web of Science was carried out to retrieve additional relevant articles.

Study selection

The titles of all identified articles were screened and those which were obviously irrelevant were eliminated at this stage. The abstracts of the remaining articles were screened independently by NI and JP. Discordances were resolved by consensus between NI, JP and MAM. The full texts of the remaining articles were then screened by NI, with JP also screening 1 in 10.

Data extraction

We extracted study characteristics including study design, setting, length of follow-up, in-hospital interventions, participant characteristics, discharged therapy and comorbidities. The outcomes of incidence of postdischarge bleeding and associated 95% CIs, time of bleed, location/type of bleed, and the adjusted and unadjusted associations of bleeding with mortality, MACE, re-infarction and rehospitalisation were extracted from individual studies onto a prepiloted and formatted spreadsheet. In studies where incidence and associated 95% CIs were not reported but relevant data were available, incidence per 100 persons at risk were calculated (ie, essentially as a proportion). For studies that combined in-hospital and postdischarge bleeds, and episodes of bleeds were stratified by time (for instance at 30 days, 6 months, 12 months), bleeds that occurred within the initial 30 days were considered to be in-hospital bleeds (decided by consensus of NI, KJP, MAM and UTK) and therefore removed from the numerator and denominator. The authors of original studies were contacted where necessary data were missing or to confirm methodological aspects or other characteristics of the study.

Quality assessment

Observational studies and post hoc observational analyses of RCTs were appraised by the Newcastle Ottawa Scale (NOS) for assessing risk of bias in non-randomised studies.[16] The NOS quality assessment scale contains eight items partitioned into three categories of selection, comparability and outcome. A maximum of one star is allocated to a high-quality study for each item under selection and outcome and a maximum of two stars under comparability, giving an overall maximum of nine stars. We considered studies with an overall number

Table 1 Inclusion and exclusion criteria specific to primary and secondary objectives

Inclusion criteria	Exclusion criteria
Primary objective	
▶ Participants aged 18 years and over	✓Cannot be ascertained whether bleed occurred in-hospital or postdischarge
▶ Participants discharged with an ACS diagnosis (UA or STEMI or NSTEMI) at index hospitalisation	✓In-hospital bleeds only
▶ Randomised controlled trial or observational study	✓Incidence and 95% CI or number of bleeding events cannot be extracted or calculated
▶ Bleeding occurred after hospital discharge	✓Study population combined patients with ACS and other coronary diseases such as stable angina
▶ Any type of bleeding examined (such as gastrointestinal bleed) post hospital discharge for ACS	✓Postdischarge bleeding after PCI, without specifying the clinical presentation for the PCI or whether the PCI was elective
▶ Incidence and associated 95% CI can be extracted or calculated	✓Only reporting CABG-related bleeds
	✓Conference/study abstracts, editorials and reviews
Secondary objective	
▶ Participants aged 18 years and over	✓Cannot be ascertained whether bleed occurred in-hospital or postdischarge
▶ Participants discharged with an ACS diagnosis (UA or STEMI or NSTEMI) at index hospitalisation	✓In-hospital bleeds only
▶ Randomised controlled trial or observational study	✓Study population combined patients with ACS and other coronary diseases such as stable angina
▶ Bleeding occurred after hospital discharge	✓Postdischarge bleeding after PCI, without specifying the clinical presentation for the PCI or whether the PCI was elective
▶ Evaluated outcome of or composite of mortality, MI, rehospitalisation and MACE in bleed vs no bleed cohorts	✓Only reporting CABG-related bleeds
	✓Conference/study abstracts, editorials and reviews

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; MACE, major adverse cardiovascular event; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

of stars greater than or equal to six stars as high-quality studies.[17] RCTs were appraised by the Scottish Intercollegiate Guideline Network quality assessment tool.[18] Each study was categorised as high quality, acceptable quality or low quality based on the standard criteria for this tool. Quality assessment was based on the primary objective of each study as incidence of bleeding was typically reported as safety or secondary outcome measure.

Data synthesis

A narrative synthesis approach was applied due to heterogeneity in relation to length of follow-up, ACS presentation, definition of bleeding used, type of bleeding examined, severity of bleeding examined, geographical location and discharge therapy across studies. For the primary objective, the narrative synthesis was carried out in stages. Initially, the incidence of bleeding overall was summarised separately for observational studies and RCTs. The incidence of bleeding was then stratified by ACS presentation (ST-elevation myocardial infarction [STEMI], non-ST-elevation myocardial infarction/unstable angina [NSTEMI/UA]) and discharge antithrombotic drug combinations and duration (single antiplatelet [SAPT], dual antiplatelet [DAPT] and receipt of oral anticoagulant) in studies that reported these. To assess the incidence of bleeding by time from hospital discharge, the incidence of bleeding was stratified by follow-up time within studies which looked at multiple time periods. Where studies allowed, the incidence of bleeding stratified by major, minor and nuisance bleeds (see online supplementary table 2 for definitions), and the incidence of different types of bleeding events were examined.

We assessed the strength of evidence (SOE) for each secondary outcome following the Agency for Healthcare Research and Quality guideline.[19] For each secondary outcome, assessment was carried out by examining risk of bias, consistency, directness and precision across studies that reported on this outcome, and a grade allocated

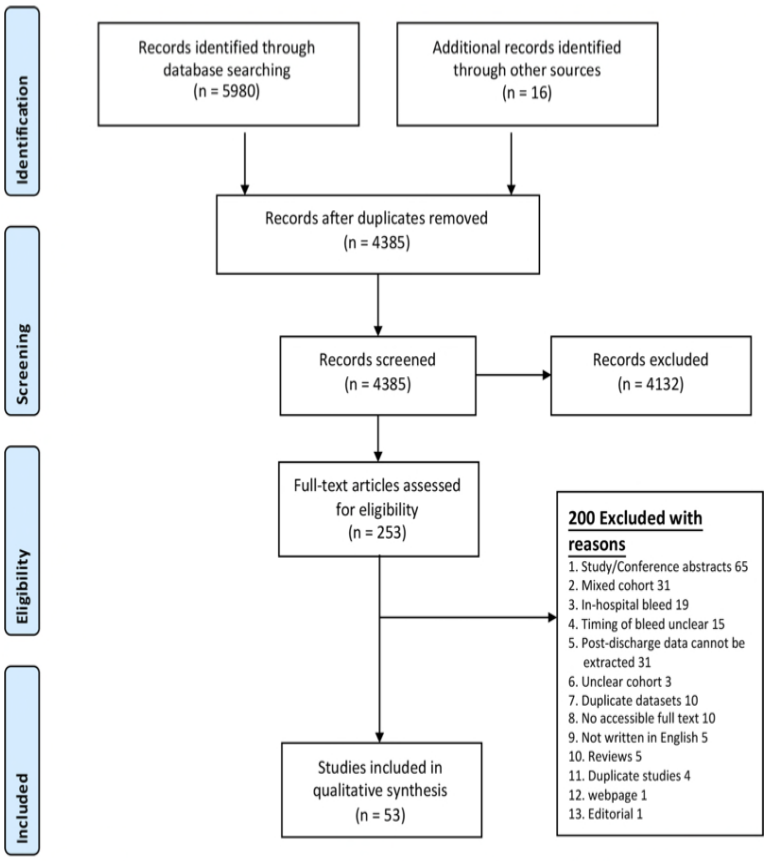

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart depicting steps involved in selecting or rejecting studies for inclusion in the review.

as high, moderate, low or insufficient based on these assessments.

Patient and public involvement

Patients and members of the public did not have any role in the design, conduct, data synthesis or reporting of the study.

RESULTS

The search of Medline, Embase, Amed and Central (Cochrane) identified 37 studies,[20–56] 4 studies were further identified from electronic search of *JACC* database,[3 57–59] 2 from Web of Science citation index,[60 61] 9 from bibliographic screening of included studies,[4 62–69] and finally, 1 from recommendation by an expert within the field.[70] Overall, 53 studies (36 observational studies and 17 RCTs) were included in the review with a combined cohort of 714 458 participants for the primary objectives and 187 317 for the secondary objectives (figure 1). Of the 53 studies, 45 only reported on the primary outcomes, 3 only reported on the secondary outcomes and 5 reported on both primary and secondary outcomes.

Characteristics of included studies

The characteristics of included studies (for the primary objective) are summarised in table 2 for observational studies and table 3 for RCTs. Overall, 50 studies reported on the primary outcome, of which 68% (n=34) were cohort studies and 32% (n=16) were RCTs. The characteristics of included studies for the secondary objective are summarised in table 4. Overall, eight studies reported on the secondary outcomes, of which seven were cohort studies and one was an RCT.

Length of follow-up varied from 30 days[29] to just over 4 years[69] post hospital discharge. The number of participants ranged from 193 to 187 386. The definition for bleeding used by each study in the review are provided in online supplementary table 2. Some studies (n=23) did not report bleeding events based on recognised definitions (such as Bleeding Academic Research Consortium [BARC]). Of the included studies, 27 had specified the in-hospital ACS management strategy. In 26 of these studies, PCI was the baseline management strategy, and in one study the management strategy was a combination of PCI, angiography and medical therapy.

Table 2 Summary of observational studies included in the review by length of follow-up, bleeding definition used and in-hospital management strategy

Primary author	Location	Setting	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed (n)	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Cuisset *et al*[29]	France	Inpatient	Prospective cohort	1 month	TIMI major/minor	PCI	597	16	2.68 (1.66 to 4.31)*	2
Braun *et al*[26]	Sweden	Registry	Retrospective cohort	3 months	BARC 2–5	PCI	263	26	9.89 (6.84 to 14.1)*	5
Amin *et al*[21]	USA	Registry	Retrospective cohort	6 months	BARC 1–5	PCI	9290	2246	24.2 (23.3 to 25.1)*	5
Amin *et al*[20]	USA	Registry	Retrospective cohort	12 months	BARC 1	PCI	3560	1335	37.5 (35.9 to 39.1)*	4
Lattuca *et al*[36]	France	Inpatient	Prospective cohort	12 months	BARC 1–3	PCI	369	132	35.8 (31.1 to 40.8)*	5
Bacquelin *et al*[22]	France	Registry	Prospective cohort	12 months	BARC 2–5	PCI	1006	79	7.85 (6.35 to 9.68)*	5
Palmerini *et al*[59]	Multicentre	Unclear	Prospective cohort	12 months	BARC (any)	PCI	1053	41	3.91 (2.89 to 5.26)*	5
Kassaian *et al*[33]	Iran	Registry	Prospective cohort	12 months	GUSTO mild, moderate, severe	NR	1640	23	1.40 (0.94 to 2.10)*	4
Yetgin *et al*[54]	The Netherlands	Registry	Cohort	12 months	TIMI major	PCI	2443	23	0.94 (0.63 to 1.41)*	5
Fosbol *et al*[30]	USA	Registry	Prospective cohort	12 months	Bleed leading to hospitalisation	NR	7619	928	12.2 (11.5 to 12.9)*	6
Tsai *et al*[85]	Taiwan	Registry	Retrospective cohort	12 months	Gastrointestinal bleed	NR	3580	273	7.63 (6.80 to 8.54)*	5
Garay *et al*[70]	Spain	Registry	Retrospective cohort	12 months	Bleed leading to hospitalisation, transfusion or suspension of antithrombotics	NR	1375	69	5.02 (3.98 to 6.30)*	3
Garay *et al*[55]	Multicentre	Registry	Cohort	12 months	Intracranial bleeding or bleed leading to hospitalisation or transfusion	PCI	15401	489	3.18 (2.91 to 3.46)*	5
Effron *et al*[50]	USA	Registry	Retrospective cohort	12 months	Bleed leading to hospitalisation or transfusion	PCI	15788	492	3.12 (2.86 to 3.40)*	4
Brinkert *et al*[47]	Canada	Registry	Cohort	12 months	Hospitalisation with major bleeding	PCI, angiography, medically	22312	588	2.72 (2.51 to 2.94)*	5
Ko *et al*[68]	Canada	Registry	Cohort	12 months	Bleed leading to hospitalisation	PCI	8672	230	2.65 (2.33 to 3.01)*	6

Continued

Table 2 Continued

Primary author	Location	Setting	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed (n)	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Boggon *et al*[25]	UK	Registry	Retrospective cohort	12 months	Any bleeding in patient GPRD or HES record	NR	7543	NR	11.4 (10.4 to 12.6)†	5
Carrero *et al*[28]	Sweden	Registry	Prospective cohort	12 months	Major bleed	NR	36001	333	0.92 (0.83 to 1.03)*	7
Graipe *et al*[31]	Sweden	Registry	Prospective cohort	12 months	Intracranial bleed	NR	187386	590	0.32 (0.30 to 0.34)	6
Wang *et al*[44]	USA	Registry	Cohort	12 months	Haemorrhagic stroke	NR	169863	335	0.20 (0.18 to 0.22)	5
Barra *et al*[23]	Portugal	Inpatient	Prospective cohort	13.4 months (mean)	TIMI/GUSTO major criteria	NR	852	60	7.04 (5.51 to 8.96)*	3
Sra *et al*[41]	Canada	Inpatient	Prospective cohort	15 months	BARC 1–5	PCI	2034	440	21.6 (19.9 to 23.5)*	5
Caneiro-Queija *et al*[48]	Spain	Registry	Cohort	455 days (median)	BARC 2–3	PCI	4229	500	11.8 (10.9 to 12.8)*	6
Sørensen *et al*[40]	Denmark	Registry	Prospective cohort	476.5 days (mean)	Fatal and non-fatal bleed	PCI	40812	1967	4.82 (4.62 to 5.03)*	5
Raposeiras-Roubin *et al*[22]	Multicentre	Registry	Cohort	17.2 months (mean)	BARC 3 or 5	PCI	4310	66	1.53 (1.21 to 1.94)*	6
Cuschieri *et al*[61]	USA	Registry	Retrospective cohort	1.7 years (mean)	Gastrointestinal bleed	NR	3218	107	3.33 (2.76 to 4.00)*	4
Wong *et al*[45]	UK	Inpatient	Retrospective cohort	21 months	CURE major/life threatening	NR	224	15	6.70 (4.10 to 10.8)*	4
Buresly *et al*[62]	Canada	Registry	Cohort	654 days (mean)	Bleed leading to hospitalisation	NR	21443	1428	6.66 (6.33 to 7.00)*	3
Voss *et al*[43]	New Zealand	Registry	Cohort	1.94 years (mean)	Other	NR	3666	206	5.88 (5.15 to 6.71)*	4
Brener *et al*[67]	USA and Germany	Registry	Prospective cohort	24 months	TIMI, GUSTO and ACUITY Major bleed	PCI	8582	430	5.17 (4.71 to 5.66)*	5
Ertaş *et al*[51]	Turkey	Registry	Cohort	24 months	Physician-confirmed bleeding event	NR	1010	21	2.08 (1.36 to 3.16)*	4
Blin *et al*[46]	France	Registry	Cohort	3 years	Hospitalisation with bleeding	NR	1585	49	3.09 (2.35 to 4.06)*	5
Chamberlain *et al*[27]	USA	Registry	Cohort	4.3 years	Other	NR	1159	312	26.9 (24.5 to 29.6)*	6
Kazi *et al*[69]	USA	Registry	Retrospective cohort	4.42 years (mean)	Major spontaneous bleeding	PCI	22527	368	1.63 (1.48 to 1.81)*	5

Continued

Table 2 Continued

Primary author	Location	Setting	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed (n)	Crude incidence of bleeding per 100 persons and 95% CI	Quality score

*Incidence and associated 95% CI calculated from data within study.
†Incidence and associated 95% CI reported within study per 100 person years.
ACUITY, acute catheterisation and urgent intervention triage strategy; AMI, acute myocardial infarction; BARC, Bleeding Academic Research Consortium; CURE, clopidogrel in unstable angina to prevent recurrent events; GPRD, General Practice Research Database; GUSTO, global use of strategies to open occluded arteries; HES, hospital episodes statistics; NR, not reported; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

Risk of bias assessment

Summaries of risk of bias of individual studies are provided in tables 2, 3 and 4. Sixty-nine per cent (n=25) of the observational studies were at high risk of bias due to lack of reporting on presence/absence of outcome at start of study, attrition rate, and comparability of cohorts based on analysis (whether study adjusted for confounders or not). Thirty-one per cent (n=11) were at low risk of bias. Two RCTs were high risk, four were at an acceptable risk of bias and two were low risk. The main reasons for low quality in RCTs were inadequate reporting on randomisation, concealment, blinding, adequacy and reliability of outcome measurements. For studies which were post hoc observational analysis of RCTs, five were high risk and four were at low risk of bias.

Incidence of bleeding

In a cohort of 611 412 participants, 14 217 (2.3%) episodes of bleeds were reported in 34 observational studies and 2685 (2.6%) episodes in a cohort of 103 046 participants in 16 RCTs (714 458 participants overall). A summary of the incidence from each study is presented by length of follow-up, bleeding definition used and in-hospital management strategy in table 2 for observational studies and table 3 for RCTs. The overall incidence of bleeding within 12 months post hospital discharge varied from 0.2%[44] to 37.5%[20] in observational studies, and between 0.96%[42] and 39.4%[63] in RCTs.

The incidence of bleeding stratified by ACS presentation (STEMI, NSTEMI/UA) and discharge antithrombotic drug combinations and duration (SAPT, DAPT and receipt of oral anticoagulant) are summarised by length of follow-up and the bleeding definition used in online supplementary tables 3, 4 and 5. Among those discharged on DAPT with aspirin and a thienopyridine, the incidence of bleeding within the first 12 months based on BARC criteria ranged from 3.91% to 38.8% (see online supplementary table 4) in observational studies, and between 0.96% and 47.4% in RCTs (see online supplementary table 5).

Eight observational studies[23 36 45 47 51 54 59 70] and two RCTs[56 58] comprising 53 318 participants reported bleeding episodes at different time points during follow-up. In these studies, around one-half of bleeds that occurred in the first year post hospital discharge for ACS happened in the initial 1–3 months (figure 2).

The incidence of major bleeding events in observational studies (based on BARC 3–5) within the first 12 months of hospital discharge was around 1.29%–3.25%. The incidence of minor bleeding events (based on BARC 2) and nuisance bleeds (based on BARC 1) within the same period were around 6.56%–10.6% and 21.9%–37.5%, respectively (see figure 3 and online supplementary table 6). Generally, bruising (defined as skin haematoma, ecchymosis, petechiae) were the most commonly reported types of bleeding events post hospital discharge (range: 1.49%–22.5% within 12 months) followed by

Table 3 Summary of randomised controlled trials included in the review by length of follow-up, bleeding definition used and in-hospital management strategy

Primary author	Location	Trial	Study design	Length of follow-up	Bleeding criteria	In-hospital management strategy	N	Participants with bleed	Crude incidence of bleeding per 100 persons and 95% CI	Quality score
Yusuf *et al*[56]	Multicentre	OASIS-5	RCT	6 months	OASIS-5 major	NR	20078	357	1.84 (1.66 to 2.03)*	High
Jolly *et al*[4]	Multicentre	CURE	Post hoc analysis of RCT	8 months	CURE major	PCI	2658	28	1.07 (0.74 to 1.54)*	6†
Khan *et al*[34]	Multicentre	APPRAISE-2	Post hoc analysis of RCT	240 days (median)	Any bleeding event	NR	7392	506	7.32 (6.73 to 7.96)*	7†
Carrabba *et al*[63]	Italy	BLESS	RCT	12 months	BARC 1–3	PCI	193	76	39.4 (32.8 to 46.4)*	Acceptable
Cuisset *et al*[49]	France	TOPIC	RCT	12 months	BARC≥2	PCI	634	106	16.7 (14.0 to 19.8)*	Low
Han *et al*[32]	China	BRIGHT	RCT	12 months	BARC 1–5	PCI	2194	47	2.33 (1.76 to 3.08)*	Acceptable
Savonitto *et al*[42]	Italy	Italian Elderly ACS	RCT	12 months	BARC 2, 3a and 3b	NR	313	3	0.96 (0.33 to 2.78)*	Acceptable
Mrdovic *et al*[38]	Serbia	RISK-PCI	Post hoc analysis of RCT	12 months	TIMI major/minor	PCI	2045	25	1.29 (0.87 to 1.89)*	5†
Atar *et al*[60]	Multicentre	OPUS-TIMI 16	Post hoc analysis of RCT	12 months	Gastrointestinal bleed	NR	10288	104	1.02 (0.84 to 1.24)*	5†
Kohli *et al*[35]	Multicentre	TRITON-TIMI 38	Post hoc analysis of RCT	15 months	TIMI major/minor	PCI	12674	407	3.23 (2.94 to 3.56) *	7†
Mahaffey *et al*[37]	Multicentre	TRACER	Post hoc analysis of RCT	502 days (median)	TIMI major/minor	NR	11368	236	2.12 (1.87 to 2.41)*	6†
Yeh *et al*[3]	USA	DAPT	RCT	18 months	BARC 2–5	PCI	3576	111	3.10 (2.58 to 3.72)*	Acceptable
Costa *et al*[66]	Italy	PRODIGY	Post hoc analysis of RCT	24 months	BARC 2–5	PCI	1465	82	5.60 (4.53 to 6.89)*	5†
Bonaca *et al*[67]	Multicentre	PEGASUS-TIMI 54	RCT	33 months	TIMI major	NR	21162	435	2.08 (1.89 to 2.28)*	High
Nikolsky *et al*[58]	Multicentre	HORIZON-AMI	Post hoc analysis of RCT	3 years	HORIZON major	PCI	3602	63	2.15 (1.68 to 2.74)*	5†
Bergen *et al*[24]	The Netherlands	ASPECT	RCT	37 months	Major bleed	NR	3404	99	2.91 (2.39 to 3.53)*	Low

*Incidence and associated 95% CI calculated from data within study.
†Quality assessed by Newcastle Ottawa Scale.
APPRAISE-2, apixaban for prevention of acute ischaemic events; ASPECT, anticoagulants in the secondary prevention of events in coronary thrombosis; BARC, Bleeding Academic Research Consortium; BLESS, bleeding events and maintenance dose of prasugrel; BRIGHT, bivalirudin in acute myocardial infarction vs heparin and glycoprotein inhibitor plus heparin; CURE, clopidogrel in unstable angina to prevent recurrent events; DAPT, dual antiplatelet therapy study; HORIZON, harmonising otcomes with revascularisation and stents; HORIZON-AMI, harmonising outcomes with revascularisation and stents in acute myocardial infarction; GI, gastrointestinal; NR, not reported; OASIS-5, the fifth organisation to assess strategies in acute ischaemic syndromes; OPUS-TIMI 16, orbofiban in patients with unstable coronary syndrome-thrombolysis in myocardial infarction 16; PCI, percutaneous coronary intervention; PRODIGY, prolonging dual antiplatelet treatment after grading stent-induced intimal hyperplasia; PEGASUS-TIMI 54, prevention of cardiovascular events in patients with prior heart attack using ticagrelor compared with placebo on a background of aspirin thrombolysis in myocardial infarction 54; RCT, randomised controlled trial; RISK-PCI, risk scoring model to predict net adverse cardiovascular outcomes after primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; TOPIC, timing of platelet inhibition after acute coronary syndrome; TRACER, thrombin receptor antagonist for clinical event reduction in acute coronary syndrome; TRITON-TIMI 38, trial to assess improvement in therapeutic outcomes by optimising platelet inhibition with prasugrel-thrombolysis in myocardial infarction 38.

Table 4 Summaries of risk of mortality, MACE and rehospitalisation from included studies by length of follow-up

Primary author	Location	Setting	Length of follow-up	Bleeding criteria	Adj/unadj outcomes			Quality score
					Mortality	MACE	Rehospitalisation	
Lamberts *et al*[64]	Denmark	Registry	12 months	Fatal and non-fatal bleed	Adj HR 2.79 (95% CI 2.39 to 3.26)	NR	NR	7
Brinkert *et al*[47]	Canada	Registry	12 months	Hospitalisation with major bleeding	Adj OR 2.97 (95% CI 1.71 to 5.15)	NR	NR	5
Caneiro-Queija *et al*[48]	Spain	Registry	455 days (median)	BARC 2–3	Adj HR 5.10 (95% CI 3.60 to 7.70)	NR	NR	6
Brener *et al*[57]	USA and Germany	Registry	24 months	TIMI, GUSTO and ACUITY Major bleed	Bleeds between 30 and 365 days: unadj HR 4.61 (95% CI 1.70 to 12.49) Bleeds>365 days; unadj HR 2.63 (95% CI 0.86 to 8.04)	NR	NR	5
Schjerning Olsen *et al*[39]	Denmark	Registry	3.5 years	Bleed leading to death or hospitalisation	Adj HR 1.51 (95% CI 1.28 to 1.79)	NR	NR	6
Valgimigli *et al*[53]	Multicentre	RCT	Unclear	BARC 1–3	BARC 1: adj HR 0.89 (95% CI 0.61 to 1.31) BARC 2: adj HR 1.70 (95% CI 1.23 to 2.36) BARC 3a: adj HR 2.77 (95% CI 1.86 to 4.12) BARC 3b: adj HR 4.51 (95% CI 2.86 to 7.10) BARC 3c: adj HR 28.2 (95% CI 17.5 to 45.7)	NR	NR	4*
Sørensen *et al*[40]	Denmark	Registry	476.5 days (mean)	Fatal and non-fatal bleed	NR	Adj HR 3.00 (95% CI 2.75 to 3.27)	NR	5
Amin *et al*[20]	USA	Registry	12 months	BARC 1	NR	NR	Adj HR 1.20 (95% CI 0.95 to 1.52)	4

*Quality assessed by Newcastle Ottawa Scale.
ACUITY, acute catheterisation and urgent intervention triage strategy; Adj, adjusted; BARC, Bleeding Academic Research Consortium; GUSTO, global use of strategies to open occluded arteries; MACE, major adverse cardiovascular event; NR, not reported; TIMI, thrombolysis in myocardial infarction; unadj, unadjusted.

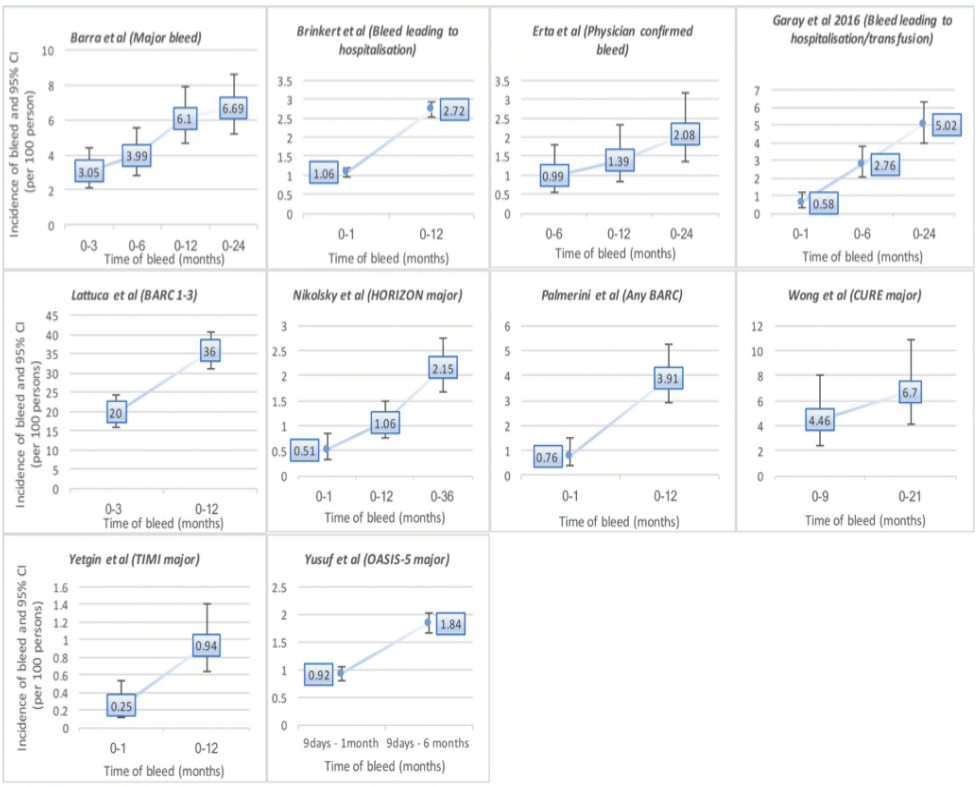

Figure 2 Cumulative incidence of bleeding as reported within individual studies at different time points (incidence expressed as proportion per 100 persons). BARC, Bleeding Academic Research Consortium; CURE, clopidogrel in unstable angina to prevent recurrent events; HORIZON, harmonising outcomes with revascularisation and stents; OASIS-5, the fifth organisation to assess strategies in acute ischaemic syndromes; TIMI, thrombolysis in myocardial infarction.

gastrointestinal bleeds (range: 0.25%–7.63% within 12 months; see figure 4 and online supplementary table 7).

Bleeding and risk of mortality

There was consistent reporting of an association between postdischarge bleeding and all-cause mortality in five observational studies[39 47 48 57 64] and one RCT[53] (table 4). Major bleeding was associated with nearly threefold increased risk of mortality in the first 12 months of hospital discharge in two studies (table 4).[47 64] Nuisance bleeding events defined as BARC 1 were not associated with mortality in one RCT, but there was an increased risk of mortality with BARC 2 and 3 bleeds in the same RCT,[53] which increased with bleeding severity (table 4). The SOE for the outcome of mortality was rated low (online supplementary table 8).

Bleeding and risk of MACE, rehospitalisation and re-infarction

The adjusted (adj) risk (HR) of MACE with bleeding (defined as bleeds leading to hospitalisation or death) was 3.00 (95% CI 2.75 to 3.27 in one study; table 4).[40] There was a statistically non-significant association between postdischarge bleed (defined as BARC 1 bleeds) and risk of rehospitalisation (adj HR 1.20, 95% CI 0.95 to 1.52 in another study; table 4).[20] There were no studies examining the association between postdischarge bleeding and subsequent risk of re-infarction. The SOE for the outcomes of MACE and rehospitalisation were rated insufficient (online supplementary table 8).

DISCUSSION

Our systematic review is the first to study the incidence, timing and types of postdischarge bleeding complications, and their association with mortality, MACE, re-infarction and rehospitalisation. Fifty-three studies were included, comprising 36 observational studies and 17 RCTs with a combined cohort of 714458 participants for the primary objectives and 187317 for the secondary objectives. We report that bleeding complications post-ACS are common following hospital discharge, and vary by length of follow-up, severity, type and the definition of bleeding used. We report that the incidence of bleeding was highest in the initial 3 months after hospital discharge for ACS, with bleeding events continuing to occur even after 1-year postdischarge. The majority of postdischarge bleeding events were nuisance bleeds such as ecchymosis and petechiae, with major bleeding events such as intracranial haemorrhage less common. While there was

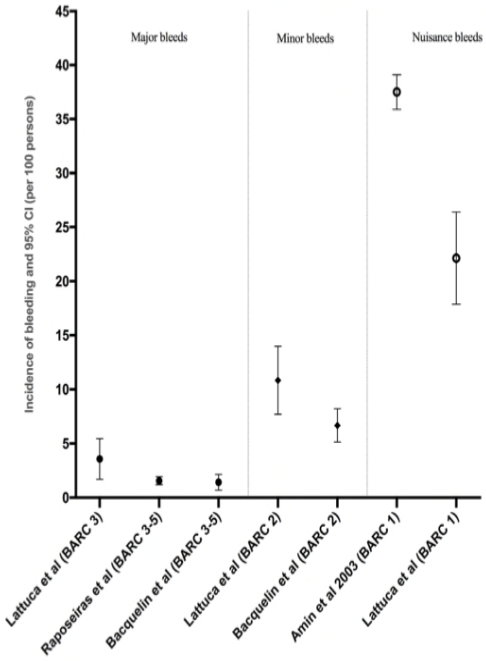

Figure 3 Incidence of bleeding stratified by severity in observational studies that reported bleeding by Bleeding Academic Research Consortium (BARC) criteria within the first 12 months after hospital discharge.

substantial heterogeneity between studies, we report that up to one-third of patients discharged on DAPT will experience bleeding complications in the first 12 months after hospital discharge, and around 1.3%–3.3% of patients will experience a major bleed.

Our review shows that major bleeding may increase the risk of mortality by nearly threefold in the first 12 months after hospital discharge, but the strength of the evidence was weak. We identified very limited data on whether postdischarge bleeding was associated with MACE and rehospitalisation. Although there was an indication of an association with MACE in one study[40] and rehospitalisation in another,[20] the latter association did not reach statistical significance.

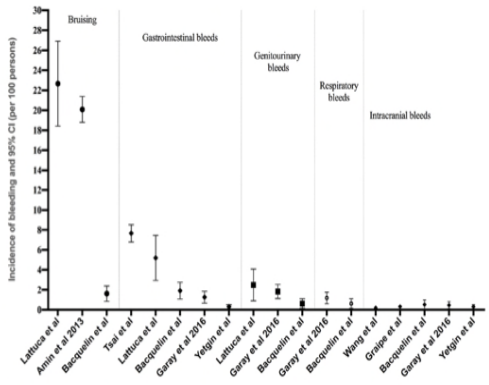

Figure 4 Incidence of each type of bleeding event within the first 12 months after hospital discharge in observational studies.

Clinical implications

Although current guidelines[71–73] have recommended dual therapy with aspirin and a thienopyridine for up to 12 months and triple therapy in the presence of comorbid conditions such as atrial fibrillation for shorter periods, it was evident from our study that these maintenance therapies are accompanied by bleeding complications which predominantly occur post hospital discharge. Consideration must therefore be given to ways of minimising these bleeding complications, such as by encouraging clinicians to use risk scoring algorithms such as DAPT,[74] precise-DAPT,[75] BleeMACS score[76] (for patients with ACS treated with PCI) or TRILOGY-ACS bleeding risk model[77] (for patients with NSTEMI/UA managed medically) to identify patients at higher risk of these bleeding complications, such that maintenance oral antithrombotics or newer oral anticoagulants that have more favourable safety profile than warfarin can be tailored to fit each patient's risk profile. However, it must be borne in mind that many of these risk algorithms were developed in the clinical trial setting, and have not yet been validated in unselected cohorts. Aspirin regardless of dose increases the risk of gastrointestinal bleeds.[78 79] In high-risk patients such as those with previous history of these types of bleeds, concomitant use of a proton pump inhibitor as advocated by the European Society of Cardiology guidelines will reduce the future risk of these bleeds.[80]

Research implications

The majority of studies in this review were not primarily designed to investigate the incidence of bleeding complications. This meant that incidences could only be reported here as per 100 persons, that is, essentially as a proportion, rather than per 100 persons years at risk. This underscores the need to examine the incidence of these bleeding events using high-quality observational studies that are more reflective of the real-world populations encountered in clinical practice. The incidence of postdischarge bleeding complications may vary by type of bleed, patient demographics and discharge pharmacotherapy. Future studies should explore factors associated with postdischarge bleeding complications so that risk stratification tools that are more representative of the unselected cohorts encountered in clinical practice (often ignored in RCTs) can be developed to identify individuals at high risk of bleeding post hospital discharge, as most contemporary bleeding risk scores predict in-hospital bleeding events.[81–83]

We also report that bleeding complications post hospital discharge may be associated with subsequent risk of mortality, although evidence from the literature was limited. The risks of MACE and rehospitalisation were only reported in two studies, and none of the studies in the review reported on re-infarction. Future research is

required to quantify these associations, with particular emphasis on whether nuisance and minor bleeding events that are much more common post hospital discharge also have a prognostic impact. Finally, future research examining these associations should stratify by the timing of the bleeding events in order to determine whether the prognostic impacts of these bleeding complications are more pronounced in the early phases of hospital discharge or are equally important in the long term after hospital discharge.

Limitations of the review

This study has several potential limitations. First, the studies included in the review were too heterogeneous in regard to bleeding definition, ACS presentation, demographic characteristics of the study participants, severity and type of bleeding examined, length of follow-up, discharge antiplatelet and anticoagulant regimens to pool data to obtain an overall incidence and mortality figures. Second, the duration and dosage of discharge antithrombotic therapy as well as in-hospital management strategies were not specified in the majority of studies (due to selective reporting), as such we were unable to adequately assess the impact of these factors on the incidence of bleeding. In the majority of studies, episodes of bleeds were extracted to calculate incidence figures. In most of these studies, there was lack of clarity on whether patients were included in the numerator more than once if they had multiple episodes of bleeds. However, since bleeding complications are rare events[5 7 84] and having more than one episode of bleeding is even rarer, it is unlikely that this would have affected the overall incidence. Similarly, for some studies where episodes of bleeds were reported at different time intervals and the number of people at risk within each time interval were not reported, incidence figures were estimated based on the assumption that there was no attrition, hence these figures may have been underestimated.

CONCLUSIONS

In this systematic review of 53 studies, bleeding complications post hospital discharge for ACS were found to be common, with bruising the most common. These bleeding complications vary by severity, anatomic source and type of discharge antithrombotic therapy, and while most common immediately postdischarge, these bleeds continue to occur in the long term. There are limited data around the long-term outcomes of patients that sustain bleeding events post hospital discharge for ACS. Further work is required to define the nature, frequency and prognostic impact of such bleeding events, using formal bleeding definitions. Real-world risk stratification tools will need to be developed that specifically predict the risk of bleeding complications postdischarge to identify high-risk individuals for a more patient-centred approach in managing optimal pharmacotherapy and care.

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Figure 3.1: Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow chart depicting steps involved in selecting or rejecting studies for inclusion in the review after the 2nd literature search.

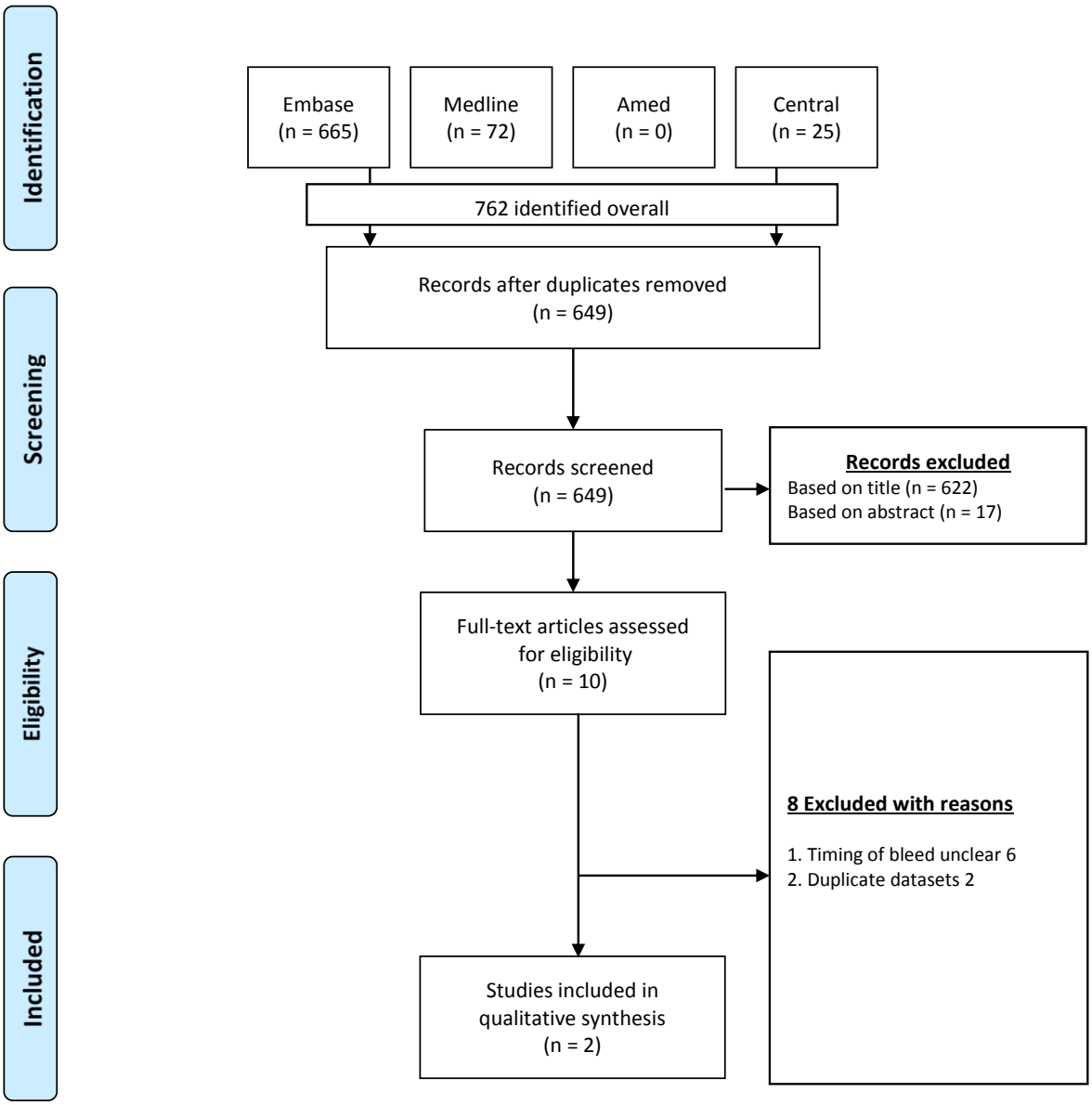

Table 3.1: Embase search strategy

1. "incidence".ab,kw,ti.
2. "prevalence".ab,kw,ti.
3. incidence/
4. prevalence/
5. 1 or 2 or 3 or 4
6. "acute coronary syndrome".ab,kw,ti.
7. "myocardial infarction".ab,kw,ti.
8. "NSTEMI".ab,kw,ti.
9. "STEMI".ab,kw,ti.
10. "st segment elevation myocardial infarction".ab,kw,ti.
11. acute coronary syndrome/
12. heart infarction/
13. unstable angina pectoris/
14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. "bleed* ".ab,kw,ti.
16. "h?emorrhage".ab,kw,ti.
17. exp bleeding/
18. 15 or 16 or 17
19. "post".ab,kw,ti.
20. "late onset".ab,kw,ti.
21. "discharge* ".ab,kw,ti.
22. "home".ab,kw,ti.
23. hospital discharge/
24. 19 or 20 or 21 or 22 or 23
25. "mortality".ab,kw,ti.
26. "death".ab,kw,ti.
27. "MACE".ab,kw,ti.
28. "major adverse cardi* event* ".ab,kw,ti.
29. "reinfarction".ab,kw,ti.
30. "readmi* ".ab,kw,ti.
31. hospital readmission/
32. heart reinfarction/
33. cardiovascular mortality/ or exp hospital mortality/ or mortality/ or mortality risk/
34. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35. 5 and 14 and 18 and 24
36. 14 and 18 and 24 and 34
37. 35 or 36
38. limit 37 to human

Table 3.2: Bleeding definitions

Criteria	Severity	Definition
BARC	**Type 0**	No bleeding
	Type 1	Bleeding that is not actionable (Nuisance bleeds)
	Type 2	Actionable bleeding requiring hospitalisation, diagnostic studies and treatment by healthcare professional, but does not fit criteria for 3, 4 & 5.
	Type 3	
	A	Overt bleeding + haemoglobin drop of 3 to <5 g/dl
		Any transfusion with overt bleeding
	B	Overt bleeding + haemoglobin drop ≥ 5 g/dl
		Cardiac tamponade
		Bleeding requiring surgical intervention
		Bleeding requiring intravenous vasoactive agents
	C	Intracranial bleed
		Intraocular bleed
	Type 4	CABG related bleeds
	Type 5	
	A	Probable fatal bleeding: no autopsy or imaging confirmation but clinically suspicious
	B	Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation
TIMI	**Major**	Intracranial or a ≥ 5 g/dl decrease in haemoglobin or Bleeding resulting in death within 7 days
	Minor	Overt blood loss or ≥ 3 to ≤ 5 g/dl decrease in haemoglobin or requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding including temporarily or permanently stopping or changing the dose of a medication or study drug or leading to or prolonging hospitalisation or prompting evaluation (leading to unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)
	Minimal	Any overt bleeding that does not meet Major or Minor bleeding criteria above.
GUSTO	**Severe or life threatening**	Intracerebral or resulting in substantial hemodynamic compromise requiring treatment
	Moderate	bleeding requiring blood transfusion or bleeding that does not cause hemodynamic compromise
	Mild	bleeding that does not meet criteria for severe or moderate bleeding
ACUITY/HORIZON	**Major**	Intracranial or intraocular or access site bleeding requiring intervention or ≥5-cm diameter hematoma or haemoglobin drop of ≥4 g/dl without an overt source or haemoglobin drop of ≥3 g/dl with an overt source or reoperation for bleeding or requiring blood product transfusion

Criteria	Severity	Definition
CURE	**Major**	Significantly disabling, intraocular bleeding leading to loss of vision or requiring transfusion of ≥ 2 units of packed cells or bleeding that is life threatening (fatal or intracranial or results in decrease haemoglobin of at least 5 g/dl or leading to substantial hypotension requiring the use of inotropic agents or requiring surgical intervention or result in transfusion of ≥ 4 units of blood
CURE	**Minor**	bleed leading to discontinuation of study medication
ISTH	**Major**	Fatal bleeding, and/or Symptomatic bleeding in a critical area or organ, such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or Bleeding causing a fall in haemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells
	Clinically non relevant non-major bleeding	Any sign or symptom of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for major bleeding but does meet at least one of the following criteria: 1) requiring medical intervention by a healthcare professional or 2) leading to hospitalization or increased level of care or 3) prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.
OASIS 5	**Major**	Clinically overt bleeding that is fatal, symptomatic intracranial, retroperitoneal, or intraocular, an HGB decrease of at least 3.0 g/dL (with each blood transfusion unit counting for 1.0 g/dL of HGB), or requiring transfusion of at least 2 units of red blood cells
	Minor	Minor bleeding is considered to be any other clinically significant bleeding not meeting the definition for major bleeding and leading to interruption of study drug for at least 24 hours, surgical intervention or transfusion of one unit of blood (whole blood or PRBC)
Fosbol et al 2012		Re-hospitalisation for bleeding defined as gastrointestinal, intracranial, haemarthrosis, haemopericardium, haematuria, haemoptysis, epistaxis, haemorrhage not specified, acute post-haemorrhagic anaemia
Tsai et al 2010		Defined as hospitalisation with a primary diagnosis of gastrointestinal haemorrhage, or ulcer or GI bleed or perforation identified by surgery.
Carrero et al 2016		Defined as intracranial haemorrhage, gastrointestinal haemorrhage or anaemia.
Graipe et al 2015		Intracranial haemorrhage defined as subarachnoid haemorrhage, intracerebral haemorrhage and other intracranial haemorrhage using WHO ICD-10 classification.

Criteria	Severity	Definition
Sorensen et al 2009		Defined as an admission to a Danish hospital with a diagnosis of non-fatal bleeding or fatal bleeding including cerebral bleed, respiratory tract bleeds, gastrointestinal bleed, urinary tract bleed, and anaemia from acute or chronic bleeding.
Cuschieri et al 2014		Gastrointestinal bleed defined as haematochezia, melena, hematemesis or coffee ground vomitus as documented by healthcare provider using ICD-9 codes
Buresly et al 2005		Bleeding was defined as any hospital admission that occurred after the index AMI hospitalization with a principal or new secondary diagnosis of intracranial haemorrhage, gastrointestinal tract haemorrhage, aortic aneurysm dissection or rupture, intraocular haemorrhage, haematuria, haemoptysis, epistaxis, or haemorrhage not otherwise specified.
Voss et al 2016		Defined as procedure related, gastrointestinal, respiratory, intracranial, intraocular, urogenital, and other, based on a list of ICD-10 codes.
Chamberlain et al 2016		Defined as intracranial haemorrhage, gastrointestinal tract haemorrhage, haemarthrosis, haemopericardium, haematuria, haemoptysis, epistaxis, or haemorrhage not otherwise specified or acute post-haemorrhagic anaemia
Atar et al 2006		Gastrointestinal bleeding was defined as blood loss from the GI tract of new onset, hematemesis, or melena with no other apparent source of acute blood loss. Severe or life-threatening GI bleeding was defined as bleeding associated with severe hemodynamic compromise. Major bleeding was defined as ≥15% absolute reduction in haematocrit or need for a transfusion
Bergen et al 1994		Major bleeding defined as intracranial or fatal bleed or bleeding that led to admission for hospital treatment.
Blin et al 2017		Defined as hospitalization with a primary diagnosis of bleeding using relevant ICD-10 codes.
Brinkert et al 2017		Defined by ICD-10 codes as hospitalization with major bleeding.
Effron et al 2018		Defined as rehospitalisation with bleeding or receipt of blood transfusion.
Kazi et al 2015		Defined as major spontaneous bleeding
Ko et al 2010		Defined as hospitalisation with bleeding post discharge

Criteria	Severity	Definition
Sorrentino et al 2018		Defined as bleeding requiring hospitalisation or blood transfusion
Boggon et al 2011		Defined as any bleeding event in patient GPRD or HES record
Wang et al 2015		Haemorrhagic stroke defined by ICD-10 codes
Erta et al 2018		Defined as physician-confirmed bleeding events.
Garay et al 2016		Defined as bleeding that required hospitalization, transfusion of more than 1 blood pack, or suspension of antithrombotic treatment
Garay et al 2018		Defined as intracranial bleeding or any other bleeding leading to hospitalization and/or red blood cell transfusion.
Khan et al 2015		Defined as any bleeding event
Lamberts et al 2013		Defined as fatal or non-fatal bleed as recorded in the Danish national patient registry and national causes of death registry
Olsen et al 2015		Defined as admission or death from diagnosis of gastrointestinal bleeding, bleeding ulcer, hematemesis, melena, and unspecified gastrointestinal bleeding from the national causes of death register and national patient register.

Table 3.3: Risk of bias of included observational studies and post hoc analysis of RCTs assessed by Newcastle Ottawa Scale (NOS)

Study ID	**Selection**			**Comparability**	**Outcome**			**Total Points**
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Comparability of cohorts on analysis	Assessment of outcome	Adequate duration of follow-up	Adequacy of follow up of cohorts	
Amin et al 2013	1	0	0	1	1	1	0	4
Amin et al 2016	1	1	1	1	1	1	0	6
Bacquelin et al 2015	1	1	1	0	1	1	1	6
Barra et al 2013	1	0	1	0	0	1	0	3
Blin et al 2017	1	0	1	1	1	1	0	5
Boggon et al 2011	1	1	1	0	1	1	0	5
Braun et al 2014	1	1	1	0	1	1	0	5
Brener et al 2016	1	0	1	0	1	1	0	4
Brinkert et al 2017	1	0	1	1	1	1	0	5
Buresly et al 2005	1	0	1	0	1	1	0	4
Chamberlain et al 2016	1	1	1	1	1	1	0	6
Chen et al 2019	1	0	1	0	1	1	1	5
Caneiro-Queija et al 2018	1	1	1	1	0	1	1	6
Carrero et al 2016	1	0	1	1	1	1	1	6
Cuisset et al 2009	1	0	1	0	0	0	0	2
Cuschieri et al 2014	1	0	1	0	1	1	0	4
Effron et al 2017	1	0	1	1	0	1	0	4
Ertas et al 2018	1	0	1	0	0	1	1	4

Study ID	**Selection**			**Comparability**	**Outcome**			**Total Points**
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Comparability of cohorts on analysis	Assessment of outcome	Adequate duration of follow-up	Adequacy of follow up of cohorts	
Fosbol et al 2013	1	1	1	1	1	1	1	7
Garay et al 2016	1	0	0	0	1	1	0	3
Garay et al 2018	1	0	1	1	1	1	0	5
Graipe et al 2015	1	1	1	1	1	1	0	6
Kassaian et al 2015	1	0	1	0	0	1	1	4
Kazi et al 2015	1	0	1	1	1	1	0	5
ko et al 2010	1	0	1	1	1	1	1	6
Lamberts et al 2013	1	1	1	1	1	1	0	6
Lattuca et al 2016	1	0	1	0	1	1	1	5
Olsen et al 2015	1	1	1	1	1	1	0	6
Palmerini et al 2014	1	0	1	1	0	1	1	5
Raposeiras-Roubin et al 2018	1	0	1	1	1	1	1	6
Sorensen et al 2009	1	0	1	1	1	1	0	5
Sorrentino et al 2018	1	1	1	0	1	1	0	5
Sra et al 2016	1	1	0	1	0	1	1	5
Tsai et al 2011	1	0	1	1	1	1	0	5
Voss et al 2016	1	0	1	0	1	1	0	4
Wang et al 2015	1	0	1	1	1	1	0	5
Wong et al 2006	1	0	1	0	1	1	0	4
Yetgin et al 2018	1	0	1	0	1	1	1	5

Post hoc observational analysis of RCTs

Study ID	Selection			Comparability	Outcome			Total Points
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Comparability of cohorts on analysis	Assessment of outcome	Adequate duration of follow-up	Adequacy of follow up of cohorts	
Atar et al 2006	1	1	0	0	1	1	0	4
Costa et al 2015	1	0	1	0	1	1	1	5
Jolly et al 2009	1	0	1	1	1	1	1	6
Khan et al 2015	1	1	1	0	1	1	1	6
Kohli et al 2014	1	0	1	1	1	1	1	6
Mrdovic et al 2013	1	0	1	1	0	1	1	5
Nikolsky et al 2015	1	0	1	0	1	1	0	4
Mahaffey et al 2014	1	1	1	1	1	1	0	6
Valgimigli et al 2017	1	0	1	1	0	0	0	3

Table 3.4: Risk of bias of included RCTs assessed by Scottish Intercollegiate Guideline Network (SIGN)

	Bergen et al 1994	Carraba et al 2016	Cuisset et al 2017	Han et al 2015	Savonitto et al 2012	Yeh et al 2015	Yusuf et al 2006	Bonaca et al 2015		
The study addresses an appropriate and clearly focused question.										
The assignment of subjects to treatment groups is randomised.										
An adequate concealment method is used.										
The design keeps subjects and investigators 'blind' about treatment allocation.										
The treatment and control groups are similar at the start of the trial.										
The only difference between groups is the treatment under investigation.										
All relevant outcomes are measured in a standard, valid and reliable way.										Yes
What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	UC	0%	1.8%%	UC	2%	UC	0.07%	UC		No
All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis).										Can't say
Where the study is carried out at more than one site, results are comparable for all sites.		N/A	N/A						UC	Unclear
How well was the study done to minimise bias? Code as follows: High quality (++) Acceptable (+) Low quality (-) Unacceptable	-	+	-	+	+	+	++	++	N/A	Not applicable

Table 3.5: Incidence of bleeding stratified by type of ACS presentation in observational studies and RCTs

Study design	Author/year	Length of follow-up	Bleeding criteria	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
STEMI					
Observational studies	Amin et al 2016	6 months	BARC 1-5	1023	24.8 (23.5, 26.1) *
	Amin et al 2013	12 months	BARC 1	628	39.8 (37.4, 42.2) *
	Lattuca et al 2016	12 months	BARC 1-3	132	35.8 (31.1, 40.8) *
	Bacquelin et al 2015	12 months	BARC 2-5	79	7.85 (6.35, 9.68) *
	Chen et al 2019	12 months	BARC ≥ 2	44	4.71 (3.53, 6.27) *
	Kassaian et al 2015	12 months	GUSTO mild, moderate, severe.	6	1.43 (0.65, 3.07) *
	Sorrentino et al 2018	12 months	Bleed leading to hospitalisation or transfusion	4	1.27 (0.49, 3.22) *
	Graipe et al 2015	12 months	Intracranial bleed	169	0.27 (0.23, 0.31) *
	Caneiro-Queija et al 2018	455 days (median)	BARC 2 - 3	195	12.0 (10.5, 13.7) *
	Wong et al 2006	21 months	CURE major/life threatening	8	6.9 (3.54, 13.0) *
	Ertas et al 2018	24 months	Physician-confirmed bleeding event	12	2.38 (1.37, 4.12) *
RCTs	Han et al 2015	12 months	BARC 1-5	42	2.37 (1.76, 3.19) *
	Mrdovic et al 2013	12 months	TIMI major/minor	25	1.29 (0.87, 1.89) *
	Nikolsky et al 2015	3 years	HORIZON major	63	2.15 (1.68, 2.74) *

Study design	Author/year	Length of follow-up	Bleeding criteria	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
NSTEMI/UA					
Observational studies	Cuisset et al 2009	1 month	TIMI major/minor	16	2.68 (1.66, 4.31) *
	Amin et al 2016	6 months	BARC 1-5	1044	24.2 (23.0, 25.5) *
	Amin et al 2013	12 months	BARC 1	707	35.7 (33.6, 37.8) *
	Chen et al 2019	12 months	BARC ≥ 2	73	5.05 (4.04, 6.31) *
	Palmerini et al 2014	12 months	BARC (any)	41	3.91 (2.89, 5.26) *
	Kassaian et al 2015	12 months	GUSTO mild, moderate, severe.	17	1.39 (0.87, 2.22) *
	Sorrentino et al 2018	12 months	Bleed leading to hospitalisation or transfusion	79	1.89 (1.52, 2.34) *
	Graipe et al 2015	12 months	Intracranial bleed	410	0.34 (0.31, 0.37) *
	Caneiro-Queija et al 2018	455 days (median)	BARC 2 - 3	305	11.7 (10.5, 13.0) *
	Wong et al 2006	21 months	CURE major/life threatening	7	6.48 (3.17, 12.8) *
	Ertas et al 2018	24 months	Physician-confirmed bleeding event	9	1.78 (0.94, 3.35) *
RCTs	Jolly et al 2009	8 months	CURE major	28	1.07 (0.74, 1.54) *
	Savonitto et al 2012	12 months	BARC 2, 3a & 3b	3	0.96 (0.33, 2.78) *
	Mahaffey et al 2014	502 days (median)	TIMI major/minor	236	2.12 (1.87, 2.41) *

Incidence and associated 95% CI calculated from data within study,* ***CI**: Confidence Interval,* ***TIMI****: Thrombolysis In Myocardial Infarction,* ***BARC****: Bleeding Academic Research Consortium,* ***GUSTO****: Global Use of Strategies To open Occluded arteries,* ***CURE****: Clopidogrel in Unstable angina to prevent Recurrent Events,* ***HORIZON****: Harmonising Outcomes with Revascularisation and stents.*

Table 3.6: Incidence of bleeding in observational studies stratified by discharge antithrombotic therapy and duration

Author/year	Length of follow-up	Bleeding definition	Discharge antithrombotic combination	Duration	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
SAPT						
Fosbol et al 2012	12 months	Bleed leading to hospitalisation	Aspirin only	NR	223	10.1 (8.89, 11.4) *
Tsai et al 2011	12 months	Gastrointestinal bleed	Aspirin + PPI	NR	148	12.3 (10.6, 14.3) *
			Clopidogrel only		34	2.57 (1.84, 3.56) *
			Clopidogrel + PPI		91	8.65 (7.1, 10.5) *
Sorensen et al 2009	476.5 days (mean)	Fatal and non-fatal bleed	Aspirin only	NR	709	3.78 (3.52, 4.06) *
			Clopidogrel only		158	2.18 (1.87, 2.54) *
Wong et al 2006	21 months	CURE major/life threatening	Aspirin	NR	7	6.48 (3.17, 12.8) *
Ertas et al 2018	24 months	Physician-confirmed bleeding event	SAPT	NR	1	0.88 (0.16, 4.80) *
DAPT						
Cuisset et al 2009	1 month	TIMI major/minor	Aspirin (75 mg) + clopidogrel (75 mg)	1 month	16	2.68 (1.66, 4.31) *
Amin et al 2016	6 months	BARC 1-5	Aspirin + thienopyridine	NR	2246	24.2 (23.3, 25.1) *
Lattuca et al 2016	12 months	BARC 1-3	Aspirin + prasugrel	NR	68	33.3 (27.2, 40.1) *
			Aspirin + clopidogrel		64	38.8 (31.7, 46.4) *

Author/year	Length of follow-up	Bleeding definition	Discharge antithrombotic combination	Duration	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
Bacquelin et al 2015	12 months	BARC 2-5	Aspirin + thienopyridine	NR	70	7.32 (5.84, 9.15) *
Chen et al 2019	12 months	BARC ≥ 2	Aspirin + clopidogrel	12 months	80	4.33 (3.49, 5.36) *
Chen et al 2019	12 months	BARC ≥ 2	Aspirin + ticagrelor	12 months	17	8.46 (5.35, 13.1) *
Palmerini et al 2014	12 months	BARC (any)	Aspirin (160 mg) + clopidogrel (75 mg)	12 months	41	3.91 (2.89, 5.26) *
Fosbol et al 2012	12 months	Bleed leading to hospitalisation	Aspirin + clopidogrel		336	11.8 (10.7, 13.1) *
Effron et al 2018	12 months	Bleed leading to hospitalisation or transfusion	Aspirin + prasugrel	NR	393	3.07 (2.79, 3.38) *
			Aspirin + ticagrelor		99	3.31 (2.73, 4.01) *
Carrero et al 2016	12 months	Major bleed	Aspirin + clopidogrel	12 months	333	0.92 (0.83, 1.03) *
Sra et al 2016	15 months	BARC 1-5	Aspirin + thienopyridine	NR	353	20.1 (18.3, 22.0) *
Caneiro-Queija et al 2018	15 months	BARC 2 - 3	Aspirin + thienopyridine	NR	428	11.9 (10.9, 13.0) *
Sorensen et al 2009	476.5 days (mean)	Fatal and non-fatal bleed	Aspirin + clopidogrel	NR	421	3.45 (3.14, 3.78) *
Cuschieri et al 2014	1.7 years (mean)	Gastrointestinal bleed	Aspirin + clopidogrel	NR	107	3.33 (2.76, 4.00) *
Wong et al 2006	21 months	CURE major/life-threatening	Aspirin + clopidogrel		8	6.90 (3.5, 13.0) *
Voss et al 2016	1.94 years (mean)	Other	Aspirin + clopidogrel	NR	206	5.88 (5.15, 6.71) *
Brener et al 2016	24 months	TIMI, GUSTO and ACUITY Major bleed	Aspirin + clopidogrel	NR	430	5.17 (4.71, 5.66) *

Author/year	Length of follow-up	Bleeding definition	Discharge antithrombotic combination	Duration	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
Ertas et al 2018	24 months	Physician-confirmed bleeding event	DAPT	NR	20	2.20 (1.43, 3.37) *
Anticoagulant						
Braun et al 2014	3 months	BARC 2-5	Ticagrelor + warfarin	3 months	10	9.43 (5.21, 16.5) *
			Aspirin + clopidogrel + warfarin		16	10.2 (6.37, 15.9) *
Bacquelin et al 2015	12 months	BARC 2-5	Aspirin + thienopyridine + vitamin k	NR	6	18.8 (8.89, 35.3) *
Chen et al 2019	12 months	BARC ≥ 2	Warfarin only	12 months	1	10.0 (1.79, 40.4) *
Fosbol et al 2012	12 months	Bleed leading to hospitalisation	Warfarin only	NR	78	13.9 (11.2, 16.9) *
			Warfarin + aspirin		182	14.3 (12.5, 16.4) *
			Warfarin + aspirin + clopidogrel		109	14.9 (12.5, 17.7) *
Sra et al 2016	15 months	BARC 1-5	Aspirin + thienopyridine + OAC	NR	87	31.4 (26.2, 37.1) *
Caneiro-Queija et al 2018	15 months	BARC 2 - 3	Anticoagulant	NR	101	21.1 (17.7, 25.0) *
Sorensen et al 2009	476.5 days (mean)	Fatal and non-fatal bleed	Vitamin k only	NR	60	4.55 (3.55, 5.81) *
			Aspirin + vitamin k		133	17.8 (15.2, 20.7) *
			Clopidogrel + vitamin k		30	15.3 (10.9, 21.0) *

Author/year	Length of follow-up	Bleeding definition	Discharge antithrombotic combination	Duration	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
Sorensen et al 2009	476.5 days (mean)	Fatal and non-fatal bleed	Aspirin + clopidogrel + vitamin k	NR	61	19.4 (15.4, 24.1) *

Incidence and associated 95% CI calculated from data within study,* ***CI**: Confidence Interval,* ***SD****: Standard deviation,* ***SAPT:*** *Single antiplatelet,* ***DAPT:*** *Dual antiplatelet,* ***PPI****: Proton Pump Inhibitor,* ***OAC:*** *Oral Anticoagulation,* ***NR****; not reported,* ***CURE****: Clopidogrel in Unstable angina to prevent Recurrent Events,* ***TIMI****: Thrombolysis In Myocardial Infarction,* ***BARC****: Bleeding Academic Research Consortium,* ***GUSTO****: Global Use of Strategies To open Occluded arteries,* ***ACUITY****; acute catheterisation and urgent intervention triage strategy.*

Table 3.7: Incidence of bleeding in RCTs stratified by discharge antithrombotic therapy and duration

Author/year	Length of follow-up	Bleeding definition	Discharge antithrombotic combination	Duration	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
SAPT						
Yeh et al 2015	18 months	BARC 2-5	Aspirin + placebo	18 months	35	1.98 (1.42, 2.74) *
Bonaca et al 2015	33 months	TIMI major	Aspirin (75 -150 mg) + placebo	33 months	72	1.03 (0.82, 1.29) *
DAPT						
Carrabba et al 2016	12 months	BARC 1-3	Aspirin (100 mg) + prasugrel (10 mg)	12 months	45	47.4 (37.6, 57.3) *
			Aspirin (100 mg) + prasugrel (5 mg)		31	31.6 (23.3, 41.4) *
Cuisset et al 2017	12 months	BARC ≥ 2	Aspirin + clopidogrel	NR	30	9.49 (6.73, 13.2) *
			Aspirin + prasugrel/ticagrelor		76	23.9 (19.5, 28.9) *
Han et al 2015	12 months	BARC 1-5	Aspirin + clopidogrel	NR	47	2.33 (1.76, 3.08) *
Savonitto et al 2012	12 months	BARC 2, 3a & 3b	Aspirin + thienopyridine	NR	3	0.96 (0.33, 2.78) *
Kohli et al 2014	450 days	TIMI major/minor	Aspirin (≤ 150 mg) + clopidogrel (75 mg)	NR	103	2.75 (2.27, 3.32) *
			Aspirin (≥ 150 mg) + clopidogrel (75 mg)		70	2.80 (2.22, 3.52) *

Author/year	Length of follow-up	Bleeding definition	Discharge antithrombotic combination	Duration	No with bleed	Crude incidence of bleeding per 100 persons and 95% CI
Kohli et al 2014	450 days	TIMI major/minor	Aspirin (≤ 150 mg) + prasugrel (75 mg)	NR	137	3.60 (3.05, 4.24) *
			Aspirin (≥ 150 mg) + prasugrel (75 mg)		97	3.82 (3.14, 4.64) *
Yeh et al 2015	18 months	BARC 2-5	Aspirin + thienopyridine	18 months	76	4.21 (3.38, 5.24) *
Costa et al 2015	6 months	BARC 2-5	Aspirin (80 - 160 mg) + clopidogrel (75 mg)	6 months	30	4.09 (2.88, 5.78) *
	24 months		Aspirin (80 - 160 mg) + clopidogrel (75 mg)	24 months	52	7.10 (5.46, 9.20) *
Bonaca et al 2015	33 months	TIMI major	Aspirin + ticagrelor (60 mg)	33 months	170	2.44 (2.11, 2.83) *
			Aspirin + ticagrelor (90 mg)		193	2.76 (2.40, 3.17) *
Nikolsky et al 2015	3 years	HORIZON major	Aspirin + thienopyridine	NR	63	2.15 (1.68, 2.74) *
Anticoagulant						
Bergen et al 1994	37 months	Major bleed	Nicoumalone or phenprocoumon	37 months	73	4.29 (3.43, 5.37) *

** Incidence and associated 95% CI calculated from data within study, **CI**: Confidence Interval, **SD**: Standard deviation, **SAPT:** Single antiplatelet, **DAPT:** Dual antiplatelet, **PPI**: Proton Pump Inhibitor, **NR**; not reported, **BARC**: Bleeding Academic Research Consortium, **TIMI**: Thrombolysis In Myocardial Infarction, **HORIZON**: Harmonising Outcomes with Revascularisation and stents.*

Table 3.8: Incidence of major, minor and nuisance bleeding events in observational studies and RCTs that used any of the formal bleeding definitions stratified by length of follow-up

Observational Studies				Randomised Controlled Trials			
Length of follow-up	Study ID	Bleeding definition used	Incidence of bleeds per 100 persons and 95% CI	Length of follow-up	Study ID	Bleeding definition used	Incidence of bleeds per 100 persons and 95% CI
Major bleeds				**Major bleeds**			
30 days	Cuisset et al 2009	TIMI major	0.84 (0.36, 1.95) *	*6 months*	Yusuf et al 2006	OASIS-5 major	1.84 (1.66, 2.03) *
3 months	Braun et al 2014	BARC 3 - 5	5.32 (3.20, 8.74) *	*8 months*	Jolly et al 2009	CURE major	1.07 (0.74, 1.54) *
12 months	Lattuca et al 2016	BARC 3	3.25 (1.87, 5.60) *	*12 months*	Carrabba et al 2016	BARC 3	2.07 (0.81, 5.21) *
	Raposeiras-Roubin et al 2018	BARC 3 - 5	1.53 (1.21, 1.94) *		Han et al 2015	BARC 3 - 5	0.10 (0.03, 0.36) *
	Bacquelin et al 2015	BARC 3 - 5	1.29 (0.76, 2.20) *		Cuisset et al 2017	TIMI major	0.79 (0.34, 1.83) *
	Yetgin et al 2018	TIMI major	0.94 (0.63, 1.41) *		Mrdovic et al 2013	TIMI major	0.15 (0.05, 0.45) *
	Kassaian et al 2015	GUSTO severe	0.67 (0.37, 1.20) *	*15 months*	Mahaffey et al 2013	TIMI major	1.37 (1.17, 1.60) *
15 months	Caneiro-Queija et al 2018	BARC 3	3.33 (2.83, 3.92) *		Kohli et al 2014	TIMI major	1.20 (1.02, 1.40) *
	Sra et al 2016	BARC 3 - 5	1.03 (0.68, 1.57) *	*> 15 months*	Costa et al 2015	BARC 3 - 5	2.73 (2.01, 3.70) *
> 15 months	Brener et al 2016	TIMI/GUSTO/ACUITY	5.17 (4.71, 5.66) *		Yeh et al 2015	BARC 3 - 5	1.48 (1.13, 1.93) *
	Wong et al 2006	CURE major	3.13 (1.52, 6.31) *		Bonaca et al 2015	TIMI major	1.41 (1.26, 1.58) *
					Nikolsky et al 2015	Horizon major	2.15 (1.68, 2.74) *
Minor bleeds				**Minor bleeds**			
30 days	Cuisset et al 2009	TIMI minor	1.84 (1.03, 3.27) *	*12 months*	Carrabba et al 2016	BARC 2	6.22 (3.59, 10.6) *

3 months	Braun et al 2014	BARC 2	4.56 (2.63, 7.80) *			Han et al 2015	BARC 2	0.35 (0.17, 0.71) *
12 months	Lattuca et al 2016	BARC 2	10.6 (7.83, 14.1) *			Cuisset et al 2017	TIMI minor	5.52 (4.00, 7.58) *
	Bacquelin et al 2015	BARC 2	6.56 (5.19, 8.26) *			Mrdovic et al 2013	TIMI minor	0.36 (0.17, 0.74) *
	Kassaian et al 2015	GUSTO mild	0.73 (0.42, 12.7) *		*15 months*	Kohli et al 2014	TIMI minor	2.03 (1.80, 2.29) *
15 months	Caneiro-Queija et al 2018	BARC 2	8.49 (7.69, 9.37) *			Mahaffey et al 2014	TIMI minor	0.76 (0.61, 0.93) *
	Sra et al 2016	BARC 2	4.67 (3.78, 5.76) *		*> 15 months*	Costa et al 2015	BARC 2	2.87 (2.13, 3.85) *
> 15 months	Wong et al 2006	CURE minor	3.57 (1.82, 6.89) *			Yeh et al 2015	BARC 2	1.71 (1.33, 2.18) *
						Bonaca et al 2015	TIMI minor	0.66 (0.56, 0.78) *
Nuisance bleeds					**Nuisance bleeds**			
6 months	Amin et al 2016	BARC 1	9.14 (8.57, 9.74) *		*12 months*	Carrabba et al 2016	BARC 1	31.9 (24.9, 37.9) *
12 months	Amin et al 2013	BARC 1	37.5 (35.9, 39.1) *			Han et al 2015	BARC 1	1.88 (1.37, 2.57) *
	Lattuca et al 2016	BARC 1	21.9 (18.0, 26.5) *			Cuisset et al 2017	TIMI minimal	10.4 (8.27, 13.0) *
15 months	Sra et al 2016	BARC 1	19.2 (17.4, 21.1) *			Mrdovic et al 2013	TIMI minimal	0.77 (0.47, 1.27) *

*Incidence and associated 95% CI calculated from data within study, **CI**: Confidence Interval, **TIMI**: Thrombolysis In Myocardial Infarction, **BARC**: Bleeding Academic Research Consortium, **GUSTO**: Global Use of Strategies To open Occluded arteries, **ACUITY**; acute catheterisation and urgent intervention triage strategy. **CURE**: Clopidogrel in Unstable angina to prevent Recurrent Events, **HORIZON**: Harmonising Outcomes with Revascularisation and stents, **OASIS-5**: the fifth Organization to Assess Strategies In acute ischemic Syndromes

Table 3.9: Incidence of different types of bleeding events stratified by length of follow-up

Type of bleed	Study design	Length of follow-up	Study ID	Incidence of bleeds per 100 persons and 95% CI
Bruising	*Observational studies*	*12 months*	Chen et al 2019	0.84 (0.54, 1.29) *
			Bacquelin et al 2015	1.49 (0.91, 2.45) *
			Amin et al 2013	20.1 (18.8, 21.4) *
			Lattuca et al 2016	22.5 (18.5, 27.0) *
Gastrointestinal	*Observational studies*	*30 days*	Cuisset et al 2009	0.50 (0.17, 1.47) *
		3 months	Braun et al 2014	4.56 (2.63, 7.80) *
		12 months	Yetgin et al 2018	0.25 (0.11, 0.53) *
			Garay et al 2016	1.16 (0.72, 1.88) *
			Bacquelin et al 2015	1.79 (1.13, 2.81) *
			Chen et al 2019	1.89 (1.42, 2.52) *
			Lattuca et al 2016	4.88 (3.11, 7.58) *
			Tsai et al 2010	7.63 (6.80, 8.54) *
		15 months	Sorensen et al 2009	1.88 (1.75, 2.02) *
		> 15 months	Cuschieri et al 2014	3.33 (2.76, 4.00) *
			Voss et al 2016	3.65 (3.08, 4.33) *
	RCTs	*12 months*	Atar et al 2006	1.02 (0.84, 1.24) *
			Mrdovic et al 2013	0.67 (0.39, 1.14) *
		15 months	Kohli et al 2014	0.66 (0.53, 0.82) *
Respiratory	*Observational studies*	*12 months*	Bacquelin et al 2015	0.50 (0.21, 1.16) *
			Chen et al 2019	0.76 (0.48, 1.19) *
			Garay et al 2016	1.09 (0.66, 1.79) *
		15 months	Sorensen et al 2009	0.54 (0.47, 0.62) *
		> 15 months	Voss et al 2016	0.91 (0.65, 1.29) *
	RCTs	*12 months*	Mrdovic et al 2013	0.51 (0.28, 0.95) *
Genito-Urinary	*Observational studies*	*12 months*	Chen et al 2019	0.46 (0.26, 0.83) *
			Bacquelin et al 2015	0.50 (0.21, 1.16) *
			Garay et al 2016	1.75 (1.18, 2.58) *
			Lattuca et al 2016	2.17 (1.10, 4.22) *
		15 months	Sorensen et al 2009	0.70 (0.62, 0.78) *
		> 15 months	Voss et al 2016	0.80 (0.55, 1.15) *
	RCTs	*12 months*	Mrdovic et al 2013	0.15 (0.05, 0.45) *
Intracranial	*Observational studies*	*30 days*	Cuisset et al 2009	0.34 (0.09, 1.21) *
		3 months	Braun et al 2014	0.76 (0.21, 2.73) *
		12 months	Chen et al 2019	0.21 (0.09, 0.49)
			Yetgin et al 2018	0.25 (0.11, 0.53) *
			Garay et al 2016	0.36 (0.16, 0.85) *
			Bacquelin et al 2015	0.40 (0.15, 10.2) *
			Graipe et al 2015	0.31 (0.29, 0.34) *
			Wang et al 2015	0.20 (0.18, 0.22) *
		15 months	Sorensen et al 2009	0.46 (0.40, 0.53) *

		> 15 months	Voss et al 2016	0.43 (0.26, 0.70) *
Type of bleed	**Study design**	**Length of follow-up**	**Study ID**	**Incidence of bleeds per 100 persons and 95% CI**
Intracranial	*RCTs*	*> 15 months*	Bonaca et al 2015	0.45 (0.37, 0.55) *
Intraocular	*Observational studies*	*12 months*	Chen et al 2019	0.25 (0.12, 0.55) *
			Lattuca et al 2016	0.27 (0.05, 1.52) *
		> 15 months	Voss et al 2016	0.20 (0.10, 0.41) *
Unspecified†	*Observational studies*	*3 months*	Braun et al 2014	1.90 (0.81, 4.37) *
		12 months	Yetgin et al 2018	0.25 (0.11, 0.53) *
			Bacquelin et al 2015	0.60 (0.27, 1.30) *
			Chen et al 2019	0.67 (0.41, 1.09) *
			Lattuca et al 2016	0.81 (0.28, 2.36) *
		> 15 months	Voss et al 2016	0.20 (0.10, 0.41) *

*Incidence and associated 95% CI calculated from data within study, †Bleeds from unspecified location, **CI**: Confidence, **RCT**: Randomised controlled trial

Chapter 4.0 appendices

Appendix 4.1: Code list used to identify ACS patients within the CiPCA database

Read code	Description
323..	ECG: myocardial infarction
3233	ECG: antero-septal infarct.
3234	ECG:posterior/inferior infarct
3235	ECG: subendocardial infarct
3236	ECG: lateral infarction
323Z.	ECG: myocardial infarct NOS
G30..	Acute myocardial infarction
G300.	Acute anterolateral infarction
G301.	Other specified anterior myocardial infarction
G3010	Acute anteroapical infarction
G30..11	Attack - heart
G3011	Acute anteroseptal infarction
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..17	Silent myocardial infarction
G301z	Anterior myocardial infarction NOS
G302.	Acute inferolateral infarction
G303.	Acute inferoposterior infarction
G304.	Posterior myocardial infarction NOS
G305.	Lateral myocardial infarction NOS
G306.	True posterior myocardial infarction
G307.	Acute subendocardial infarction
G3070	Acute non-Q wave infarction
G3071	Acute non-ST segment elevation myocardial infarction
G308.	Inferior myocardial infarction NOS
G309.	Acute Q-wave infarct
G30B.	Acute posterolateral myocardial infarction
G30X.	Acute transmural myocardial infarction of unspecified site
G30X0	Acute ST segment elevation myocardial infarction
G30y.	Other acute myocardial infarction
G30y1	Acute papillary muscle infarction
G30y2	Acute septal infarction
G30yz	Other acute myocardial infarction NOS
G30z.	Acute myocardial infarction NOS
G3110	Myocardial infarction aborted
G311011	MI - acute myocardial infarction aborted
G3115	Acute coronary syndrome

G31y1	Microinfarction of heart
G344.00	Silent myocardial infarction
G35..	Subsequent myocardial infarction
G350.	Subsequent myocardial infarction of anterior wall
G351.	Subsequent myocardial infarction of inferior wall
G353.	Subsequent myocardial infarction of other sites
G35X.	Subsequent myocardial infarction of unspecified site
G362.	Ventricular septal defect as current complication following acute myocardial infarction
G363.	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction
G364.	Rupture of chordae tendinae as current complication following acute myocardial infarction
G365.	Rupture of papillary muscle as current complication following acute myocardial infarction
Gyu3400	[X] Acute transmural myocardial infarction of unspecified site
Gyu3500	[X] Subsequent myocardial infarction of other sites
Gyu3600	[X] Subsequent myocardial infarction of unspecified site

Appendix 4.2: Code list used in the consensus exercise after de-duplication

QUESTION ASKED: Does the code define a bleed likely to have occurred following ACS?

Read code	Description	Yes (Include in definition)	No (Exclude from definition)	Maybe (Unsure)
14C8.00	H/O: haematemesis			
14C9.00	H/O: melaena			
14CA.11	H/O: GI Bleed			
158..00	H/O: abnormal uterine bleeding			
158Z.00	H/O:abnormal uterine bleed NOS			
15A1.00	H/O: ante-partum haemorrhage			
15A6.00	H/O: post-partum haemorrhage			
7421300	Surgical arrest of postoperative bleeding of adenoid			
7517500	Surgical arrest of postoperative bleeding from tooth socket			
7531400	Surgical arrest of postoperative bleeding from tonsillar bed			
7H22600	Reopen abdo reexplore intraabd op site surg arr postop bleed			
7J01300	Reopen cranium reexploration op site arrest post op bleeding			
7M0U400	Reexploration of organ & surgical arrest postop bleeding NOC			
SP21.11	Haematoma - postoperative			
SP21.12	Haemorrhage - postoperative			
SP21100	Post-operative haemorrhage			
SP21200	Post-operative haematoma formation			
7004200	Evacuation of haematoma from cerebellum			
7004300	Evacuation of intracerebral haematoma NEC			
7032000	Evacuation of extradural haematoma			
7303000	Drainage of haematoma of external ear			
7303200	Drainage haematoma ext ear control cavity c bolster suture			
7736000	Evacuation of perianal haematoma			
7D05200	Evacuation of haematoma of vulva			
7G2H400	Liposuction removal of haematoma			
7G31400	Drainage of subungual haematoma			
7M0G000	Aspiration of haematoma of organ NOC			
7M0G400	Evacuation of haematoma NEC			
F503100	Haematoma of pinna			
K138300	Intrarenal haematoma			
K13y800	Perirenal haematoma			
K275100	Corpus cavernosum haematoma			
K286000	Scrotal haematoma due to nontraumatic cause			

K286300	Testicular haematoma due to nontraumatic cause			
K286v00	Male genital haematoma NOS			
K31y000	Breast haematoma due to nontraumatic cause			
K537.00	Haematoma of the broad ligament			
K575.00	Haematoma of vulva			
L345.00	Vulval and perineal haematoma during delivery			
L345.11	Perineal haematoma			
L345.12	Vulval and perineal haematoma during delivery			
L345000	Vulval and perineal haematoma during delivery, unspecified			
L345100	Vulval and perineal haematoma during delivery - delivered			
L345z00	Vulval and perineal haematoma during delivery NOS			
L357.00	Obstetric trauma causing pelvic haematoma			
L357000	Obstetric pelvic haematoma unspecified			
L357100	Obstetric pelvic haematoma - delivered			
L394600	Haematoma of obstetric wound			
L443.11	Haematoma - perineal wound			
S62A.00	Traumatic extradural haematoma			
S740100	Liver haematoma and contusion without open wound into cavity			
S750100	Spleen haematoma without mention of open wound into cavity			
S751100	Spleen haematoma with open wound into cavity			
S760100	Kidney haematoma without mention of open wound into cavity			
S760111	Renal haematoma without mention of open wound into cavity			
S761100	Kidney haematoma with open wound into cavity			
SE...11	Haematoma with intact skin			
SE22300	Haematoma of rectus sheath			
SE33011	Subungal haematoma			
SE33200	Contusion, fingernail (includes subungual haematoma)			
SE45.11	Haematoma of leg			
SE46.00	Traumatic haematoma			
SE4z.11	Haematoma NOS			
SE4z.12	Intramuscular haematoma NOS			
SP21.00	Peri-operative haemorrhage or haematoma			
ZA13600	Drainage of subungual haematoma			
ZA13700	Drainage of subungual haematoma with hot wire			
ZA13800	Drainage of subungual haematoma with drill			
7004100	Evacuation of haematoma from temporal lobe of brain			
7008200	Aspiration of haematoma of brain tissue			
7017000	Evacuation of subdural haematoma			

G60..00	Subarachnoid haemorrhage			
G600.00	Ruptured berry aneurysm			
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation			
G602.00	Subarachnoid haemorrhage from middle cerebral artery			
G603.00	Subarachnoid haemorrhage from anterior communicating artery			
G604.00	Subarachnoid haemorrhage from posterior communicating artery			
G605.00	Subarachnoid haemorrhage from basilar artery			
G606.00	Subarachnoid haemorrhage from vertebral artery			
G60z.00	Subarachnoid haemorrhage NOS			
G61..00	Intracerebral haemorrhage			
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage			
G61..12	Stroke due to intracerebral haemorrhage			
G610.00	Cortical haemorrhage			
G611.00	Internal capsule haemorrhage			
G612.00	Basal nucleus haemorrhage			
G613.00	Cerebellar haemorrhage			
G614.00	Pontine haemorrhage			
G615.00	Bulbar haemorrhage			
G616.00	External capsule haemorrhage			
G617.00	Intracerebral haemorrhage, intraventricular			
G618.00	Intracerebral haemorrhage, multiple localized			
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified			
G61z.00	Intracerebral haemorrhage NOS			
G62..00	Other and unspecified intracranial haemorrhage			
G620.00	Extradural haemorrhage - nontraumatic			
G621.00	Subdural haemorrhage - nontraumatic			
G622.00	Subdural haematoma - nontraumatic			
G623.00	Subdural haemorrhage NOS			
G62z.00	Intracranial haemorrhage NOS			
G680.00	Sequelae of subarachnoid haemorrhage			
G682.00	Sequelae of other nontraumatic intracranial haemorrhage			
Gyu6100	[X]Other subarachnoid haemorrhage			
Gyu6200	[X]Other intracerebral haemorrhage			
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified			
S62..12	Subarachnoid haemorrhage following injury			
S62..13	Subdural haemorrhage following injury			
S620.00	Closed traumatic subarachnoid haemorrhage			
S621.00	Open traumatic subarachnoid haemorrhage			
S622.00	Closed traumatic subdural haemorrhage			

S623.00	Open traumatic subdural haemorrhage			
S629.00	Traumatic subdural haematoma			
S629000	Traumatic subdural haematoma without open intracranial wound			
S629100	Traumatic subdural haematoma with open intracranial wound			
S630.12	Intracranial haematoma following injury			
2BB5.00	O/E - retinal haemorrhages			
2BB8.00	O/E - vitreous haemorrhages			
F404500	Intra-ocular haemorrhage			
F424300	Retinal pigment epithelium haemorrhagic detachment			
F42y.11	Haemorrhage - retinal			
F42y100	Superficial retinal haemorrhage			
F42y300	Deep retinal haemorrhage			
F42y400	Subretinal haemorrhage			
F42y500	Retinal haemorrhage NOS			
F436000	Unspecified choroidal haemorrhage			
F436100	Expulsive choroidal haemorrhage			
F437200	Haemorrhagic choroidal detachment			
F4K2800	Vitreous haemorrhage			
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere			
S624.11	Epidural haematoma following injury			
S626.00	Epidural haemorrhage			
793B000	Decompression of cardiac tamponade			
G360.00	Haemopericardium/current comp folow acut myocard infarct			
G530.00	Haemopericardium			
G53z.11	Cardiac tamponade			
S714.00	Injury of heart with haemopericardium			
1C6..00	Nose bleed symptom			
1C62.00	Has nose bleeds - epistaxis			
1C6Z.00	Nose bleed symptom NOS			
7404	Surgical arrest of bleeding from internal nose			
7404y00	Surgical arrest of bleeding from internal nose OS			
7404z00	Surgical arrest of bleeding from internal nose NOS			
R047.11	[D]Nosebleed			
172..00	Blood in sputum - haemoptysis			
172..12	Haemoptysis - symptom			
2DE7.00	O/E - throat haemorrhage			
R048.00	[D]Throat haemorrhage			
R063.00	[D]Haemoptysis			
R063000	[D]Cough with haemorrhage			
R063100	[D]Pulmonary haemorrhage NOS			
R063z00	[D]Haemoptysis NOS			

196B.00	Painful rectal bleeding			
196C.00	Painless rectal bleeding			
1994	Vomiting blood - fresh			
1994.11	Blood in vomit - symptom			
1995	Vomiting blood - coffee ground			
19E4.12	C/O - melaena			
19E6.00	Blood in faeces			
19E6.11	Blood in faeces symptom			
4737.11	Melaena - O/E of faeces			
4762	Faeces: fresh blood present			
4762.11	Blood in faeces			
4A23.00	Vomit: frank blood present			
4A23.11	Blood in vomit O/E			
4A5..00	Vomit occult blood			
4A5..11	Occult blood in vomit			
4A51.00	Vomit occult blood positive			
4A5Z.00	Vomit occult blood NOS			
7609y11	Tanner devascularisation for bleeding varices			
7619100	Gastrotomy and ligation of bleeding point of stomach			
7627200	Oversew of blood vessel of duodenal ulcer			
G850.00	Oesophageal varices with bleeding			
G852000	Oesophageal varices with bleeding in diseases EC			
J107.00	Mallory-Weiss syndrome			
J10y000	Haemorrhage of oesophagus			
J110100	Acute gastric ulcer with haemorrhage			
J110111	Bleeding acute gastric ulcer			
J110300	Acute gastric ulcer with haemorrhage and perforation			
J111100	Chronic gastric ulcer with haemorrhage			
J111111	Bleeding chronic gastric ulcer			
J111300	Chronic gastric ulcer with haemorrhage and perforation			
J11y100	Unspecified gastric ulcer with haemorrhage			
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation			
J120100	Acute duodenal ulcer with haemorrhage			
J120300	Acute duodenal ulcer with haemorrhage and perforation			
J121100	Chronic duodenal ulcer with haemorrhage			
J121111	Bleeding chronic duodenal ulcer			
J121300	Chronic duodenal ulcer with haemorrhage and perforation			
J12y100	Unspecified duodenal ulcer with haemorrhage			
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation			
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation			

J130100	Acute peptic ulcer with haemorrhage			
J130300	Acute peptic ulcer with haemorrhage and perforation			
J131100	Chronic peptic ulcer with haemorrhage			
J13y100	Unspecified peptic ulcer with haemorrhage			
J13y300	Unspecified peptic ulcer with haemorrhage and perforation			
J140100	Acute gastrojejunal ulcer with haemorrhage			
J14y100	Unspecified gastrojejunal ulcer with haemorrhage			
J150000	Acute haemorrhagic gastritis			
J573.00	Haemorrhage of rectum and anus			
J573.11	Bleeding PR			
J573000	Rectal haemorrhage			
J573011	Rectal bleeding			
J573012	PRB - Rectal bleeding			
J573z00	Haemorrhage of rectum and anus NOS			
J68..00	Gastrointestinal haemorrhage			
J680.00	Haematemesis			
J680.11	Vomiting of blood			
J681.00	Melaena			
J681.11	Blood in stool			
J681.12	Altered blood in stools			
J681.13	Blood in stools altered			
J68z.00	Gastrointestinal haemorrhage unspecified			
J68z.11	GIB - Gastrointestinal bleeding			
J68z000	Gastric haemorrhage NOS			
J68z100	Intestinal haemorrhage NOS			
J68z200	Upper gastrointestinal haemorrhage			
J68zz00	Gastrointestinal tract haemorrhage NOS			
158..12	Vaginal bleeding			
1584	Heavy episode of vaginal bleeding			
7D1C000	Evacuation of haematoma from vagina			
7F22700	Pack to control postnatal vaginal bleeding			
7F22711	Pack to control postnatal vaginal bleeding			
7F22712	Pack to control postnatal haemorrhage			
K566.00	Vaginal haematoma			
K56y100	Haemorrhage of vagina			
K56y111	Bleeding - vaginal NOS			
K56y112	BPV - Vaginal bleeding			
K587.00	Contact bleeding of cervix			
K5E..00	Other abnormal uterine and vaginal bleeding			
K5E1.00	Abnormal uterine bleeding, unspecified			
K5E2.00	Abnormal vaginal bleeding, unspecified			
K5Ez.00	Abnormal uterine and vaginal bleeding, unspecified			

Kyu9D00	[X]Other specified abnormal uterine and vaginal bleeding			
L040100	Unspec spontaneous abortion + delayed/excessive haemorrhage			
L040111	Spontaneous abortion with heavy bleeding			
L041100	Incomp spontaneous abortion + delayed/excessive haemorrhage			
L051100	Incomplete legal abortion + delayed or excessive haemorrhage			
L052100	Complete legal abortion with delayed/excessive haemorrhage			
L091.00	Delayed/excessive haemorrhage following abortive pregnancy			
L091z00	Delayed/excess haemorrhage NOS following abortive pregnancy			
L10..00	Haemorrhage in early pregnancy			
L10y.00	Other haemorrhage in early pregnancy			
L10y.11	Bleeding in early pregnancy			
L10y000	Other haemorrhage in early pregnancy unspecified			
L10y200	Other haemorrhage in early pregnancy - not delivered			
L10yz00	Other haemorrhage in early pregnancy NOS			
L10z.00	Early pregnancy haemorrhage NOS			
L10z000	Early pregnancy haemorrhage NOS unspecified			
L10z200	Early pregnancy haemorrhage NOS - not delivered			
L10zz00	Early pregnancy haemorrhage NOS			
L11..00	Antepartum haemorrhage, abruptio placentae, placenta praevia			
L11..11	Antepartum haemorrhage			
L11..12	Antepartum bleeding			
L113.00	Antepartum haemorrhage with coagulation defect			
L113.13	Antepartum haemorrhage with hypofibrinogenaemia			
L113000	Antepartum haemorrhage with coagulation defect unspecified			
L114100	Antepartum haemorrhage with trauma - delivered			
L115.00	Antepartum haemorrhage with uterine leiomyoma			
L115.11	Antepartum haemorrhage with fibroid			
L115.12	Antepartum haemorrhage with uterine fibroid			
L115100	Antepartum haemorrhage with uterine leiomyoma - delivered			
L11y.00	Other antepartum haemorrhage			
L11y000	Other antepartum haemorrhage unspecified			
L11y100	Other antepartum haemorrhage - delivered			
L11y200	Other antepartum haemorrhage - not delivered			
L11yz00	Other antepartum haemorrhage NOS			

L11z.00	Antepartum haemorrhage NOS			
L11z000	Antepartum haemorrhage NOS, unspecified			
L11z100	Antepartum haemorrhage NOS - delivered			
L11z200	Antepartum haemorrhage NOS - not deliv			
L11zz00	Antepartum haemorrhage NOS			
L36..00	Postpartum haemorrhage (PPH)			
L36..11	Bleeding postpartum			
L360.00	Third-stage postpartum haemorrhage			
L360000	Third-stage postpartum haemorrhage unspecified			
L360100	Third-stage postpartum haemorrhage - deliv with p/n problem			
L360200	Third-stage postpartum haemorrhage with postnatal problem			
L360z00	Third-stage postpartum haemorrhage NOS			
L361.00	Other immediate postpartum haemorrhage			
L361z00	Other immediate postpartum haemorrhage NOS			
L362.00	Secondary and delayed postpartum haemorrhage			
L362000	Secondary postpartum haemorrhage unspecified			
L362200	Secondary postpartum haemorrhage with postnatal problem			
L362z00	Secondary and delayed postpartum haemorrhage NOS			
L36z.00	Postpartum haemorrhage NOS			
L371200	Retained products with no haemorrhage with postnatal problem			
L3A..00	Intrapartum haemorrhage with coagulation defect			
L3X..00	Intrapartum haemorrhage, unspecified			
J11y3	Unspecified gastric ulcer with haemorrhage and perforation			
J1313	Chronic peptic ulcer with haemorrhage and perforation			
J1403	Gastrojejunal ulcer, acute with both haemorrhage and perforation			
J1411	Chronic gastrojejunal ulcer with haemorrhage			
J1413	Chronic gastrojejunal ulcer with haemorrhage and perforation			
J14y3	Unspecified gastrojejunal ulcer with haemorrhage and perforation			
J56y0	Haemoperitoneum			
4A24.11	Coffee ground vomit			
J108.00	Mallory - Weiss tear			
4737	Faeces colour: tarry			
4A24.00	Vomit: coffee ground			
Gyu60	Subarachnoid haemorrhage from other intracranial arteries			
G60X.	Subarachnoid haemorrhage from intracranial artery, unspecified			

X00DN	Intracerebral haemorrhage in hemisphere, subcortical			
X00DQ	Intracerebral haemorrhage in brain stem			
G681.	Sequelae of intracerebral haemorrhage			
14AF.00	H/O sub-arachnoid haemorrhage			
G61X000	Left sided intracerebral haemorrhage, unspecified			
G61X100	Right sided intracerebral haemorrhage, unspecified			
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction			
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage			
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif			
R047.	Epistaxis			
Ryu02	Haemorrhage from other sites in respiratory passages			
Ryu07	Haemorrhage from respiratory passages, unspecified			
H51y2	haemothorax			
N0919	Haemarthrosis, multiple sites			
N0911	Haemarthrosis, shoulder region			
N0912	Haemarthrosis, upper arm			
N0913	Haemarthrosis, forearm			
N0914	Haemarthrosis, hand			
N0915	Haemarthrosis, pelvic region and thigh			
N0916	Haemarthrosis, lower leg			
N0917	Haemarthrosis, ankle and foot			
N0918	Haemarthrosis, other site			
N0910	Haemarthrosis, site unspecified			
K197.	Unspecified haematuria			
K0A2.	recurrent and persistent haematuria			
K0A26	recurrent and persistent haematuria, dense deposit disease			
F5862	Otorrhagia			
G711.	Thoracic aortic aneurysm, ruptured			
G713.	Abdominal aortic aneurysm, ruptured			
G7150	Thoracoabdominal aortic aneurysm, ruptured			
G715.	Aortic aneurysm of unspecified site, ruptured			
G842.	Internal haemorrhoids with other complications			
G844.	External thrombosed haemorrhoids			
G845.	External haemorrhoids with other complications			
G848.	Unspecified haemorrhoids with other complications			
K221.	Congestion and haemorrhage of prostate			
K53y6	Haematosalpinx			
K544.	Haematometra			

K5C2.	Haematocolpos			
K592z	Excessive and frequent menstruation with irregular cycle			
Kyu9C	Other specified irregular menstruation			
K594z	Irregular menstruation, unspecified			
K5A1.	postmenopausal bleeding			
R027z	spontaneous ecchymosis			
Ryu73	haemorrhage, not elsewhere classified			
D305.	Haemorrhagic disorder due to circulating anticoagulants			
XE13x	Acute posthemorrhagic anaemia			
D000.	Iron deficiency anaemia secondary to blood loss			
158..11	C/O p.v. bleeding			
1583	H/O: post-menopausal bleeding			
16B..	Bruising symptom			
16B3.	Spontaneous bruising			
16BZ.	Bruising symptom NOS			
1A45.	Blood in urine - haematuria			
26A6.	O/E - blood stained vag. disch			
2D25.	O/E - epistaxis			
7A6G8	Thrombin inject pseudoaneurysm			
7L142	IV blood transfusion platelets			
7L143	Blood transfusion			
7L143	IV blood transfusion NEC			
D00	Iron deficiency anaemias			
D00y1	Microcytic hypochromic anaemia			
D00z	Unspec iron deficiency anaemia			
D00zz	Iron deficiency anaemia NOS			
D010	Pernicious anaemia			
D011X	Vit B12 defic anaemia unsp			
D0125	Macrocytic anaemia unspecified			
D2150	Anaemia secondary to CRF			
D21z	Anaemia NOS			
D2y	Other specified anaemias			
F4C71	Subconjunctival haemorrhage			
F4C72	Conjunctival haemorrhage NOS			
K1970	Painless haematuria			
K1971	Painful haematuria			
K1972	Microscopic haematuria			
K1973	Frank haematuria			
K286w	Haematospermia			
K5920	Menorrhagia			
N091A	Haemarthrosis of shoulder			
N091M	Haemarthrosis of knee			
R027	[D]Spontaneous bruising			

R0270	[D]Petechiae			
SE3z	Bruise - upper limb NOS			
SE4	Leg bruise			
SE4z	Bruise NOS			

Appendix 4.3: The final code list for bleeding categorised based on site of the bleeding events

Read code	Description	Classification
16B..00	Bruising symptom	Bruising
16B3.00	Spontaneous bruising	Bruising
16BZ.00	Bruising symptom NOS	Bruising
R027.11	[D]Spontaneous bruising	Bruising
R027000	[D]Petechiae	Bruising
R027z00	[D]Spontaneous ecchymosis NOS	Bruising
R027.00	[D]Spontaneous ecchymosis	Bruising
SE...00	Contusion (bruise) with intact skin (+ Daughter codes)	Bruising
172..00	Blood in sputum - haemoptysis	Respiratory/ENT
172..12	Haemoptysis - symptom	Respiratory/ENT
1C6..00	Nose bleed symptom	Respiratory/ENT
1C6..11	Epistaxis symptom	Respiratory/ENT
1C62.00	Has nose bleeds - epistaxis	Respiratory/ENT
1C6Z.00	Nose bleed symptom NOS	Respiratory/ENT
2D25.00	O/E - epistaxis	Respiratory/ENT
2DE7.00	O/E - throat haemorrhage	Respiratory/ENT
F503100	Haematoma of pinna	Respiratory/ENT
F586200	Otorrhagia	Respiratory/ENT
H51y200	Haemothorax	Respiratory/ENT
R047.00	[D]Epistaxis	Respiratory/ENT
R047.11	[D]Nosebleed	Respiratory/ENT
R048.00	[D]Throat haemorrhage	Respiratory/ENT
R063.00	[D]Haemoptysis	Respiratory/ENT
R063000	[D]Cough with haemorrhage	Respiratory/ENT
R063100	[D]Pulmonary haemorrhage NOS	Respiratory/ENT
R063z00	[D]Haemoptysis NOS	Respiratory/ENT
1720	Massive haemoptysis	Respiratory/ENT
7303000	Drainage of haematoma of external ear	Respiratory/ENT
7303200	Drainage haematoma ext ear control cavity c bolster suture	Respiratory/ENT
7404	Surgical arrest of bleeding from internal nose	Respiratory/ENT
7404y00	Surgical arrest of bleeding from internal nose OS	Respiratory/ENT
7404z00	Surgical arrest of bleeding from internal nose NOS	Respiratory/ENT
4737	Faeces colour: tarry	Gastrointestinal
4737.11	Melaena - O/E of faeces	Gastrointestinal
4762	Faeces: fresh blood present	Gastrointestinal
4762.11	Blood in faeces	Gastrointestinal
4A23.00	Vomit: frank blood present	Gastrointestinal
4A23.11	Blood in vomit O/E	Gastrointestinal
4A24.00	Vomit: coffee ground	Gastrointestinal
4A24.11	Coffee ground vomit	Gastrointestinal
4A5..00	Vomit occult blood	Gastrointestinal

4A5..11	Occult blood in vomit	Gastrointestinal
4A51.00	Vomit occult blood positive	Gastrointestinal
4A5Z.00	Vomit occult blood NOS	Gastrointestinal
1994	Vomiting blood - fresh	Gastrointestinal
1994.11	Blood in vomit - symptom	Gastrointestinal
1995	Vomiting blood - coffee ground	Gastrointestinal
196B.00	Painful rectal bleeding	Gastrointestinal
196C.00	Painless rectal bleeding	Gastrointestinal
19E4.12	C/O - melaena	Gastrointestinal
19E6.00	Blood in faeces	Gastrointestinal
19E6.11	Blood in faeces symptom	Gastrointestinal
19E6.12	Haematochezia	Gastrointestinal
G850.00	Oesophageal varices with bleeding	Gastrointestinal
G852000	Oesophageal varices with bleeding in diseases EC	Gastrointestinal
J107.00	Mallory-Weiss syndrome	Gastrointestinal
J10y000	Haemorrhage of oesophagus	Gastrointestinal
J110100	Acute gastric ulcer with haemorrhage	Gastrointestinal
J110111	Bleeding acute gastric ulcer	Gastrointestinal
J110300	Acute gastric ulcer with haemorrhage and perforation	Gastrointestinal
J111100	Chronic gastric ulcer with haemorrhage	Gastrointestinal
J111111	Bleeding chronic gastric ulcer	Gastrointestinal
J111300	Chronic gastric ulcer with haemorrhage and perforation	Gastrointestinal
J11y100	Unspecified gastric ulcer with haemorrhage	Gastrointestinal
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation	Gastrointestinal
J120100	Acute duodenal ulcer with haemorrhage	Gastrointestinal
J120300	Acute duodenal ulcer with haemorrhage and perforation	Gastrointestinal
J121100	Chronic duodenal ulcer with haemorrhage	Gastrointestinal
J121111	Bleeding chronic duodenal ulcer	Gastrointestinal
J121300	Chronic duodenal ulcer with haemorrhage and perforation	Gastrointestinal
J12y100	Unspecified duodenal ulcer with haemorrhage	Gastrointestinal
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation	Gastrointestinal
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation	Gastrointestinal
J130100	Acute peptic ulcer with haemorrhage	Gastrointestinal
J130300	Acute peptic ulcer with haemorrhage and perforation	Gastrointestinal
J131100	Chronic peptic ulcer with haemorrhage	Gastrointestinal
J13y100	Unspecified peptic ulcer with haemorrhage	Gastrointestinal
J13y300	Unspecified peptic ulcer with haemorrhage and perforation	Gastrointestinal
J140100	Acute gastrojejunal ulcer with haemorrhage	Gastrointestinal
J140300	Acute gastrojejunal ulcer with haemorrhage and perforation	Gastrointestinal
J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation	Gastrointestinal
J14y100	Unspecified gastrojejunal ulcer with haemorrhage	Gastrointestinal
J150000	Acute haemorrhagic gastritis	Gastrointestinal
J56y000	Haemoperitoneum - nontraumatic	Gastrointestinal
J573.00	Haemorrhage of rectum and anus	Gastrointestinal
J573.11	Bleeding PR	Gastrointestinal

J573000	Rectal haemorrhage	Gastrointestinal
J573011	Rectal bleeding	Gastrointestinal
J573012	PRB - Rectal bleeding	Gastrointestinal
J573z00	Haemorrhage of rectum and anus NOS	Gastrointestinal
J68..00	Gastrointestinal haemorrhage	Gastrointestinal
J680.00	Haematemesis	Gastrointestinal
J680.11	Vomiting of blood	Gastrointestinal
J681.00	Melaena	Gastrointestinal
J681.11	Blood in stool	Gastrointestinal
J681.12	Altered blood in stools	Gastrointestinal
J681.13	Blood in stools altered	Gastrointestinal
J68z.00	Gastrointestinal haemorrhage unspecified	Gastrointestinal
J68z.11	GIB - Gastrointestinal bleeding	Gastrointestinal
J68z000	Gastric haemorrhage NOS	Gastrointestinal
J68z100	Intestinal haemorrhage NOS	Gastrointestinal
J68z200	Upper gastrointestinal haemorrhage	Gastrointestinal
J68zz00	Gastrointestinal tract haemorrhage NOS	Gastrointestinal
J573100	Anal haemorrhage	Gastrointestinal
7609y11	Tanner devascularisation for bleeding varices	Gastrointestinal
7619100	Gastrotomy and ligation of bleeding point of stomach	Gastrointestinal
7627200	Oversew of blood vessel of duodenal ulcer	Gastrointestinal
1A45.00	Blood in urine - haematuria	Genitourinary
K0A2.00	Recurrent and persistent haematuria	Genitourinary
K0A2600	Recurrent and persistent haematuria, dense deposit disease	Genitourinary
K197.00	Haematuria	Genitourinary
K197.12	Essential haematuria	Genitourinary
K197000	Painless haematuria	Genitourinary
K197100	Painful haematuria	Genitourinary
K197200	Microscopic haematuria	Genitourinary
K197300	Frank haematuria	Genitourinary
K221.00	Prostatic congestion or haemorrhage	Genitourinary
K221100	Prostatic haemorrhage	Genitourinary
K275100	Corpus cavernosum haematoma	Genitourinary
K286000	Scrotal haematoma due to nontraumatic cause	Genitourinary
K286300	Testicular haematoma due to nontraumatic cause	Genitourinary
K286v00	Male genital haematoma NOS	Genitourinary
K286w00	Male genital haemorrhage NOS	Genitourinary
K286w11	Haematospermia	Genitourinary
K53y600	Haematosalpinx	Genitourinary
K544.00	Haematometra	Genitourinary
K566.00	Vaginal haematoma	Genitourinary
K56y100	Haemorrhage of vagina	Genitourinary
K56y111	Bleeding - vaginal NOS	Genitourinary
K56y112	BPV - Vaginal bleeding	Genitourinary
K575.00	Haematoma of vulva	Genitourinary

K592000	Menorrhagia	Genitourinary
K592011	Heavy periods	Genitourinary
K592012	Heavy menstrual bleeding	Genitourinary
K5A1.00	Postmenopausal bleeding	Genitourinary
K5C2.00	Haematocolpos	Genitourinary
K5E..00	Other abnormal uterine and vaginal bleeding	Genitourinary
K5E1.00	Abnormal uterine bleeding, unspecified	Genitourinary
K5E2.00	Abnormal vaginal bleeding, unspecified	Genitourinary
K5Ez.00	Abnormal uterine and vaginal bleeding, unspecified	Genitourinary
Kyu9C00	[X]Other specified irregular menstruation	Genitourinary
Kyu9D00	[X]Other specified abnormal uterine and vaginal bleeding	Genitourinary
2BB5.00	O/E - retinal haemorrhages	Intraocular
2BB8.00	O/E - vitreous haemorrhages	Intraocular
F404500	Intra-ocular haemorrhage	Intraocular
F424300	Retinal pigment epithelium haemorrhagic detachment	Intraocular
F42y.11	Haemorrhage - retinal	Intraocular
F42y000	Preretinal haemorrhage	Intraocular
F42y100	Superficial retinal haemorrhage	Intraocular
F42y300	Deep retinal haemorrhage	Intraocular
F42y400	Subretinal haemorrhage	Intraocular
F42y500	Retinal haemorrhage NOS	Intraocular
F436000	Unspecified choroidal haemorrhage	Intraocular
F436100	Expulsive choroidal haemorrhage	Intraocular
F437200	Haemorrhagic choroidal detachment	Intraocular
F4C7100	Subconjunctival haemorrhage	Intraocular
F4C7200	Conjunctival haemorrhage NOS	Intraocular
F4K2800	Vitreous haemorrhage	Intraocular
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere	Intraocular
G60..00	Subarachnoid haemorrhage	Intracranial
G600.00	Ruptured berry aneurysm	Intracranial
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation	Intracranial
G602.00	Subarachnoid haemorrhage from middle cerebral artery	Intracranial
G603.00	Subarachnoid haemorrhage from anterior communicating artery	Intracranial
G604.00	Subarachnoid haemorrhage from posterior communicating artery	Intracranial
G605.00	Subarachnoid haemorrhage from basilar artery	Intracranial
G606.00	Subarachnoid haemorrhage from vertebral artery	Intracranial
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif	Intracranial
G60z.00	Subarachnoid haemorrhage NOS	Intracranial
G61..00	Intracerebral haemorrhage	Intracranial
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage	Intracranial
G61..12	Stroke due to intracerebral haemorrhage	Intracranial
G610.00	Cortical haemorrhage	Intracranial
G611.00	Internal capsule haemorrhage	Intracranial
G612.00	Basal nucleus haemorrhage	Intracranial
G613.00	Cerebellar haemorrhage	Intracranial

G614.00	Pontine haemorrhage	Intracranial
G615.00	Bulbar haemorrhage	Intracranial
G616.00	External capsule haemorrhage	Intracranial
G617.00	Intracerebral haemorrhage, intraventricular	Intracranial
G618.00	Intracerebral haemorrhage, multiple localized	Intracranial
G619.00	Lobar cerebral haemorrhage	Intracranial
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified	Intracranial
G61X000	Left sided intracerebral haemorrhage, unspecified	Intracranial
G61X100	Right sided intracerebral haemorrhage, unspecified	Intracranial
G61z.00	Intracerebral haemorrhage NOS	Intracranial
G62..00	Other and unspecified intracranial haemorrhage	Intracranial
G620.00	Extradural haemorrhage - nontraumatic	Intracranial
G621.00	Subdural haemorrhage - nontraumatic	Intracranial
G622.00	Subdural haematoma - nontraumatic	Intracranial
G623.00	Subdural haemorrhage NOS	Intracranial
G62z.00	Intracranial haemorrhage NOS	Intracranial
G680.00	Sequelae of subarachnoid haemorrhage	Intracranial
G681.00	Sequelae of intracerebral haemorrhage	Intracranial
G682.00	Sequelae of other nontraumatic intracranial haemorrhage	Intracranial
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction	Intracranial
Gyu6000	[X]Subarachnoid haemorrhage from other intracranial arteries	Intracranial
Gyu6100	[X]Other subarachnoid haemorrhage	Intracranial
Gyu6200	[X]Other intracerebral haemorrhage	Intracranial
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif	Intracranial
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified	Intracranial
S626.00	Epidural haemorrhage	Intracranial
7004100	Evacuation of haematoma from temporal lobe of brain	Intracranial
7004200	Evacuation of haematoma from cerebellum	Intracranial
7004300	Evacuation of intracerebral haematoma NEC	Intracranial
7008200	Aspiration of haematoma of brain tissue	Intracranial
7017000	Evacuation of subdural haematoma	Intracranial
7032000	Evacuation of extradural haematoma	Intracranial
D00..00	Iron deficiency anaemias	Other
D00..11	Hypochromic - microcytic anaemia	Other
D00..12	Microcytic - hypochromic anaemia	Other
D00y.00	Other specified iron deficiency anaemia	Other
D00y100	Microcytic hypochromic anaemia	Other
D00z.00	Unspecified iron deficiency anaemia	Other
D00zz00	Iron deficiency anaemia NOS	Other
D000.00	Iron deficiency anaemia due to chronic blood loss	Other
D000.11	Normocytic anaemia due to chronic blood loss	Other
D000.12	Iron deficiency anaemia due to blood loss	Other
D305.00	Haemorrhagic disorder due to circulating anticoagulants	Other
G360.00	Haemopericardium/current comp folow acut myocard infarct	Other
G530.00	Haemopericardium	Other

G711.00	Thoracic aortic aneurysm which has ruptured	Other
G711.11	Ruptured thoracic aortic aneurysm	Other
G713000	Ruptured suprarenal aortic aneurysm	Other
G713.00	Abdominal aortic aneurysm which has ruptured	Other
G713.11	Ruptured abdominal aortic aneurysm	Other
G715.00	Ruptured aortic aneurysm NOS	Other
G715000	Thoracoabdominal aortic aneurysm, ruptured	Other
N091.00	Haemarthrosis (+ Daughter codes)	Other
7G2H400	Liposuction removal of haematoma	Other
7M0G000	Aspiration of haematoma of organ NOC	Other
7M0G400	Evacuation of haematoma NEC	Other
K138300	Intrarenal haematoma	Other
K13y800	Perirenal haematoma	Other
K31y000	Breast haematoma due to nontraumatic cause	Other
K537.00	Haematoma of the broad ligament	Other
S750100	Spleen haematoma without mention of open wound into cavity	Other
S751100	Spleen haematoma with open wound into cavity	Other
S760100	Kidney haematoma without mention of open wound into cavity	Other
S760111	Renal haematoma without mention of open wound into cavity	Other
S761100	Kidney haematoma with open wound into cavity	Other
SE23111	Perianal haematoma	Other
SE22300	Haematoma of rectus sheath	Other
SE45.11	Haematoma of leg	Other
SE4z.11	Haematoma NOS	Other
SE4z.12	Intramuscular haematoma NOS	Other
Ryu7300	[X]Haemorrhage, not elsewhere classified	Other

Appendix 4.4: Code list included in the definition of bleeding within primary care

Read code	Description
1994	Vomiting blood - fresh
1994.11	Blood in vomit - symptom
1995	Vomiting blood - coffee ground
4737	Faeces colour: tarry
4737.11	Melaena - O/E of faeces
4762	Faeces: fresh blood present
4762.11	Blood in faeces
7404	Surgical arrest of bleeding from internal nose
7004100	Evacuation of haematoma from temporal lobe of brain
7004200	Evacuation of haematoma from cerebellum
7004300	Evacuation of intracerebral haematoma NEC
7008200	Aspiration of haematoma of brain tissue
7017000	Evacuation of subdural haematoma
7032000	Evacuation of extradural haematoma
7303000	Drainage of haematoma of external ear
7303200	Drainage haematoma ext ear control cavity c bolster suture
7619100	Gastrotomy and ligation of bleeding point of stomach
7627200	Oversew of blood vessel of duodenal ulcer
16B..	Bruising symptom
16B3.	Spontaneous bruising
16BZ.	Bruising symptom NOS
172..00	Blood in sputum - haemoptysis
172..12	Haemoptysis - symptom
196B.00	Painful rectal bleeding
196C.00	Painless rectal bleeding
19E4.12	C/O - melaena
19E6.00	Blood in faeces
19E6.11	Blood in faeces symptom
1A45.	Blood in urine - haematuria
1C6..00	Nose bleed symptom
1C62.00	Has nose bleeds - epistaxis
1C6Z.00	Nose bleed symptom NOS
2BB5.00	O/E - retinal haemorrhages
2BB8.00	O/E - vitreous haemorrhages
2D25.	O/E - epistaxis
2DE7.00	O/E - throat haemorrhage
4A23.00	Vomit: frank blood present
4A23.11	Blood in vomit O/E
4A24.00	Vomit: coffee ground
4A24.11	Coffee ground vomit
4A5..00	Vomit occult blood
4A5..11	Occult blood in vomit

4A51.00	Vomit occult blood positive
4A5Z.00	Vomit occult blood NOS
7404y00	Surgical arrest of bleeding from internal nose OS
7404z00	Surgical arrest of bleeding from internal nose NOS
7609y11	Tanner devascularisation for bleeding varices
7G2H400	Liposuction removal of haematoma
7M0G000	Aspiration of haematoma of organ NOC
7M0G400	Evacuation of haematoma NEC
D00	Iron deficiency anaemias
D000.	Iron deficiency anaemia secondary to blood loss
D00y1	Microcytic hypochromic anaemia
D00z	Unspec iron deficiency anaemia
D00zz	Iron deficiency anaemia NOS
D305.	Haemorrhagic disorder due to circulating anticoagulants
F404500	Intra-ocular haemorrhage
F424300	Retinal pigment epithelium haemorrhagic detachment
F42y.11	Haemorrhage - retinal
F42y0	Preretinal haemorrhage
F42y100	Superficial retinal haemorrhage
F42y300	Deep retinal haemorrhage
F42y400	Subretinal haemorrhage
F42y500	Retinal haemorrhage NOS
F436000	Unspecified choroidal haemorrhage
F436100	Expulsive choroidal haemorrhage
F437200	Haemorrhagic choroidal detachment
F4C71	Subconjunctival haemorrhage
F4C72	Conjunctival haemorrhage NOS
F4K2800	Vitreous haemorrhage
F503100	Haematoma of pinna
F5862	Otorrhagia
FyuH400	[X]Vitreous haemorrhage in diseases classified elsewhere
G360.00	Haemopericardium/current comp folow acut myocard infarct
G530.00	Haemopericardium
G60..00	Subarachnoid haemorrhage
G600.00	Ruptured berry aneurysm
G601.00	Subarachnoid haemorrhage from carotid siphon and bifurcation
G602.00	Subarachnoid haemorrhage from middle cerebral artery
G603.00	Subarachnoid haemorrhage from anterior communicating artery
G604.00	Subarachnoid haemorrhage from posterior communicating artery
G605.00	Subarachnoid haemorrhage from basilar artery
G606.00	Subarachnoid haemorrhage from vertebral artery
G60X.	Subarachnoid haemorrhage from intracranial artery, unspecified
G60z.00	Subarachnoid haemorrhage NOS
G61..00	Intracerebral haemorrhage
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage

G61..12	Stroke due to intracerebral haemorrhage
G610.00	Cortical haemorrhage
G611.00	Internal capsule haemorrhage
G612.00	Basal nucleus haemorrhage
G613.00	Cerebellar haemorrhage
G614.00	Pontine haemorrhage
G615.00	Bulbar haemorrhage
G616.00	External capsule haemorrhage
G617.00	Intracerebral haemorrhage, intraventricular
G618.00	Intracerebral haemorrhage, multiple localized
G61X.00	Intracerebral haemorrhage in hemisphere, unspecified
G61X000	Left sided intracerebral haemorrhage, unspecified
G61X100	Right sided intracerebral haemorrhage, unspecified
G61z.00	Intracerebral haemorrhage NOS
G62..00	Other and unspecified intracranial haemorrhage
G620.00	Extradural haemorrhage - nontraumatic
G621.00	Subdural haemorrhage - nontraumatic
G622.00	Subdural haematoma - nontraumatic
G623.00	Subdural haemorrhage NOS
G62z.00	Intracranial haemorrhage NOS
G680.00	Sequelae of subarachnoid haemorrhage
G681.	Sequelae of intracerebral haemorrhage
G682.00	Sequelae of other nontraumatic intracranial haemorrhage
G68X.00	Sequelae of stroke,not specfd as h'morrhage or infarction
G711.	Thoracic aortic aneurysm, ruptured
G713.	Abdominal aortic aneurysm, ruptured
G715.	Aortic aneurysm of unspecified site, ruptured
G7150	Thoracoabdominal aortic aneurysm, ruptured
G850.00	Oesophageal varices with bleeding
G852000	Oesophageal varices with bleeding in diseases EC
Gyu60	Subarachnoid haemorrhage from other intracranial arteries
Gyu6100	[X]Other subarachnoid haemorrhage
Gyu6200	[X]Other intracerebral haemorrhage
Gyu6B00	[X]Sequelae of other nontraumatic intracranial haemorrhage
Gyu6E00	[X]Subarachnoid haemorrh from intracranial artery, unspecif
Gyu6F00	[X]Intracerebral haemorrhage in hemisphere, unspecified
H51y2	haemothorax
J107.00	Mallory-Weiss syndrome
J10y000	Haemorrhage of oesophagus
J110100	Acute gastric ulcer with haemorrhage
J110111	Bleeding acute gastric ulcer
J110300	Acute gastric ulcer with haemorrhage and perforation
J111100	Chronic gastric ulcer with haemorrhage
J111111	Bleeding chronic gastric ulcer
J111300	Chronic gastric ulcer with haemorrhage and perforation

J11y100	Unspecified gastric ulcer with haemorrhage
J11y3	Unspecified gastric ulcer with haemorrhage and perforation
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J120100	Acute duodenal ulcer with haemorrhage
J120300	Acute duodenal ulcer with haemorrhage and perforation
J121100	Chronic duodenal ulcer with haemorrhage
J121111	Bleeding chronic duodenal ulcer
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J130100	Acute peptic ulcer with haemorrhage
J130300	Acute peptic ulcer with haemorrhage and perforation
J131100	Chronic peptic ulcer with haemorrhage
J1313	Chronic peptic ulcer with haemorrhage and perforation
J13y100	Unspecified peptic ulcer with haemorrhage
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J140100	Acute gastrojejunal ulcer with haemorrhage
J1403	Gastrojejunal ulcer, acute with both haemorrhage and perforation
J1411	Chronic gastrojejunal ulcer with haemorrhage
J1413	Chronic gastrojejunal ulcer with haemorrhage and perforation
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y3	Unspecified gastrojejunal ulcer with haemorrhage and perforation
J150000	Acute haemorrhagic gastritis
J56y0	Haemoperitoneum
J573.00	Haemorrhage of rectum and anus
J573.11	Bleeding PR
J573000	Rectal haemorrhage
J573011	Rectal bleeding
J573012	PRB - Rectal bleeding
J573z00	Haemorrhage of rectum and anus NOS
J68..00	Gastrointestinal haemorrhage
J680.00	Haematemesis
J680.11	Vomiting of blood
J681.00	Melaena
J681.11	Blood in stool
J681.12	Altered blood in stools
J681.13	Blood in stools altered
J68z.00	Gastrointestinal haemorrhage unspecified
J68z.11	GIB - Gastrointestinal bleeding
J68z000	Gastric haemorrhage NOS
J68z100	Intestinal haemorrhage NOS
J68z200	Upper gastrointestinal haemorrhage
J68zz00	Gastrointestinal tract haemorrhage NOS
K0A2.	recurrent and persistent haematuria

K0A26	recurrent and persistent haematuria, dense deposit disease
K138300	Intrarenal haematoma
K13y800	Perirenal haematoma
K197.	Unspecified haematuria
K1970	Painless haematuria
K1971	Painful haematuria
K1972	Microscopic haematuria
K1973	Frank haematuria
K221.	Congestion and haemorrhage of prostate
K275100	Corpus cavernosum haematoma
K286000	Scrotal haematoma due to nontraumatic cause
K286300	Testicular haematoma due to nontraumatic cause
K286v00	Male genital haematoma NOS
K286w	Haematospermia
K31y000	Breast haematoma due to nontraumatic cause
K537.00	Haematoma of the broad ligament
K53y6	Haematosalpinx
K544.	Haematometra
K566.00	Vaginal haematoma
K56y100	Haemorrhage of vagina
K56y111	Bleeding - vaginal NOS
K56y112	BPV - Vaginal bleeding
K575.00	Haematoma of vulva
K5920	Menorrhagia
K5A1.	postmenopausal bleeding
K5C2.	Haematocolpos
K5E..00	Other abnormal uterine and vaginal bleeding
K5E1.00	Abnormal uterine bleeding, unspecified
K5E2.00	Abnormal vaginal bleeding, unspecified
K5Ez.00	Abnormal uterine and vaginal bleeding, unspecified
Kyu9C	Other specified irregular menstruation
Kyu9D00	[X]Other specified abnormal uterine and vaginal bleeding
N0910	Haemarthrosis, site unspecified
N0911	Haemarthrosis, shoulder region
N0912	Haemarthrosis, upper arm
N0913	Haemarthrosis, forearm
N0914	Haemarthrosis, hand
N0915	Haemarthrosis, pelvic region and thigh
N0916	Haemarthrosis, lower leg
N0917	Haemarthrosis, ankle and foot
N0918	Haemarthrosis, other site
N0919	Haemarthrosis, multiple sites
N091A	Haemarthrosis of shoulder
N091M	Haemarthrosis of knee
R027	[D]Spontaneous bruising

R0270	[D]Petechiae
R027z	spontaneous ecchymosis
R047.	Epistaxis
R047.11	[D]Nosebleed
R048.00	[D]Throat haemorrhage
R063.00	[D]Haemoptysis
R063000	[D]Cough with haemorrhage
R063100	[D]Pulmonary haemorrhage NOS
R063z00	[D]Haemoptysis NOS
Ryu02	Haemorrhage from other sites in respiratory passages
Ryu07	Haemorrhage from respiratory passages, unspecified
Ryu73	haemorrhage, not elsewhere classified
S626.00	Epidural haemorrhage
S750100	Spleen haematoma without mention of open wound into cavity
S751100	Spleen haematoma with open wound into cavity
S760100	Kidney haematoma without mention of open wound into cavity
S760111	Renal haematoma without mention of open wound into cavity
S761100	Kidney haematoma with open wound into cavity
SE...11	Haematoma with intact skin
SE22300	Haematoma of rectus sheath
SE3z	Bruise - upper limb NOS
SE4	Leg bruise
SE45.11	Haematoma of leg
SE4z	Bruise NOS
SE4z.11	Haematoma NOS
SE4z.12	Intramuscular haematoma NOS
X00DN	Intracerebral haemorrhage in hemisphere, subcortical
X00DQ	Intracerebral haemorrhage in brain stem

Appendix 4.5: Code list excluded from the definition of bleeding within primary care

Read code	Description
1583	H/O: post-menopausal bleeding
7421300	Surgical arrest of postoperative bleeding of adenoid
7517500	Surgical arrest of postoperative bleeding from tooth socket
7531400	Surgical arrest of postoperative bleeding from tonsillar bed
14AF.00	H/O sub-arachnoid haemorrhage
14C8.00	H/O: haematemesis
14C9.00	H/O: melaena
14CA.11	H/O: GI Bleed
158..00	H/O: abnormal uterine bleeding
158Z.00	H/O:abnormal uterine bleed NOS
15A1.00	H/O: ante-partum haemorrhage
15A6.00	H/O: post-partum haemorrhage
26A6.	O/E - blood stained vag. disch
793B000	Decompression of cardiac tamponade
7A6G8	Thrombin inject pseudoaneurysm
7D05200	Evacuation of haematoma of vulva
7D1C000	Evacuation of haematoma from vagina
7F22700	Pack to control postnatal vaginal bleeding
7F22711	Pack to control postnatal vaginal bleeding
7F22712	Pack to control postnatal haemorrhage
7G31400	Drainage of subungual haematoma
7H22600	Reopen abdo reexplore intraabd op site surg arr postop bleed
7J01300	Reopen cranium reexploration op site arrest post op bleeding
7L142	IV blood transfusion platelets
7L143	Blood transfusion
7L143	IV blood transfusion NEC
7M0U400	Reexploration of organ & surgical arrest postop bleeding NOC
D010	Pernicious anaemia
D011X	Vit B12 defic anaemia unsp
D0125	Macrocytic anaemia unspecified
D2150	Anaemia secondary to CRF
D21z	Anaemia NOS
D2y	Other specified anaemias
G53z.11	Cardiac tamponade
G842.	Internal haemorrhoids with other complications
G844.	External thrombosed haemorrhoids
G845.	External haemorrhoids with other complications
G848.	Unspecified haemorrhoids with other complications
J108.00	Mallory - Weiss tear
K587.00	Contact bleeding of cervix
K592z	Excessive and frequent menstruation with irregular cycle
K594z	Irregular menstruation, unspecified

L040100	Unspec spontaneous abortion + delayed/excessive haemorrhage
L040111	Spontaneous abortion with heavy bleeding
L041100	Incomp spontaneous abortion + delayed/excessive haemorrhage
L051100	Incomplete legal abortion + delayed or excessive haemorrhage
L052100	Complete legal abortion with delayed/excessive haemorrhage
L091.00	Delayed/excessive haemorrhage following abortive pregnancy
L091z00	Delayed/excess haemorrhage NOS following abortive pregnancy
L10..00	Haemorrhage in early pregnancy
L10y.00	Other haemorrhage in early pregnancy
L10y.11	Bleeding in early pregnancy
L10y000	Other haemorrhage in early pregnancy unspecified
L10y200	Other haemorrhage in early pregnancy - not delivered
L10yz00	Other haemorrhage in early pregnancy NOS
L10z.00	Early pregnancy haemorrhage NOS
L10z000	Early pregnancy haemorrhage NOS unspecified
L10z200	Early pregnancy haemorrhage NOS - not delivered
L10zz00	Early pregnancy haemorrhage NOS
L11..00	Antepartum haemorrhage, abruptio placentae, placenta praevia
L11..11	Antepartum haemorrhage
L11..12	Antepartum bleeding
L113.00	Antepartum haemorrhage with coagulation defect
L113.13	Antepartum haemorrhage with hypofibrinogenaemia
L113000	Antepartum haemorrhage with coagulation defect unspecified
L114100	Antepartum haemorrhage with trauma - delivered
L115.00	Antepartum haemorrhage with uterine leiomyoma
L115.11	Antepartum haemorrhage with fibroid
L115.12	Antepartum haemorrhage with uterine fibroid
L115100	Antepartum haemorrhage with uterine leiomyoma - delivered
L11y.00	Other antepartum haemorrhage
L11y000	Other antepartum haemorrhage unspecified
L11y100	Other antepartum haemorrhage - delivered
L11y200	Other antepartum haemorrhage - not delivered
L11yz00	Other antepartum haemorrhage NOS
L11z.00	Antepartum haemorrhage NOS
L11z000	Antepartum haemorrhage NOS, unspecified
L11z100	Antepartum haemorrhage NOS - delivered
L11z200	Antepartum haemorrhage NOS - not deliv
L11zz00	Antepartum haemorrhage NOS
L345.00	Vulval and perineal haematoma during delivery
L345.11	Perineal haematoma
L345.12	Vulval and perineal haematoma during delivery
L345000	Vulval and perineal haematoma during delivery, unspecified
L345100	Vulval and perineal haematoma during delivery - delivered
L345z00	Vulval and perineal haematoma during delivery NOS
L357.00	Obstetric trauma causing pelvic haematoma

L357000	Obstetric pelvic haematoma unspecified
L357100	Obstetric pelvic haematoma - delivered
L36..00	Postpartum haemorrhage (PPH)
L36..11	Bleeding postpartum
L360.00	Third-stage postpartum haemorrhage
L360000	Third-stage postpartum haemorrhage unspecified
L360100	Third-stage postpartum haemorrhage - deliv with p/n problem
L360200	Third-stage postpartum haemorrhage with postnatal problem
L360z00	Third-stage postpartum haemorrhage NOS
L361.00	Other immediate postpartum haemorrhage
L361z00	Other immediate postpartum haemorrhage NOS
L362.00	Secondary and delayed postpartum haemorrhage
L362000	Secondary postpartum haemorrhage unspecified
L362200	Secondary postpartum haemorrhage with postnatal problem
L362z00	Secondary and delayed postpartum haemorrhage NOS
L36z.00	Postpartum haemorrhage NOS
L371200	Retained products with no haemorrhage with postnatal problem
L394600	Haematoma of obstetric wound
L3A..00	Intrapartum haemorrhage with coagulation defect
L3X..00	Intrapartum haemorrhage, unspecified
L443.11	Haematoma - perineal wound
S62..12	Subarachnoid haemorrhage following injury
S62..13	Subdural haemorrhage following injury
S620.00	Closed traumatic subarachnoid haemorrhage
S621.00	Open traumatic subarachnoid haemorrhage
S622.00	Closed traumatic subdural haemorrhage
S623.00	Open traumatic subdural haemorrhage
S624.11	Epidural haematoma following injury
S629.00	Traumatic subdural haematoma
S629000	Traumatic subdural haematoma without open intracranial wound
S629100	Traumatic subdural haematoma with open intracranial wound
S62A.00	Traumatic extradural haematoma
S630.12	Intracranial haematoma following injury
S714.00	Injury of heart with haemopericardium
S740100	Liver haematoma and contusion without open wound into cavity
SE33011	Subungal haematoma
SE33200	Contusion, fingernail (includes subungual haematoma)
SE46.00	Traumatic haematoma
SP21.00	Peri-operative haemorrhage or haematoma
SP21.11	Haematoma - postoperative
SP21.12	Haemorrhage - postoperative
SP21100	Post-operative haemorrhage
SP21200	Post-operative haematoma formation
XE13x	Acute posthemorrhagic anaemia
ZA13600	Drainage of subungual haematoma

ZA13700	Drainage of subungual haematoma with hot wire
ZA13800	Drainage of subungual haematoma with drill

Chapter 5.0 appendices

Appendix 5.1: ISAC Protocol

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

For ISAC use only		
Protocol No. Submission date (DD/MM/YYYY)	....	***IMPORTANT*** *Please refer to the **guidance** for '**Completing the ISAC application form'** found on the CPRD website (www.cprd.com/isac). If you have any queries, please contact the ISAC Secretariat at isac@cprd.com.*

SECTION A: GENERAL INFORMATION ABOUT THE PROPOSED RESEARCH STUDY

1. Study Title[§] (*Please state the study title below)*

Epidemiology of bleeding complications post-Acute Coronary Syndrome within the UK primary care setting

[§]*Please note: This information will be published on the CPRD's website as part of its transparency policy.*

2. Has any part of this research proposal or a related proposal been previously submitted to ISAC?

Yes* ☐ No ☒

**If yes, please provide the previous protocol number/s below. Please also state in your current submission how this/these are related or relevant to this study.*

3. Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)

Yes* ☐ No ☒

**If Yes, please state the name of the reviewing Committee(s) below and provide an outline of the review process and outcome as an Appendix to this protocol :*

4. Type of Study (please tick all the relevant boxes which apply)

Adverse Drug Reaction/Drug Safety	☐	Drug Effectiveness	☐
Drug Utilisation	☐	Pharmacoeconomics	☐
Disease Epidemiology	☒	Post-authorisation Safety	☐
Health care resource utilisation	☐	Methodological Research	☐
Health/Public Health Services Research	☐	Other*	☐

**If Other, please specify the type of study here and in the lay summary below:*

5. Health Outcomes to be Measured[§]

[§]Please note: This information will be published on CPRD's website as part of its transparency policy.

Please summarise below the primary/secondary health outcomes to be measured in this research protocol:

- Bleeding complications
- All-cause mortality
-

-
-
-

-
-
-

[Please add more bullet points as necessary]

6. Publication: This study is intended for (please tick all the relevant boxes which apply)**:**

Publication in peer-reviewed journals	☒	Presentation at scientific conference	☒
Presentation at company/institutional meetings	☐	Regulatory purposes	☐
Other*	☐		

**If Other, please provide further information:*

SECTION B: INFORMATION ON INVESTIGATORS AND COLLABORATORS

7. Chief Investigator[§]

Please state the full name, job title, organisation name & e-mail address for correspondence - see guidance notes for eligibility. Please note that there can only be one Chief Investigator per protocol.

Name: Professor Mamas A. Mamas
Job Title: Professor of Cardiology and Interventional Cardiologist
Organisation: Centre for Prognosis Research, Institute for Primary Care and Health Sciences,
Keele University.
Email: Mamasmamas1@yahoo.co.uk

[§]Please note: The name and organisation of the Chief Investigator and will be published on CPRD's website as part of its transparency policy

CV has been previously submitted to ISAC	☒ **CV number:**	210_17
A new CV is being submitted with this protocol	☐	
An updated CV is being submitted with this protocol	☐	

8. Affiliation of Chief Investigator (full address)

Keele Cardiovascular Research Group, Institute for Applied Clinical Science and Centre for Prognosis Research, Institute for Primary Care and Health Sciences, David Weatherall Building, Keele University, Stoke-on-Trent, UK, ST5 5BG.

9. Corresponding Applicant[§]

Please state the full name, affiliation(s) and e-mail address below:

Name: Mr Nafiu Ismail
Job Title: PhD Student
Affiliation: Centre for Prognosis Research, Institute for Primary Care and Health Sciences,
Keele University.
Email: n.ismail@keele.ac.uk

[§]Please note: The name and organisation of the corresponding applicant and their organisation name will be published on

CPRD's website as part of its transparency policy

Same as chief investigator ☐
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being submitted with this protocol ☐

10. List of all investigators/collaborators§

Please list the full name, affiliation(s) and e-mail address* of all collaborators, other than the Chief Investigator below:

§*Please note: The name of all investigators and their organisations/institutions will be published on CPRD's website as part of its transparency policy*

Other investigator: Mr Nafiu Ismail
Primary affiliation: Research Institute for Primary Care and Health Sciences, David Weatherall Building, Keele University, Stoke-on-Trent, UK, ST5 5BG.
Email: n.ismail@keele.ac.uk

CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☒
An updated CV is being sumitted with this protocol ☐

Other investigator: Professor Kelvin P. Jordan
Primary affiliation: Research Institute for Primary Care and Health Sciences, David Weatherall Building, Keele University, Stoke-on-Trent, UK, ST5 5BG.
Email: k.p.jordan@keele.ac.uk

CV has been previously submitted to ISAC ☒ **CV number:** 248-15CESL
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator: Professor Umesh T. Kadam
Primary affiliation: Institute of Science and Technology in Medicine, Guy Hilton Research Centre, Thornburrow Drive, Hartshill, Stoke-on-trent, UK, ST4 7QB.
Email: u.kadam@keele.ac.uk

CV has been previously submitted to ISAC ☒ **CV number:** 208_17
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

Other investigator:
CV has been previously submitted to ISAC ☐ **CV number:**
A new CV is being submitted with this protocol ☐
An updated CV is being submitted with this protocol ☐

[Please add more investigators as necessary]

Please note that your ISAC application form and protocol **must be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.*

11. Conflict of interest statement*

Please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work

The study is funded by the North Staffordshire Medical Institute 50th Anniversary Award. Professor Mamas receives an unrestricted educational grant from Terumo, Daiichi Sankyo and personal fees from AZ, Cordis outside of submitted work.

**Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI.*

12. Experience/expertise available

Please complete the following questions to indicate the experience/ expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results.

	Previous GPRD/CPRD Studies	**Publications using GPRD/CPRD data**
None	☐	☐
1-3	☐	☐
> 3	☒	☒

Experience/Expertise available	**Yes**	**No**
Is statistical expertise available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Professor Kelvin P. Jordan (Professor of statistic and primary care epidemiology)	☒	☐
Is experience of handling large data sets (>1 million records) available within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Professor Kelvin P. Jordan (Professor of statistic and primary care epidemiology)	☒	☐
Is experience of practising in UK primary care available to or within the research team? *If yes, please indicate the name(s) of the relevant investigator(s)* Professor Umesh T. Kadam (Professor of epidemiology and pharmaco-epidemiology who is also a practicing General Practitioner)	☒	☐

13. References relating to your study

Please list up to 3 references (most relevant) relating to your proposed study:

Lattuca, B. et al., 2016. One-year incidence and clinical impact of bleeding events in patients treated with prasugrel or clopidogrel after ST-segment elevation myocardial infarction. *Archives of Cardiovascular Diseases*, 109(5), pp.337–347. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27079469.

Sørensen, R. et al., 2009. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *The Lancet*, 374(9706), pp.1967–1974. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0140673609617517.

Voss, W.B. et al., 2016. Incidence and type of bleeding complications early and late after acute coronary syndrome admission in a New Zealand cohort (ANZACS-QI-7). *New Zealand Medical Journal*, 129(1437), pp.27–38. Available at: http://search.ebscohost.com/login.aspx?direct=true&AuthType=ip,url,uid,shib&db=rzh&AN=116598996&site=ehost-live.

SECTION C: ACCESS TO THE DATA

14. Financial Sponsor of study[§]

[§]*Please note: The name of the source of funding will be published on CPRD's website as part of its transparency policy*

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☐	*Please specify name and country:*
Government / NHS	☒	North Staffordshire Medical Institute, UK.
Charity	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*
None	☐	

15. Type of Institution conducting the research

Pharmaceutical Industry	☐	*Please specify name and country:*
Academia	☒	*Institute for Primary Care and Health Sciences, Keele University, UK*
Government Department	☐	*Please specify name and country:*
Research Service Provider	☐	*Please specify name and country:*
NHS	☐	*Please specify name and country:*
Other	☐	*Please specify name and country:*

16. Data access arrangements

The financial sponsor/ collaborator* has a licence for CPRD GOLD and will extract the data ☐

The institution carrying out the analysis has a licence for CPRD GOLD and will extract the data** ☒

A data set will be provided by the CPRD[¥€] ☐

CPRD has been commissioned to extract the data and perform the analyses[€] ☐

Other: ☐

If Other, please specify:

**Collaborators supplying data for this study must be named on the protocol as co-applicants.*
***If data sources other than CPRD GOLD are required, these will be supplied by CPRD*
[¥]*Please note that datasets provided by CPRD are limited in size; applicants should contact CPRD (enquiries@cprd.com) if a dataset of >300,000 patients is required.*
[€]*Investigators must discuss their request with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email (enquiries@cprd.com) to discuss your requirements. Please also state the name of CPRD Research team with whom you have discussed this request (provide the date of discussion and any relevant reference information):*

Name of CPRD Researcher Reference number (where available) Date of contact

17. Primary care data

Please specify which primary care data set(s) are required)

Vision only (Default for CPRD studies ☒ Both Vision and EMIS®* ☐

EMIS® only* ☐

Note: Vision and EMIS are different practice management systems. CPRD has traditionally collected data from Vision practice. Data collected from EMIS is currently under evaluation prior to wider release.
Investigators requiring the use of EMIS data **must discuss the study with a member of the CPRD Research team before submitting an ISAC application*

Please state the name of the CPRD Researcher with whom you have discussed your request for EMIS data:

Name of CPRD Researcher Reference number (where available) Date of contact

SECTION D: INFORMATION ON DATA LINKAGES

18. Does this protocol seek access to linked data

Yes* ☒ No☐ If No, please move to section E.

Research groups which have not previously accessed CPRD linked data resources **must discuss access to these resources with a member of the CPRD Research team, before submitting an ISAC application. Investigators requiring access to HES Accident and Emergency data, HES Diagnostic Imaging Dataset PROMS data and the Pregnancy Register **must** also discuss this with a member of the CPRD Research team before submitting an ISAC application. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email enquiries@cprd.comto discuss your requirements **before** submitting your application.*

Please state the name of the CPRD Researcher with whom you have discussed your linkage request.

Name of CPRD Researcher Reference number (where available) Date of contact

Please note that as part of the ISAC review of linkages, your protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.

19. Please select the source(s) of linked data being requested§

§Please note: This information will be published on the CPRD's website as part of its transparency policy.

☒ ONS Death Registration Data
☒ HES Admitted Patient Care
☐ HES Outpatient
☐ HES Accident and Emergency
☐ HES Diagnostic Imaging Dataset
☐ MINAP (Myocardial Ischaemia National Audit Project)
☐ Cancer Registration Data*
☐ PROMS (Patient Reported Outcomes Measure)**
☐ CPRD Mother Baby Link
☐ Pregnancy Register

☐ Practice Level Index of Multiple Deprivation (Standard)
☐ Practice Level Index of Multiple Deprivation (Bespoke)
☒ Patient Level Index of Multiple Deprivation***
☐ Patient Level Townsend Score ***
☐ Other**** *Please specify:*

**Applicants seeking access to cancer registration data must complete a Cancer Dataset Agreement form (available from CPRD). This should be submitted to the ISAC as an appendix to your protocol. Please also note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website.*
***Assessment of the quality of care delivered to NHS patients in England undergoing four procedures: hip replacement, knee replacement, groin hernia and varicose veins. Please note that patient level PROMS data are only accessible by academics*
**** 'Patient level IMD and Townsend scores will not be supplied for the same study*
*****If "Other" is specified, please provide the name of the individual in the CPRD Research team with whom this linkage has been discussed.*

Name of CPRD Researcher Reference number (where available) Date of contact

20. Total number of linked datasets requested <u>including</u> CPRD GOLD

Number of linked datasets requested *(practice/ 'patient' level Index of Multiple Deprivation, Townsend Score, the CPRD Mother Baby Link and the Pregnancy Register should **not** be included in this count)* **3**

Please note: Where ≥5 linked datasets are requested, approval may be required from the Confidentiality Advisory Group (CAG) to access these data

21. Is linkage to a <u>local</u>¥ dataset with <1 million patients being requested?

Yes* ☐ No ☒

If yes, please provide further details:

¥ *Data from defined geographical areas i.e. non-national datasets.*

22. If you have requested one or more linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in question 5 above, have access to these data in a patient identifiable form (e.g. full date of birth, NHS number, patient post code), or associated with an identifiable patient index.

Yes* ☐ No ☒

** If yes, please provide further details:*

23. Does this study involve linking to patient *identifiable* data (e.g. hold date of birth, NHS number, patient post code) from other sources?

Yes ☐ No ☒

SECTION E: VALIDATION/VERIFICATION

24. Does this protocol describe a purely observational study using CPRD data?

Yes* ☒ No** ☐

** Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*
*** No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.*

25. Does this protocol involve requesting any additional information from GPs?

Yes* ☐ No ☒

** If yes, please indicate what will be required:*

Completion of questionnaires by the GP℣ Yes ☐ No ☐
Is the questionnaire a validated instrument? Yes ☐ No ☐
If yes, has permission been obtained to use the instrument? Yes ☐ No ☐
Please provide further information:

Other (please describe)

℣ *Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.*

26. Does this study require contact with patients in order for them to complete a questionnaire?

Yes* ☐ No ☒

**Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.*

27. Does this study require contact with patients in order to collect a sample?

Yes* ☐ No ☒

** Please state what will be collected:*

SECTION F: DECLARATION

28. Signature from the Chief Investigator

- I have read the guidance on '***Completion of the ISAC application form***' and '***Contents of CPRD ISAC Research Protocols***' and have understood these;

- I have read the submitted version of this research protocol, including all supporting documents, and confirm that these are accurate.
- I am suitably qualified and experienced to perform and/or supervise the research study proposed.
- I agree to conduct or supervise the study described in accordance with the relevant, current protocol
- I agree to abide by all ethical, legal and scientific guidelines that relate to access and use of CPRD data for research
- I understand that the details provided in sections marked with (§) in the application form and protocol will be published on the CPRD website in line with CPRD's transparency policy.
- I agree to inform the CPRD of the final outcome of the research study: publication, prolonged delay, completion or termination of the study.

Name: Prof Mamas A Mamas Date:24/07/2017 e-Signature (type name): Mamas A Mamas

PROTOCOL INFORMATION REQUIRED

The following sections below **must** be included in the CPRD ISAC research protocol. Please refer to the guidance on '***Contents of CPRD ISAC Research Protocols***' (www.cprd.com/isac) for more information on how to complete the sections below. Pages should be numbered. All abbreviations must be defined on first use.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

A. Study Title[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Epidemiology of bleeding complications post-Acute Coronary Syndrome within the UK primary care setting

B. Lay Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Antithrombotic drugs are medications that are given to someone who has had a heart attack in order to prevent them from further heart attacks. These antithrombotic drugs while preventing further heart attack also cause bleeding. This bleeding can occur while the patient is still in the hospital or late after hospital discharge. Evidence has shown that the rate of bleeds that occur in the hospital setting is between 1% and 10%, and these in-hospital bleeds may cause death. Whereas the rate of bleeds that occur in the longer term after the patient has been discharge from hospital and whether these bleeds also cause death is not known. This study will determine the rate of these longer term bleeds that occur after hospital discharge and the characteristics of patients likely to develop these bleeds using routinely collected health information from the Clinical Practice Research Datalink. The study will also examine whether patients who sustained these longer term bleeds are more likely to die than those who did not. The finding from this study will help improve how patients are treated after discharge from hospital for heart attack.

C. Technical Summary (Max. 200 words)[§]

[§]*Please note: This information will be published on CPRD's website as part of its transparency policy*

Objectives: To determine the rate of bleeding post hospital discharge, the characteristics of patients likely to develop these bleeding complication and whether these bleeds increase the rate of death.

Methods: Using a retrospective cohort design, we will identify patients 18 years and over with a new diagnosis of heart attack and no prior record of heart attack in the preceding 2 years within CPRD and follow them for bleeding consultation records. Follow-up will start from date of hospital discharge until date they no longer contribute to CPRD due to death or leaving practice or practice leaving CPRD or end of 2016. We will use the study population identified and compare the rate of death among those with bleeding consultation post hospital discharge and those without.

Data analysis: First the rate of bleeding post hospital discharge will be determined per 1000 person years at risk. Second, associations between bleeding post hospital discharge with socio-demographic characteristics, baseline clinical characteristics, in-hospital intervention and discharge medication will be investigated to determine the risk factors of bleeding. Finally, association between bleeding post-hospital discharge and death from all cause will be investigated, adjusting for risk factors identified in stage 2 above using Cox

proportional hazard regression.

D. Objectives, Specific Aims and Rationale

AIM

The overall aim is to determine the incidence of bleeding complications in patients with stable ACS, their predictors, and relationship with long-term outcomes within the primary care setting

OBJECTIVES

This overall aim is anticipated to be achieved via the following objectives

1. To determine the incidence of bleeding complications in the adult post-ACS population in primary care and variation by time since hospital discharge, socio-demographic characteristics (age, gender, deprivation, general practice and geographic region) and discharge pharmacotherapy (single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), triple antithrombotic therapy (TT), Non-steroidal anti-inflammatory drugs (NSAIDs), Selective serotonin re-uptake inhibitors (SSRIs)).

2. To determine the risk factors for bleeding complications in the adult post-ACS population in primary care.

3.To determine if bleeding complication post-hospital discharge is associated with all-cause mortality in the adult post-ACS population in primary care.

RATIONALE FOR THE CURRENT STUDY

The management of ACS whether medically or invasively or a combination of both achieves the desired goal of reducing ischaemic events and restoring perfusion. These strategies which reduce ischaemic events are often accompanied by bleeding complications. These bleeding complications can occur in the in-hospital setting or in the longer term after hospital discharge. Bleeding complications that occur in the in-hospital setting have been well described, whereas the incidence, timing and types of bleeds that occur in the longer term after hospital discharge are unclear. The characteristics of patients likely to develop these longer term bleeding complications post-ACS and the prognostic impacts of these bleeds are likewise ambiguous within the primary care setting. The majority of studies conducted within the primary care setting that examined these characteristics are RCT's testing the efficacy and safety of pharmacotherapies mostly in North American population (in which lower risk individuals are enrolled) where significant disparities in management practices exist compared to the UK (Kohli et al 2014, Mahaffey

et al 2011, Jolly et al 2008).
Furthermore, we conducted a systematic review examining the incidence and prognostic impact of these longer term bleeding complications within the primary care setting. The review confirmed that in previous studies, there has been less emphasis on bleeding complications that occur in the longer term after hospital discharge, hence data on the incidence and prognostic impact of these bleeds are very limited. The review also identified only two studies which were conducted within the UK population, and none of these two studies reported on types and timing of these longer term bleeds, nor their prognostic impact on mortality or the characteristics of patients likely to develop these bleeding complications. In one study (Wong et al 2006) data were extracted to calculate the incidence of bleeding and in another which used linked MINAP-CPRD data (Boggon et al 2011), the incidence was only examined in select population of patients discharged on clopidogrel which cannot be extrapolated onto the majority of ACS patients within primary care. Likewise, a bibliographic search of the CPRD database only yielded one relevant study (Boggon et al 2011). This dearth in knowledge underscores the need to define and characterise these bleeding complications in the UK adult post-ACS population using a large primary care database, which form the basis of this study. In doing so, it is anticipated that outputs from this study may inform guidelines and clinical practice which may translate to better management practices for patients.

E. Study Background

ACS is a terminology often used to describe the spectrum of clinical presentations that are compatible with acute myocardial ischaemia, namely Unstable Angina (UA), ST-Segment Elevation Myocardial Infarction (STEMI) and Non ST-Segment Elevation Myocardial Infarction (NSTEMI) (Kumar et al 2009). Traditionally, the management of ACS depends on the clinical presentation (UA/NSTEMI or STEMI), with an overall aim of reducing myocardial ischaemia, and prevention of adverse ischaemic events (O'Connor et al 2010). This goal is fundamentally achieved via therapy with anti-thrombotic and invasive strategies.
For UA/NSTEMI, management strategy is guided by risk stratification, and depending on the patient's risk profile, management could involve a combination of antiplatelet's/anticoagulant, or angiography/Percutaneous Coronary Intervention (PCI) (Steg et al 2012). For STEMI, the preferred management strategy is primary PCI, which is the gold standard reperfusion strategy for this patient population and for those with high risk UA/NSTEMI (Hamm et al 2011). Post hospital discharge, and regardless of the in-hospital management strategy, aspirin therapy is continued indefinitely, and adjunctively with a P2Y12 receptor inhibitor for up to 12 months depending on the in-hospital intervention, the type of stent implanted and the presence/absence of comorbidities (Hamm et al 2011, Amsterdam et al 2014). In patients with comorbidities such as atrial fibrillation, triple therapy with aspirin, a P2Y12 receptor inhibitor and an anticoagulant is continued at the discretion of the treating clinician (Hamm et al 2011).
Paradoxically, these management strategies whilst achieving the desired goal of reducing ischemic events, may also cause bleeding complications (Cayla et al 2013, Yeh et al 2015, Jolly et al 2008). Bleeding is one of the most important non-ischaemic complications of ACS management. These bleeding complications vary in severity and types, and range from major gastrointestinal bleeds to minor epistaxis (Bacquelin et al 2015, Lattuca et al 2016, Amin et al 2013). There are over ten definitions of these bleeding complications for use in clinical practice and clinical trials, although a lack of consensus exists regarding

which definition is optimal (Eisen et al 2016). Two of the most widely applied definition's, the Thrombolysis In Myocardial Infarction and Global Use of Strategies To Open Occluded Arteries criteria have been extensively applied in most trials over the past few decades (Mehran et al 2011). However, these definitions were developed in the fibrinolytic era to measure bleeding associated with fibrinolysis in patients with STEMI and may not be applicable to patients on newer antithrombotic agents or undergoing invasive procedures such as PCI (Manoukian et al 2010). For these reasons, several definitions have since been developed in trials and registries to address the drawbacks of both the TIMI and GUSTO definition's. However, using multiple criteria to define a single entity (bleeding) makes comparison (such as the efficacy and safety of pharmacotherapies in ACS) across studies very problematic (Steinhubl et al 2007). More recently, the Bleeding Academic Research Consortium (BARC) proposed a new standardized definition with the aim of alleviating the problem of using multiple criteria and to allow consistent reporting across studies (Mehran et al 2011). These variabilities in definition, further compounded by variation in patient characteristic's, concomitant therapy, timing of event reporting and study design, has made establishing the incidence of bleeding post-ACS very challenging (Mehran et al 2011, Eikelboom and Hirsh 2006). In the clinical trial setting, this incidence is reported to be between 1% and 10% (Rao et al 2007, Mehta et al 2007, and Doyle et al 2009). However, emphasis in majority of these trials was on major in-hospital bleeds or 30 day bleeding complications, whereas bleeds which occur in the longer term after hospital discharge are either under reported or neglected. Similarly, the incidences derived from these trials are likely to underestimate the real world frequency of these bleeding complications for the reason that multi-morbid elderly patients often encountered in the primary care setting are frequently excluded in these trials (Steg et al 2007).

Furthermore, characteristics of patients likely to develop these bleeding complications post-ACS have been well described for the in-hospital setting mostly in clinical trials or in studies using data generated from clinical trials (Kinnaird et al 2003, Moscucci et al 2003, Chew et al 2005, Sadeghi et al 2003, Kirtane et al 2006, Mehran et al 2010, Subherwal et al 2009, Matthews et al 2011, Manoukian et al 2007). In the real world setting, these distinctive characteristics have not been well characterised, and the generalisation of data derived from trials (mostly carried out within the in-hospital setting) in informing characteristics of patients likely to be at risk of these bleeding complications in the real world setting is uncertain, since trials often exclude elderly patients with comorbid conditions that may precipitate these bleeding outcomes.

Bleeding was initially thought to be a benign complication. However growing body of evidence on the importance of bleeding has indicated that bleeding is a powerful independent predictor of adverse outcomes, including mortality, recurrent MI, stroke and stent thrombosis (Rao et al 2007, Eikelboom et al 2006, Manoukian et al 2007, Rao et al 2005, Kinnaird et al 2003). The association between in-hospital bleeding and adverse outcomes (most notably mortality) appears to be maintained regardless of the definition of bleeding used (Eikelboom et al 2006, Rao et al 2005, Manoukian et al 2007, Rao et al 2007, Kwok et al 2014). While the association of bleeds with mortality has been well described for in-hospital bleeding, the association of bleeding events that occur late after hospital discharge (in primary care) with clinical outcomes such as mortality is unclear.

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
F. Study Type **Objective 1** The study will be a descriptive cohort study **Objective 2** This study will be a hypothesis testing study testing the null hypothesis that there is no significant association between bleeding in the adult post-ACS population in primary care and socio-demographic, clinical, pharmacological characteristics and in-hospital interventions. **Objective 3** This study will be testing the null hypothesis that there is no association between bleeding post hospital discharge and all-cause mortality within 1 year.
G. Study Design **Objective 1** This will be a descriptive retrospective cohort study set within the Clinical Practice Research Datalink (CPRD) with linkage to Hospital Episode Statistics (HES) data, and Office of National Statistics (ONS) mortality data. We will identify patients with a primary diagnosis of ACS from 2006 onwards and follow them longitudinally from date of hospital discharge to the earliest of, date of first bleed, date they no longer contribute to CPRD due to death or leaving practice or practice leaving CPRD or end of 2016. Identified patients should have no prior diagnostic record of ACS (see study population). The actual time at risk (for bleeding) for each patient will be determined in person-years as minimum of time from discharge to first bleed, or date the patient cease contributing to CPRD due to death or leaving practice or practice leaving CPRD or end of 2016. Incidence of bleeding will then be determined overall and by each type of bleed (for example gastrointestinal bleed) per 1000 person-years at risk, followed by stratification by the timing of the bleeding event post-discharge. **Objective 2** The design of the study will be a retrospective cohort study set within CPRD with linkage to HES, and ONS mortality data. We will use the study population identified from objective 1 above and compare those with bleeding consultation post hospital discharge (post-ACS) and those without. Associations between bleeding consultation and socio-demographic characteristics (age, gender, body mass index, smoking), baseline clinical characteristics (diabetes, hypertension, prior heart failure, chronic kidney disease, history of bleeding, hyperlipidaemia, peripheral vascular disease, gastroduodenal ulcer, systolic blood pressure, baseline haemoglobin, white cell count, type of ACS indication, COPD, cancer), discharge pharmacological characteristics (single antiplatelet therapy (SAPT), dual antiplatelet therapy (DAPT), triple antithrombotic therapy (TT), Non-steroidal anti-inflammatory drugs (NSAIDs), Selective serotonin re-uptake inhibitors (SSRIs)) and in-hospital intervention (angiography and PCI) will be examined. **Objective 3** The design of this study will also be a retrospective cohort study. Patients with bleeding consultation records within the initial 30 day's post–hospital discharge (for ACS) will be identified (exposed group). Similarly, ACS patients without a coded consultation for

bleeding complications within the same initial 30 day's post-hospital discharge will be identified (unexposed group). The exposed and unexposed groups will be followed longitudinally from the end of the initial 30 day's post-discharge for 12 months until death or date they no longer contribute to CPRD due to leaving practice or practice leaving CPRD or end of 2016 (figure 1). Association between bleeding complication within 30 day's post hospital discharge and mortality will be examined. This will be repeated examining the association of bleeding complications occurring between 30 days and 12 month's post hospital discharge with mortality after 12 months. The association between each type of bleeding complication (such as intracranial bleed) and bleeding overall with mortality will also be investigated (with bleeding measured from date of hospital discharge and assessed as a time varying covariate).

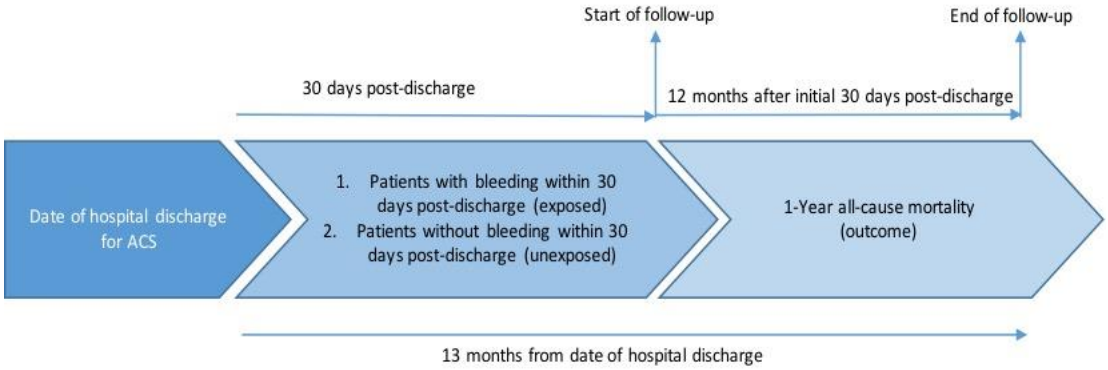

Figure 1: Illustration of the study design using the landmark 30 day's analysis as an example.

H. Feasibility counts

A feasibility count within CPRD using the Research Institute GOLD online access reveals that there are 63,681 patients meeting our study inclusion criteria (see study population). Since we will require linkage with HES, deprivation and ONS mortality data, and assuming 55% of all CPRD practices have consented to linkage, this will give us 35,024 patients with ACS in our study.

I. Sample size considerations

Assuming 24% (based on Amin et al 2016) of the 35,024 patients had a coded consultation for bleeding complication, this will give us approximately 8400 patients in the exposed group. Assuming for example a mortality rate of 5.42% based on a study (Brener et al 2016) with similar length of follow-up (12 months) to our study, there will be approximately 455 mortality records in the exposed group between 2006 and 2016 in our study. With a ratio of 1:3 in the exposed to unexposed groups for assessing whether bleeding consultation after hospital discharge is predictive of all-cause mortality, this will allow 80% power at 5% significance level to detect a hazard ratio of 1.3 or greater.

J. Data Linkage Required (if applicable):[§]

[§]*Please note that the data linkage/s requested in research protocols will be published by the CPRD as part of its transparency policy*

We will require linkage with HES to identify in-hospital interventions, discharged diagnosis and date of hospital discharge. We will also require linkage with ONS mortality data to identify the date and cause of death, and finally linkage with patient level deprivation data as deprivation may potentially be associated with bleeding.

Applicants must complete all sections listed below
Sections which do not apply should be completed as '*Not Applicable*'

K. Study population

- Aged 18 years or older at the time of index ACS diagnosis.
- Have recorded ACS diagnosis in CPRD between 2006 and 2016, with no record of ACS in the preceding 2 years and at least 2 years of up to standard data in CPRD. Date of hospital discharge for ACS will be the index date.
- Patients must be registered at one of the 407 practices in England that have consented to linkage with HES, ONS mortality data and deprivation data.

L. Selection of comparison group(s) or controls

In the landmark 30 day's analysis (Objective 3), the unexposed cohort will constitute patients with stable ACS, who within the initial 30 day's post hospital discharge have not had a bleeding consultation recorded in CPRD. The unexposed group will have 2 years of up to standard data in CPRD post hospital discharge but no bleeding record within the initial 30 day's. For the 30 days to 12 month's landmark analysis, the same approach as described for the 30-day analysis will be used but this time changing the timing of bleeding to between 30 days and 12 month's post hospital discharge.

M. Exposures, Health Outcomes[§] and Covariates

[§]*Please note: Summary information on health outcomes (as included on the ISAC application form above)will be published on CPRD's website as part of its transparency policy*

EXPOSURE'S

Objective 2

Risk factors for bleeding complications were compiled from extensive review of studies that had examined predictors of bleeding post hospital discharge in the adult post-ACS population (Costa et al 2017, Barra et al 2013, Lattuca et al 2016, Cuschieri et al 2014, Buresly et al 2005, Graipe et al 2015, Genereux et al 2015). These risk factors were then categorised into socio-demographic, clinical, pharmacological characteristics and in-hospital intervention.

Socio-demographic factors

Age, gender, ethnicity, general practice and geographical region (North East, North West, Yorkshire and Humber, East Midlands, West Midlands, East England, London, South West and South East) will be as defined within CPRD. Deprivation will be defined by quintile ranks (based on the English Index of Multiple Deprivation (IMD)), as recorded in linked CPRD-deprivation data. Body mass index and smoking status will be defined as last recorded measurement/status within CPRD before the index date of hospital discharge.

Clinical characteristics

Baseline clinical characteristics including diabetes, hypertension, prior heart failure, history of bleeding, peripheral vascular disease, gastroduodenal ulcer, type of ACS presentation, COPD, cancer will be considered as risk factors for bleeding. These risk factors will be defined by Read codes in the 2 years prior to the index date of hospital discharge via consensus of a General Practitioner and a Cardiologist.

Chronic kidney disease will be defined by glomerular filtration rate (GFR). GFR will be stratified into ≥ 90, 60 – 89, 30 – 59, 15 – 29 and < 15 mL/min/1.73m^2 based on the classification by Kidney Disease Improving Global Outcome guideline for the evaluation and management of chronic kidney diseases (Stevens et al 2013).

Hyperlipidaemia will be defined as having recorded total cholesterol level ≥ 5 mmol/L (NICE 2016) or diagnostic code for hyperlipidaemia or a prescription for statin within CPRD in the 2 years prior to index hospital discharge date.

Baseline haemoglobin, white cell count and systolic blood pressure will be defined as last recorded measurements in CPRD in the 2 years prior to the index date of hospital discharge.

Pharmacological factors will be defined as:
SAPT: Having recorded prescription in CPRD for one of aspirin, clopidogrel, prasugrel or ticagrelor within 90 days from index discharge date.
DAPT: Having recorded prescription in CPRD for both aspirin and one of clopidogrel, prasugrel and ticagrelor within 90 days from index discharge date.
TT: Having recorded prescription in CPRD for an oral anticoagulant within 90 days from index discharge date.
SSRI's: Having recorded prescription in CPRD for Fluoxetine, Paroxetine, Citalopram, Escitalopram, Sertraline and Fluvoxamine within 6 months before the date of hospital discharge.
NSAID's: Having recorded prescription in CPRD for Ibuprofen, Naproxen, Diclofenac, Celecoxib, Mefenamic acid, Etoricoxib and Indometacin within 6 months before the date of hospital discharge.

In-hospital intervention
In-hospital intervention will be defined as having a record for angiography or PCI during the index ACS hospitalisation. These characteristics will be identified from patients HES records using the UK Office of Population Census and Surveys classification codes (OPCS). OPCS codes will be determined by consensus of two interventional cardiologists.

Objective 3
Exposure will be defined as having any of the appended bleeding Read codes in CPRD post-ACS, post hospital discharge (see appendix 1 for codes). These Read codes were derived via consensus of three General Practitioners and an Interventional Cardiologist.

COVARIATES
All the exposures from objective two above will be considered as potential covariates in the analysis to be carried out for objective three.

OUTCOMES
The outcome of interest specific to objective 2 is consultation for bleeding complications post-ACS, post hospital discharge (see appendix 1 for definition of bleeding). For

objective 3, the main outcome after the index date of consultation for bleeding complication, post hospital discharge is all-cause mortality. We will identify the date and cause of death via linkage with ONS mortality data.

N. Data/ Statistical Analysis

Objective 1

Patients with new diagnosis of ACS from 2006 onwards will be identified and followed longitudinally for records of bleeding consultation in CPRD. Follow-up will start from date of hospital discharge to the earliest of, date of first recorded bleed, date they no longer contribute to CPRD due to death or leaving practice or practice leaving CPRD or end of 2016. The actual time at risk (for bleeding) for each patient will be determined in person-years as the minimum of time from discharge to first bleed, or date the patient cease contributing to CPRD due to death or leaving practice or practice leaving CPRD or end of 2016. Incidence of bleeding will then be determined overall and by each type of bleed (for example gastrointestinal bleed) per 1000 person-years at risk with 95% confidence interval, followed by stratification by the timing of the bleeding events post-discharge.

Objective 2

The outcome variable of bleeding will be dichotomous (patients with and those without recorded bleeding consultation). First, multivariable analysis will be carried out using a competing risk regression model to determine independent associations between consultation for bleeding after hospital discharge and each of the socio-demographic, clinical, pharmacological characteristics and in-hospital interventions listed above. Adjusted associations between consultation for bleeding after hospital discharge and each predictor in the model will be quantified by adjusted hazard ratios and 95% confidence intervals.

Objective 3

Analysis will be carried out in three stages with mortality within 12 months (binary) as the outcome variable and bleeding (binary) as the predictor variable. First, in the 30 day's landmark analysis, univariable associations between bleeding within 30 day's with mortality in the following 12 month's will be examined using Cox proportional hazard regression analysis. Patients will be followed longitudinally from the end of the landmark period for 12 months, until death or date they no longer contribute to CPRD due to leaving practice or practice leaving CPRD or end of 2016. Second, to assess the adjusted association of bleeding post-discharge with mortality, Cox proportional hazard regression analysis adjusting for the significant socio-demographic, clinical, pharmacological characteristics and in-hospital interventions identified from objective two above will be modelled. Third, the adjusted association from stage 2 will be stratified by gender, age, in-hospital procedure and discharge pharmacotherapy. If a moderating effect is detected (i.e. differing hazard ratios between strata), interaction terms will be incorporated into the model to quantify these moderating effects as well as account for the effects on the association between bleeding and mortality. Adjusted associations will be quantified by hazard ratios and associated 95% confidence intervals. The analysis will be repeated for bleeding between 30 day's and 12 months (with the outcome of mortality identified within 12-24 month's). When examining the association between each type of bleeding and bleeding overall, with mortality, bleeding will be incorporated into the models as a time varying exposure. Proportionality assumption will be examined using Schoenfeld and

Applicants must complete all sections listed below Sections which do not apply should be completed as '*Not Applicable*'
scaled Schoenfeld residuals. Patients will be censored at the point they are recorded as deceased or leave practice or practice leaves CPRD or end of 2016.
O. Plan for addressing confounding For objective 2, all associations will be adjusted for potential confounding from the other socio-demographic, clinical, pharmacological characteristics and in-hospital interventions examined. For objective 3, the association of bleeding with mortality will be adjusted for characteristics identified to be significantly associated with bleeding in objective 2. Confounding by indication when examining the association between bleeding and discharge pharmacotherapies (objective 2) will be addressed by adjusting for the clinical indications for these pharmacotherapies (such as STEMI. NSTEMI, atrial fibrillation) in the analysis.
P. Plans for addressing missing data Missing data on characteristics such as body mass index and smoking are unlikely to be missing at random. However, we will compare the effect of using complete case analysis, to incorporating a missing category and multiple imputation by chain equation.
Q. Patient or user group involvement (if applicable) This study is a quantitative analyses of primary care data, therefore involvement of patients or user groups is unlikely to inform analysis and interpretation of results. However, should the need arise, we have full access to a Research User Group within the Research Institute for Primary Care and Health Sciences at Keele University, which include over 80 members of the public with either experience of living with a health condition or are carers or close relatives of someone who does.
R. Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication We will aim to publish the results of the study in high impact journals. Journals that will be targeted will include Journal of the American College of Cardiology, Circulation, European Heart Journal. We will aim to publish three papers from this study. The first paper will concentrate on the incidence and types of bleeding complications (post-ACS) in primary care (objective 1). The second paper will concentrate on characteristics of patients likely to sustain bleeding complications post-ACS in primary care (objective 2). The final paper will focus on the prognostic value of post-discharge bleeding complications in predicting mortality (objective 3). Abstracts will be submitted to the British Cardiovascular Society annual conference, and the European Society of Cardiology. These conferences will provide the perfect opportunity to communicate the finding of the study to renowned experts within the field of Cardiology. Since this is likely to be the first study of bleeding complications post-ACS post hospital discharge within the English population, findings of potential scientific importance will be communicated to the National Institute for Health and Care Excellence (NICE). We will disseminate our finding to local and national NHS services in collaboration with the North Staffordshire Medical Institute who are also the funders of this study. When reporting results, we will follow Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline and any other relevant guideline in the Enhancing the Quality and Transparency of health research (EQUATOR) network to enhance transparency.
S. Limitations of the study design, data sources, and analytic methods

Applicants must complete all sections listed below **Sections which do not apply should be completed as '*Not Applicable'***
Like every other observational study, this study may contain variables with incomplete or missing data. For example, blood pressure may be recorded more frequently for patients with cardiovascular problems than in those without, and body mass index more frequently in those who look overweight. We will perform our analysis on imputed data and compare the results with those generated using complete case analysis. GP's might enter information as free text and not Read codes. In this study, absence of a relevant Read code will imply absence of the outcome of interest which could lead to some misclassification. Although every effort will be made to adjust for confounding, the study cannot adjust for the confounding effects of unmeasured/unrecorded confounders which could potentially influence the results of the study. This will be stated as a limitation in publications, however, it is unlikely any major confounder will be missed.
T. References
List of Appendices *(Submit all appendices as separate documents to this application)*

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Appendix 5.2: Code list for bleeding events within the first 12 months after hospital discharge for ACS categorised based on severity

Read code	Description	Severity
16B..00	Bruising symptom	Typically non-serious bleed
16B3.00	Spontaneous bruising	Typically non-serious bleed
16BZ.00	Bruising symptom NOS	Typically non-serious bleed
R027.11	[D]Spontaneous bruising	Typically non-serious bleed
R027z00	[D]Spontaneous ecchymoses NOS	Typically non-serious bleed
SE...11	Haematoma with intact skin	Typically non-serious bleed
SE4..11	Leg bruise	Typically non-serious bleed
SE4z.00	Contusion, site NOS	Typically non-serious bleed
R027.00	[D]Spontaneous ecchymoses	Typically non-serious bleed
SE...00	Contusion (bruise) with intact skin	Typically non-serious bleed
SE00.00	Contusion, forehead	Typically non-serious bleed
SE01.00	Contusion, cheek	Typically non-serious bleed
SE04.00	Contusion, gum	Typically non-serious bleed
SE09.00	Contusion, scalp	Typically non-serious bleed
SE0z.00	Contusion of face, scalp and neck NOS	Typically non-serious bleed
SE1..00	Contusion, eye and adnexa	Typically non-serious bleed
SE2..00	Contusion, trunk	Typically non-serious bleed
SE20.00	Contusion, breast	Typically non-serious bleed
SE21.00	Contusion, chest wall	Typically non-serious bleed
SE22.00	Contusion, abdominal wall	Typically non-serious bleed
SE22000	Contusion, anterior abdominal wall	Typically non-serious bleed
SE23100	Contusion, buttock	Typically non-serious bleed
SE23z00	Contusion, back NOS	Typically non-serious bleed
SE3..00	Contusion, upper limb	Typically non-serious bleed
SE30000	Contusion, shoulder area	Typically non-serious bleed
SE30300	Contusion, upper arm	Typically non-serious bleed
SE31000	Contusion, forearm area	Typically non-serious bleed
SE32.00	Contusion wrist or hand	Typically non-serious bleed
SE32000	Contusion, hand, excluding finger	Typically non-serious bleed
SE32100	Contusion, wrist	Typically non-serious bleed
SE32300	Contusion hand, dorsum	Typically non-serious bleed
SE33000	Contusion, finger, unspecified	Typically non-serious bleed
SE4..00	Contusion, lower limb and other unspecified sites	Typically non-serious bleed
SE40.00	Contusion, hip and thigh	Typically non-serious bleed
SE40000	Contusion, hip	Typically non-serious bleed
SE40100	Contusion, thigh	Typically non-serious bleed
SE41100	Contusion, knee	Typically non-serious bleed
SE42000	Contusion, foot	Typically non-serious bleed
SE43.00	Contusion, toe	Typically non-serious bleed
SEz..00	Contusion with skin intact, NOS	Typically non-serious bleed
SE0..12	Bruise of head	Typically non-serious bleed

SE1..11	Bruise of eye	Typically non-serious bleed
SE2..11	Bruise, trunk	Typically non-serious bleed
SE3..11	Arm bruise	Typically non-serious bleed
SE30011	Shoulder bruise	Typically non-serious bleed
1C6..00	Nose bleed symptom	Typically non-serious bleed
1C6..11	Epistaxis symptom	Typically non-serious bleed
1C62.00	Has nose bleeds - epistaxis	Typically non-serious bleed
1C6Z.00	Nose bleed symptom NOS	Typically non-serious bleed
2D25.00	O/E - epistaxis	Typically non-serious bleed
R047.00	[D]Epistaxis	Typically non-serious bleed
R047.11	[D]Nosebleed	Typically non-serious bleed
F4C7100	Subconjunctival haemorrhage	Typically non-serious bleed
F4C7200	Conjunctival haemorrhage NOS	Typically non-serious bleed
172..00	Blood in sputum - haemoptysis	Typically/potentially serious bleed
172..12	Haemoptysis - symptom	Typically/potentially serious bleed
H51y200	Haemothorax	Typically/potentially serious bleed
R063.00	[D]Haemoptysis	Typically/potentially serious bleed
4A24.11	Coffee ground vomit	Typically/potentially serious bleed
196B.00	Painful rectal bleeding	Typically/potentially serious bleed
196C.00	Painless rectal bleeding	Typically/potentially serious bleed
19E6.00	Blood in faeces	Typically/potentially serious bleed
19E6.11	Blood in faeces symptom	Typically/potentially serious bleed
J107.00	Mallory-Weiss syndrome	Typically/potentially serious bleed
J110111	Bleeding acute gastric ulcer	Typically/potentially serious bleed
J121111	Bleeding chronic duodenal ulcer	Typically/potentially serious bleed
J573.11	Bleeding PR	Typically/potentially serious bleed
J573000	Rectal haemorrhage	Typically/potentially serious bleed
J573011	Rectal bleeding	Typically/potentially serious bleed
J573012	PRB - Rectal bleeding	Typically/potentially serious bleed
J68..00	Gastrointestinal haemorrhage	Typically/potentially serious bleed
J680.00	Haematemesis	Typically/potentially serious bleed
J680.11	Vomiting of blood	Typically/potentially serious bleed
J681.00	Melaena	Typically/potentially serious bleed
J681.11	Blood in stool	Typically/potentially serious bleed
J681.13	Blood in stools altered	Typically/potentially serious bleed
J68z.11	GIB - Gastrointestinal bleeding	Typically/potentially serious bleed
J68z000	Gastric haemorrhage NOS	Typically/potentially serious bleed
J68z200	Upper gastrointestinal haemorrhage	Typically/potentially serious bleed
J573100	Anal haemorrhage	Typically/potentially serious bleed
1A45.00	Blood in urine - haematuria	Typically/potentially serious bleed
K0A2.00	Recurrent and persistent haematuria	Typically/potentially serious bleed
K197.00	Haematuria	Typically/potentially serious bleed
K197000	Painless haematuria	Typically/potentially serious bleed
K197100	Painful haematuria	Typically/potentially serious bleed
K197200	Microscopic haematuria	Typically/potentially serious bleed

K197300	Frank haematuria	Typically/potentially serious bleed
K286w11	Haematospermia	Typically/potentially serious bleed
K56y112	BPV - Vaginal bleeding	Typically/potentially serious bleed
K592000	Menorrhagia	Typically/potentially serious bleed
K592011	Heavy periods	Typically/potentially serious bleed
K5A1.00	Postmenopausal bleeding	Typically/potentially serious bleed
K5E..00	Other abnormal uterine and vaginal bleeding	Typically/potentially serious bleed
K5E2.00	Abnormal vaginal bleeding, unspecified	Typically/potentially serious bleed
K5Ez.00	Abnormal uterine and vaginal bleeding, unspecified	Typically/potentially serious bleed
2BB5.00	O/E - retinal haemorrhages	Typically/potentially serious bleed
2BB8.00	O/E - vitreous haemorrhages	Typically/potentially serious bleed
F42y.11	Haemorrhage - retinal	Typically/potentially serious bleed
F42y400	Subretinal haemorrhage	Typically/potentially serious bleed
F42y500	Retinal haemorrhage NOS	Typically/potentially serious bleed
F4K2800	Vitreous haemorrhage	Typically/potentially serious bleed
G60..00	Subarachnoid haemorrhage	Typically/potentially serious bleed
G60X.00	Subarachnoid haemorrh from intracranial artery, unspecif	Typically/potentially serious bleed
G60z.00	Subarachnoid haemorrhage NOS	Typically/potentially serious bleed
G61..00	Intracerebral haemorrhage	Typically/potentially serious bleed
G61..11	CVA - cerebrovascular accid due to intracerebral haemorrhage	Typically/potentially serious bleed
G614.00	Pontine haemorrhage	Typically/potentially serious bleed
G617.00	Intracerebral haemorrhage, intraventricular	Typically/potentially serious bleed
G61z.00	Intracerebral haemorrhage NOS	Typically/potentially serious bleed
G621.00	Subdural haemorrhage - nontraumatic	Typically/potentially serious bleed
G622.00	Subdural haematoma - nontraumatic	Typically/potentially serious bleed
G623.00	Subdural haemorrhage NOS	Typically/potentially serious bleed
G682.00	Sequelae of other nontraumatic intracranial haemorrhage	Typically/potentially serious bleed
7017000	Evacuation of subdural haematoma	Typically/potentially serious bleed
D00..00	Iron deficiency anaemias	Typically/potentially serious bleed
D00..11	Hypochromic - microcytic anaemia	Typically/potentially serious bleed
D00..12	Microcytic - hypochromic anaemia	Typically/potentially serious bleed
D00y.00	Other specified iron deficiency anaemia	Typically/potentially serious bleed
D00y100	Microcytic hypochromic anaemia	Typically/potentially serious bleed
D00z.00	Unspecified iron deficiency anaemia	Typically/potentially serious bleed
D00zz00	Iron deficiency anaemia NOS	Typically/potentially serious bleed
D000.00	Iron deficiency anaemia due to chronic blood loss	Typically/potentially serious bleed
D000.11	Normocytic anaemia due to chronic blood loss	Typically/potentially serious bleed
N091.00	Haemarthrosis	Typically/potentially serious bleed
7M0G400	Evacuation of haematoma NEC	Typically/potentially serious bleed
K13y800	Perirenal haematoma	Typically/potentially serious bleed
SE23111	Perianal haematoma	Typically/potentially serious bleed
SE22300	Haematoma of rectus sheath	Typically/potentially serious bleed

SE45.11	Haematoma of leg	Typically/potentially serious bleed
SE4z.11	Haematoma NOS	Typically/potentially serious bleed

Appendix 5.3: Code list used to define risk factors and covariates

Smoking

Read code	Description	Category (code)
1371.00	Never smoked tobacco	Non smoker (1)
1371.11	Non-smoker	Non smoker (1)
1372.00	Trivial smoker - < 1 cig/day	Current smoker (4)
1372.11	Occasional smoker	Current smoker (4)
1373.00	Light smoker - 1-9 cigs/day	Current smoker (4)
1374.00	Moderate smoker - 10-19 cigs/d	Current smoker (4)
1375.00	Heavy smoker - 20-39 cigs/day	Current smoker (4)
1376.00	Very heavy smoker - 40+cigs/d	Current smoker (4)
1377.00	Ex-trivial smoker (<1/day)	Ex smoker (2)
1378.00	Ex-light smoker (1-9/day)	Ex smoker (2)
1379.00	Ex-moderate smoker (10-19/day)	Ex smoker (2)
6791.00	Health ed. - smoking	Current smoker (4)
137..11	Smoker - amount smoked	Current smoker (4)
137a.00	Pipe tobacco consumption	Current smoker (4)
137A.00	Ex-heavy smoker (20-39/day)	Ex smoker (2)
137b.00	Ready to stop smoking	Current smoker (4)
137B.00	Ex-very heavy smoker (40+/day)	Ex smoker (2)
137c.00	Thinking about stopping smoking	Current smoker (4)
137C.00	Keeps trying to stop smoking	Current smoker (4)
137d.00	Not interested in stopping smoking	Current smoker (4)
137e.00	Smoking restarted	Current smoker (4)
137f.00	Reason for restarting smoking	Current smoker (4)
137F.00	Ex-smoker - amount unknown	Ex smoker (2)
137G.00	Trying to give up smoking	Current smoker (4)
137h.00	Minutes from waking to first tobacco consumption	Current smoker (4)
137H.00	Pipe smoker	Current smoker (4)
137J.00	Cigar smoker	Current smoker (4)
137K.00	Stopped smoking	Ex smoker (2)
137K000	Recently stopped smoking	Ex smoker (2)
137L.00	Current non-smoker	Non smoker (1)
137M.00	Rolls own cigarettes	Current smoker (4)
137N.00	Ex pipe smoker	Ex smoker (2)
137O.00	Ex cigar smoker	Ex smoker (2)
137P.00	Cigarette smoker	Current smoker (4)
137P.11	Smoker	Current smoker (4)
137Q.00	Smoking started	Current smoker (4)
137Q.11	Smoking restarted	Current smoker (4)
137R.00	Current smoker	Current smoker (4)
137S.00	Ex smoker	Ex smoker (2)
137T.00	Date ceased smoking	Ex smoker (2)
137V.00	Smoking reduced	Current smoker (4)

137X.00	Cigarette consumption	Current smoker (4)
137Y.00	Cigar consumption	Current smoker (4)
137Z.00	Tobacco consumption NOS	Current smoker (4)
13p..00	Smoking cessation milestones	Current smoker (4)
13p0.00	Negotiated date for cessation of smoking	Current smoker (4)
13p1.00	Smoking status at 4 weeks	Current smoker (4)
13p2.00	Smoking status between 4 and 52 weeks	Current smoker (4)
13p3.00	Smoking status at 52 weeks	Current smoker (4)
13p4.00	Smoking free weeks	Current smoker (4)
13p5.00	Smoking cessation programme start date	Current smoker (4)
13p5000	Practice based smoking cessation programme start date	Current smoker (4)
13p6.00	Carbon monoxide reading at 4 weeks	Current smoker (4)
13p7.00	Smoking status at 12 weeks	Current smoker (4)
13p8.00	Lost to smoking cessation follow-up	Current smoker (4)
38DH.00	Fagerstrom test for nicotine dependence	Current smoker (4)
67A3.00	Pregnancy smoking advice	Current smoker (4)
67H1.00	Lifestyle advice regarding smoking	Current smoker (4)
67H6.00	Brief intervention for smoking cessation	Current smoker (4)
745H.00	Smoking cessation therapy	Current smoker (4)
745H000	Nicotine replacement therapy using nicotine patches	Current smoker (4)
745H100	Nicotine replacement therapy using nicotine gum	Current smoker (4)
745H200	Nicotine replacement therapy using nicotine inhalator	Current smoker (4)
745H300	Nicotine replacement therapy using nicotine lozenges	Current smoker (4)
745H400	Smoking cessation drug therapy	Current smoker (4)
745Hy00	Other specified smoking cessation therapy	Current smoker (4)
745Hz00	Smoking cessation therapy NOS	Current smoker (4)
8B2B.00	Nicotine replacement therapy	Current smoker (4)
8B3f.00	Nicotine replacement therapy provided free	Current smoker (4)
8B3Y.00	Over the counter nicotine replacement therapy	Current smoker (4)
8BP3.00	Nicotine replacement therapy provided by community pharmacis	Current smoker (4)
8CAg.00	Smoking cessation advice provided by community pharmacist	Current smoker (4)
8CAL.00	Smoking cessation advice	Current smoker (4)
8CdB.00	Stop smoking service opportunity signposted	Current smoker (4)
8H7i.00	Referral to smoking cessation advisor	Current smoker (4)
8HBM.00	Stop smoking face to face follow-up	Current smoker (4)
8HBP.00	Smoking cessation 12 week follow-up	Current smoker (4)
8HkQ.00	Referral to NHS stop smoking service	Current smoker (4)
8HTK.00	Referral to stop-smoking clinic	Current smoker (4)
8I2I.00	Nicotine replacement therapy contraindicated	Current smoker (4)
8I2J.00	Bupropion contraindicated	Current smoker (4)
8I39.00	Nicotine replacement therapy refused	Current smoker (4)
8IAj.00	Smoking cessation advice declined	Current smoker (4)
9kc..00	Smoking cessation - enhanced services administration	Current smoker (4)
9kc0.00	Smoking cessatn monitor template complet - enhanc serv admin	Current smoker (4)
9km..00	Ex-smoker annual review - enhanced services administration	Ex smoker (2)

9km..11	Ex-smoker annual review	Ex smoker (2)
9kn..00	Non-smoker annual review - enhanced services administration	Non smoker (1)
9kn..11	Non-smoker annual review	Non smoker (1)
9ko..00	Current smoker annual review - enhanced services admin	Current smoker (4)
9ko..11	Current smoker annual review	Current smoker (4)
9N2k.00	Seen by smoking cessation advisor	Current smoker (4)
9N4M.00	DNA - Did not attend smoking cessation clinic	Current smoker (4)
9NS0200	Referral for smoking cessation service offered	Current smoker (4)
9OO..00	Anti-smoking monitoring admin.	Current smoker (4)
9OO..11	Stop smoking clinic admin.	Current smoker (4)
9OO..12	Stop smoking monitoring admin.	Current smoker (4)
9OO1.00	Attends stop smoking monitor.	Current smoker (4)
9OO2.00	Refuses stop smoking monitor	Current smoker (4)
9OO3.00	Stop smoking monitor default	Current smoker (4)
9OO4.00	Stop smoking monitor 1st lettr	Current smoker (4)
9OO5.00	Stop smoking monitor 2nd lettr	Current smoker (4)
9OO6.00	Stop smoking monitor 3rd lettr	Current smoker (4)
9OO7.00	Stop smoking monitor verb.inv.	Current smoker (4)
9OO8.00	Stop smoking monitor phone inv	Current smoker (4)
9OO9.00	Stop smoking monitoring delete	Current smoker (4)
9OOA.00	Stop smoking monitor.chck done	Current smoker (4)
9OOZ.00	Stop smoking monitor admin.NOS	Current smoker (4)
E023.00	Nicotine withdrawal	Current smoker (4)
E251.00	Tobacco dependence	Current smoker (4)
E251000	Tobacco dependence, unspecified	Current smoker (4)
E251100	Tobacco dependence, continuous	Current smoker (4)
E251300	Tobacco dependence in remission	Ex smoker (2)
E251z00	Tobacco dependence NOS	Current smoker (4)
Eu17.00	[X]Mental and behavioural disorder due to use of tobacco	Current smoker (4)
Eu17100	[X]Mental and behav dis due to use of tobacco: harmful use	Current smoker (4)
H310100	Smokers' cough	Ex or current smoker (3)
ZG23300	Advice on smoking	Current smoker (4)
ZRaM.00	Motives for smoking scale	Current smoker (4)
ZRao.00	Occasions for smoking scale	Current smoker (4)
ZRBm200	Fagerstrom test for nicotine dependence	Current smoker (4)
ZRBm211	FTND - Fagerstrom test for nicotine dependence	Current smoker (4)
ZRh4.00	Reasons for smoking scale	Current smoker (4)
ZRh4.11	RFS - Reasons for smoking scale	Current smoker (4)
ZV11600	[V]Personal history of tobacco abuse	Ex or current smoker (3)
ZV4K000	[V]Tobacco use	Current smoker (4)
ZV6D800	[V]Tobacco abuse counselling	Current smoker (4)

Hypertension

Read code	Description
2126100	Hypertension resolved

6624.00	Borderline hyperten:yearly obs
6627.00	Good hypertension control
6628.00	Poor hypertension control
6629.00	Hypertension:follow-up default
6146200	Hypertension induced by oral contraceptive pill
14A2.00	H/O: hypertension
1JD..00	Suspected hypertension
212K.00	Hypertension resolved
246M.00	White coat hypertension
662..12	Hypertension monitoring
662b.00	Moderate hypertension control
662c.00	Hypertension six month review
662d.00	Hypertension annual review
662F.00	Hypertension treatm. started
662G.00	Hypertensive treatm.changed
662H.00	Hypertension treatm.stopped
662O.00	On treatment for hypertension
662P.00	Hypertension monitoring
662P000	Hypertension 9 month review
662q.00	Trial reduction of antihypertensive therapy
662r.00	Trial withdrawal of antihypertensive therapy
67H8.00	Lifestyle advice regarding hypertension
7Q01.00	High cost hypertension drugs
7Q01y00	Other specified high cost hypertension drugs
8B26.00	Antihypertensive therapy
8BL0.00	Patient on maximal tolerated antihypertensive therapy
8CR4.00	Hypertension clinical management plan
8HT5.00	Referral to hypertension clinic
8I3N.00	Hypertension treatment refused
9h3..00	Exception reporting: hypertension quality indicators
9h31.00	Excepted from hypertension qual indicators: Patient unsuit
9h32.00	Excepted from hypertension qual indicators: Informed dissent
9N03.00	Seen in hypertension clinic
9N1y200	Seen in hypertension clinic
9N4L.00	DNA - Did not attend hypertension clinic
9OI..00	Hypertension monitoring admin.
9OI..11	Hypertension clinic admin.
9OI1.00	Attends hypertension monitor.
9OI2.00	Refuses hypertension monitor.
9OI3.00	Hyperten.monitor offer default
9OI4.00	Hypertens.monitor.1st letter
9OI5.00	Hypertens.monitor 2nd letter
9OI6.00	Hypertens.monitor 3rd letter
9OI7.00	Hypertens.monitor verbal inv.
9OI8.00	Hypertens.monitor phone invite

9OI9.00	Hypertens.monitor deleted
9OIA.00	Hypertension monitor.chck done
9OIA.11	Hypertension monitored
9OIZ.00	Hypertens.monitoring admin.NOS
F404200	Blind hypertensive eye
F421300	Hypertensive retinopathy
G2...00	Hypertensive disease
G2...11	BP - hypertensive disease
G20..00	Essential hypertension
G20..11	High blood pressure
G20..12	Primary hypertension
G200.00	Malignant essential hypertension
G201.00	Benign essential hypertension
G202.00	Systolic hypertension
G203.00	Diastolic hypertension
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G21..00	Hypertensive heart disease
G210.00	Malignant hypertensive heart disease
G210000	Malignant hypertensive heart disease without CCF
G210100	Malignant hypertensive heart disease with CCF
G210z00	Malignant hypertensive heart disease NOS
G211.00	Benign hypertensive heart disease
G211000	Benign hypertensive heart disease without CCF
G211100	Benign hypertensive heart disease with CCF
G211z00	Benign hypertensive heart disease NOS
G21z.00	Hypertensive heart disease NOS
G21z000	Hypertensive heart disease NOS without CCF
G21z011	Cardiomegaly - hypertensive
G21z100	Hypertensive heart disease NOS with CCF
G21zz00	Hypertensive heart disease NOS
G22..00	Hypertensive renal disease
G22..11	Nephrosclerosis
G220.00	Malignant hypertensive renal disease
G221.00	Benign hypertensive renal disease
G222.00	Hypertensive renal disease with renal failure
G22z.00	Hypertensive renal disease NOS
G22z.11	Renal hypertension
G23..00	Hypertensive heart and renal disease
G230.00	Malignant hypertensive heart and renal disease
G231.00	Benign hypertensive heart and renal disease
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G233.00	Hypertensive heart and renal disease with renal failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G23z.00	Hypertensive heart and renal disease NOS

G24..00	Secondary hypertension
G240.00	Secondary malignant hypertension
G240000	Secondary malignant renovascular hypertension
G240z00	Secondary malignant hypertension NOS
G241.00	Secondary benign hypertension
G241000	Secondary benign renovascular hypertension
G241z00	Secondary benign hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z.00	Secondary hypertension NOS
G24z000	Secondary renovascular hypertension NOS
G24z100	Hypertension secondary to drug
G24zz00	Secondary hypertension NOS
G25..00	Stage 1 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G25..11	Stage 1 hypertension
G26..00	Severe hypertension (Nat Inst for Health Clinical Ex 2011)
G26..11	Severe hypertension
G27..00	Hypertension resistant to drug therapy
G28..00	Stage 2 hypertension (NICE - Nat Ins for Hth Clin Excl 2011)
G2y..00	Other specified hypertensive disease
G2z..00	Hypertensive disease NOS
G672.00	Hypertensive encephalopathy
G672.11	Hypertensive crisis
Gyu2.00	[X]Hypertensive diseases
Gyu2000	[X]Other secondary hypertension
Gyu2100	[X]Hypertension secondary to other renal disorders
L120.00	Benign essential hypertension in pregnancy/childbirth/puerp
L120000	Benign essential hypertension in preg/childb/puerp unspec
L120100	Benign essential hypertension in preg/childb/puerp - deliv
L120300	Benign essential hypertension in preg/childb/puerp-not deliv
L120400	Benign essential hypertension in preg/childb/puerp +p/n comp
L120z00	Benign essential hypertension in preg/childb/puerp NOS
L121.00	Renal hypertension in pregnancy/childbirth/puerperium
L121000	Renal hypertension in pregnancy/childbirth/puerp unspecified
L121100	Renal hypertension in pregnancy/childbirth/puerp - delivered
L121200	Renal hypertension in preg/childb/puerp -deliv with p/n comp
L121300	Renal hypertension in preg/childbirth/puerp - not delivered
L121z00	Renal hypertension in pregnancy/childbirth/puerperium NOS
L122.00	Other pre-existing hypertension in preg/childbirth/puerp
L122000	Other pre-existing hypertension in preg/childb/puerp unspec
L122100	Other pre-existing hypertension in preg/childb/puerp - deliv
L122300	Other pre-exist hypertension in preg/childb/puerp-not deliv
L122z00	Other pre-existing hypertension in preg/childb/puerp NOS
L127.00	Pre-eclampsia or eclampsia with pre-existing hypertension
L127z00	Pre-eclampsia or eclampsia + pre-existing hypertension NOS
L128.00	Pre-exist hypertension compl preg childbirth and puerperium

L128000	Pre-exist hyperten heart dis compl preg childbth+puerperium
L128200	Pre-exist 2ndry hypertens comp preg childbth and puerperium
TJC7.00	Adverse reaction to other antihypertensives
TJC7z00	Adverse reaction to antihypertensives NOS
U60C500	[X]Oth antihyperten drug caus advers eff in therap use, NEC
U60C511	[X] Adverse reaction to other antihypertensives
U60C51A	[X] Adverse reaction to antihypertensives NOS

Heart Failure

Read code	Description
1736.00	Paroxysmal nocturnal dyspnoea
14A6.00	H/O: heart failure
14AM.00	H/O: Heart failure in last year
1J60.00	Suspected heart failure
1O1..00	Heart failure confirmed
23E1.00	O/E - pulmonary oedema
33BA.00	Impaired left ventricular function
388D.00	New York Heart Assoc classification heart failure symptoms
585f.00	Echocardiogram shows left ventricular systolic dysfunction
585g.00	Echocardiogram shows left ventricular diastolic dysfunction
585k.00	Echocardiogram shows normal left ventricular function
661M500	Heart failure self-management plan agreed
662f.00	New York Heart Association classification - class I
662g.00	New York Heart Association classification - class II
662h.00	New York Heart Association classification - class III
662i.00	New York Heart Association classification - class IV
662p.00	Heart failure 6 month review
662T.00	Congestive heart failure monitoring
662W.00	Heart failure annual review
679W100	Education about deteriorating heart failure
679X.00	Heart failure education
67D4.00	Heart failure information given to patient
8B29.00	Cardiac failure therapy
8CeC.00	Preferred place of care for next exacerbation heart failure
8CL3.00	Heart failure care plan discussed with patient
8CMK.00	Has heart failure management plan
8CMW800	Heart failure clinical pathway
8H2S.00	Admit heart failure emergency
8HBE.00	Heart failure follow-up
8Hg8.00	Discharge from practice nurse heart failure clinic
8HgD.00	Discharge from heart failure nurse service
8HHb.00	Referral to heart failure nurse
8HHz.00	Referral to heart failure exercise programme
8Hk0.00	Referred to heart failure education group
8HTL.00	Referral to heart failure clinic

8HTL000	Referral to rapid access heart failure clinic
8IE0.00	Referral to heart failure education group declined
8IE1.00	Referral to heart failure exercise programme declined
9h1..00	Exception reporting: LVD quality indicators
9h11.00	Excepted from LVD quality indicators: Patient unsuitable
9h12.00	Excepted from LVD quality indicators: Informed dissent
9hH..00	Exception reporting: heart failure quality indicators
9hH0.00	Excepted heart failure quality indicators: Patient unsuitabl
9hH1.00	Excepted heart failure quality indicators: Informed dissent
9N0k.00	Seen in heart failure clinic
9N2p.00	Seen by community heart failure nurse
9N4s.00	Did not attend practice nurse heart failure clinic
9N4w.00	Did not attend heart failure clinic
9N6T.00	Referred by heart failure nurse specialist
9On..00	Left ventricular dysfunction monitoring administration
9On0.00	Left ventricular dysfunction monitoring first letter
9On1.00	Left ventricular dysfunction monitoring second letter
9On2.00	Left ventricular dysfunction monitoring third letter
9On3.00	Left ventricular dysfunction monitoring verbal invite
9On4.00	Left ventricular dysfunction monitoring telephone invite
9Or..00	Heart failure monitoring administration
9Or0.00	Heart failure review completed
9Or1.00	Heart failure monitoring telephone invite
9Or2.00	Heart failure monitoring verbal invite
9Or3.00	Heart failure monitoring first letter
9Or4.00	Heart failure monitoring second letter
9Or5.00	Heart failure monitoring third letter
G1yz100	Rheumatic left ventricular failure
G210.00	Malignant hypertensive heart disease
G210100	Malignant hypertensive heart disease with CCF
G211100	Benign hypertensive heart disease with CCF
G21z100	Hypertensive heart disease NOS with CCF
G230.00	Malignant hypertensive heart and renal disease
G232.00	Hypertensive heart&renal dis wth (congestive) heart failure
G234.00	Hyperten heart&renal dis+both(congestv)heart and renal fail
G400.00	Acute cor pulmonale
G41z.11	Chronic cor pulmonale
G554000	Congestive cardiomyopathy
G554011	Congestive obstructive cardiomyopathy
G557100	Beriberi heart disease
G575.11	Cardio-respiratory arrest
G575100	Sudden cardiac death, so described
G58..00	Heart failure
G58..11	Cardiac failure
G580.00	Congestive heart failure

G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G580400	Congestive heart failure due to valvular disease
G581.00	Left ventricular failure
G581.11	Asthma - cardiac
G581.12	Pulmonary oedema - acute
G581.13	Impaired left ventricular function
G581000	Acute left ventricular failure
G582.00	Acute heart failure
G583.00	Heart failure with normal ejection fraction
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction
G584.00	Right ventricular failure
G58z.00	Heart failure NOS
G58z.11	Weak heart
G58z.12	Cardiac failure NOS
G5y4z00	Post cardiac operation heart failure NOS
G5yy900	Left ventricular systolic dysfunction
G5yyA00	Left ventricular diastolic dysfunction
G5yyB00	Right ventricular diastolic dysfunction
H54..00	Pulmonary congestion and hypostasis
H541.00	Pulmonary congestion
H541000	Chronic pulmonary oedema
H541z00	Pulmonary oedema NOS
H54z.00	Pulmonary congestion and hypostasis NOS
H584.00	Acute pulmonary oedema unspecified
H584z00	Acute pulmonary oedema NOS
R2y1000	[D]Cardiorespiratory failure
SP11100	Cardiac insufficiency as a complication of care
SP11111	Heart failure as a complication of care
ZRad.00	New York Heart Assoc classification heart failure symptoms

Peripheral Vascular Disease (PVD)

Read code	Description
14AE.00	H/O: aortic aneurysm
14NB.00	H/O: Peripheral vascular disease procedure
16I..00	Claudication distance
2G63.00	Ischaemic toe
38DJ.00	Edinburgh claudication questionnaire

662U.00	Peripheral vascular disease monitoring
7A10100	Bypass aorta by anastomosis axillary to femoral artery NEC
7A11.00	Replacement of aneurysmal bifurcation of aorta
7A11000	Emerg repl aneurysm bifurc aorta by anast aorta to fem art
7A11100	Replace aneurysm bifurc aorta by anast aorta to femoral art
7A11200	Emerg repl aneurysm bifurc aorta by anast aorta to iliac a
7A11211	Y graft of abdominal Aortic aneurysm (emergency)
7A11300	Replace aneurysm bifurc aorta by anast aorta to iliac artery
7A11311	Y graft abdominal Aortic aneurysm
7A11y00	Replacement of aneurysmal bifurcation of aorta OS
7A11z00	Replacement of aneurysmal bifurcation of aorta NOS
7A12000	Emerg bypass bifurc aorta by anast aorta to femoral artery
7A12100	Bypass bifurc aorta by anastom aorta to femoral artery NEC
7A12300	Bypass bifurcation aorta by anastom aorta to iliac artery
7A13100	Emerg replace aneurysm thor aorta by anastom aorta to aorta
7A13300	Emerg replace aneurysm infrarenal aorta by anast aorta/aorta
7A13400	Emerg replace aneurysm abdom aorta by anast aorta/aorta NEC
7A13411	Tube graft abdominal Aortic aneurysm (emergency)
7A14100	Replace aneurysm thoracic aorta by anast of aorta/aorta NEC
7A14400	Replace aneurysm abdominal aorta by anast aorta to aorta NEC
7A14411	Tube graft of Abdominal aortic aneurysm
7A1B000	Endovascular stenting infrarenal abdominal aortic aneurysm
7A1B200	Endovascular stenting of thoracic aortic aneurysm
7A22000	Percutaneous transluminal angioplasty of carotid artery
7A27C00	Operation on aneurysm of subclavian artery
7A27D00	Operation on aneurysm of axillary artery
7A27E00	Operation on aneurysm of brachial artery
7A28000	Percutaneous transluminal angioplasty of subclavian artery
7A28100	Percutaneous transluminal angioplasty of brachial artery
7A28200	Percutaneous transluminal angioplasty of vertebral artery
7A28C00	Percutaneous transluminal angioplasty of axillary artery
7A31300	Operation on aneurysm of renal artery
7A32000	Percutaneous transluminal angioplasty of renal artery
7A34D00	Operation on aneurysm of superior mesenteric artery NEC
7A34E00	Operation on aneurysm of inferior mesenteric artery NEC
7A34F00	Operation on aneurysm of suprarenal artery NEC
7A34K00	Operation on aneurysm visceral branch of abdominal aorta NEC
7A35000	Percutaneous transluminal angioplasty of coeliac artery NEC
7A35300	Percutaneous transluminal angioplasty suprarenal artery NEC
7A40.00	Replacement of aneurysmal iliac artery
7A40.11	Replacement of aneurysmal iliac artery by anastomosis
7A40000	Emerg replace aneurysm iliac art by iliac/femoral art anast
7A40200	Emerg replace aneurysmal iliac artery by fem/fem art anast
7A40A00	Replace aneurysm iliac art by aorta/ext iliac art anast NEC
7A40y00	Other specified replacement of aneurysmal iliac artery

7A40z00	Replacement of aneurysmal iliac artery NOS
7A41.00	Other bypass of iliac artery
7A41.11	Other bypass of iliac artery by anastomosis
7A41100	Bypass iliac artery by iliac/femoral artery anastomosis NEC
7A41200	Emerg bypass iliac artery by femoral/femoral art anast NEC
7A41300	Bypass iliac artery by femoral/femoral art anastomosis NEC
7A41900	Bypass common iliac artery by aorta/com iliac art anast NEC
7A41D00	Bypass iliac artery by iliac/iliac artery anastomosis NEC
7A41y00	Other specified other bypass of iliac artery
7A41z00	Other bypass of iliac artery NOS
7A43200	Operation on aneurysm of iliac artery NEC
7A44000	Percutaneous transluminal angioplasty of iliac artery
7A45.00	Emergency replacement of aneurysmal femoral/popliteal artery
7A45.12	Emergency replacement of aneurysmal common femoral artery
7A45.14	Emergency replacement of aneurysmal popliteal artery
7A45.15	Emergency replacement aneurysmal superficial femoral artery
7A45000	Emerg replace aneurysm fem art by fem/pop art anast c prosth
7A45200	Emerg replace aneurysm fem art by fem/pop anast c vein graft
7A45700	Emerg replace aneurysm pop art by pop/tib anast c vein graft
7A45C00	Emerg replace aneurysm fem artery by fem/fem art anastomosis
7A45D00	Emerg replace aneurysm pop artery by pop/fem art anastomosis
7A45y00	Emergency replacement aneurysmal femoral/popliteal artery OS
7A46.00	Other replacement of aneurysmal femoral artery
7A46.11	Other replacement aneurysmal femoral artery by anastomosis
7A46.12	Other replacement of aneurysmal common femoral artery
7A46.14	Other replacement of aneurysmal popliteal artery
7A46.15	Other replacement of aneurysmal superficial femoral artery
7A46000	Replace aneurysm fem art by fem/pop art anastom c prosth NEC
7A46100	Replace aneurysm pop art by pop/pop art anastom c prosth NEC
7A46300	Replace aneurysm pop art by pop/pop a anast c vein graft NEC
7A46C00	Replace aneurysm fem artery by fem/fem art anastomosis NEC
7A46D00	Replace aneurysm popliteal artery by pop/fem anastomosis NEC
7A46y00	Other replacement of aneurysmal femoral/popliteal artery OS
7A46z00	Other replacement of aneurysmal femoral/popliteal artery NOS
7A47.00	Other emergency bypass of femoral artery or popliteal artery
7A47.12	Other emergency bypass of common femoral artery
7A47.13	Other emergency bypass of deep femoral artery
7A47.15	Other emergency bypass of superficial femoral artery
7A47.16	Other emergency bypass of femoral artery
7A47C00	Emerg bypass femoral artery by fem/fem art anastomosis NEC
7A48.00	Other bypass of femoral artery or popliteal artery
7A48.12	Other bypass of common femoral artery
7A48.14	Other bypass of femoral artery
7A48.16	Other bypass of superficial femoral artery
7A48000	Bypass femoral artery by fem/pop art anast c prosthesis NEC

7A48200	Bypass femoral artery by fem/pop art anast c vein graft NEC
7A48400	Bypass femoral artery by fem/tib art anast c prosthesis NEC
7A48600	Bypass femoral artery by fem/tib art anast c vein graft NEC
7A48800	Bypass femoral artery by fem/peron a anast c prosthesis NEC
7A48A00	Bypass femoral artery by fem/peron a anast c vein graft NEC
7A48C00	Bypass femoral artery by femoral/femoral art anastomosis NEC
7A48y00	Other bypass of femoral artery or popliteal artery OS
7A48z00	Other bypass of femoral artery or popliteal artery NOS
7A4A400	Ligation of aneurysm of popliteal artery
7A4A500	Operation on aneurysm of femoral artery NEC
7A4B000	Percutaneous transluminal angioplasty of femoral artery
7A4B100	Percutaneous transluminal angioplasty of popliteal artery
9N4h.00	DNA - Did not attend peripheral vascular disease clinic
A3A0F00	Gas gangrene-foot
G5y2.00	Cardiovascular arteriosclerosis unspecified
G673200	Carotid artery dissection
G70..00	Atherosclerosis
G70..11	Arteriosclerosis
G700.00	Aortic atherosclerosis
G700.11	Aorto-iliac disease
G701.00	Renal artery atherosclerosis
G702.00	Extremity artery atheroma
G702z00	Extremity artery atheroma NOS
G703.00	Acquired renal artery stenosis
G70y.00	Other specified artery atheroma
G70y000	Carotid artery atherosclerosis
G70z.00	Arteriosclerotic vascular disease NOS
G71..00	Aortic aneurysm
G710.00	Dissecting aortic aneurysm
G712.00	Thoracic aortic aneurysm without mention of rupture
G714.00	Abdominal aortic aneurysm without mention of rupture
G714.11	AAA - Abdominal aortic aneurysm without mention of rupture
G714000	Juxtarenal aortic aneurysm
G716.00	Aortic aneurysm without mention of rupture NOS
G716000	Thoracoabdominal aortic aneurysm, without mention of rupture
G718.00	Leaking abdominal aortic aneurysm
G71z.00	Aortic aneurysm NOS
G720.00	Aneurysm of artery of arm
G720000	Aneurysm of brachial artery
G720100	Aneurysm of radial artery
G720200	Aneurysm of ulnar artery
G720z00	Aneurysm of arm artery NOS
G721.00	Aneurysm of renal artery
G722.00	Aneurysm of iliac artery
G722000	Aneurysm of common iliac artery

G722100	Aneurysm of external iliac artery
G722200	Aneurysm of internal iliac artery
G722z00	Aneurysm of iliac artery NOS
G723.00	Aneurysm of leg artery
G723000	Aneurysm of femoral artery
G723100	Aneurysm of popliteal artery
G723200	Aneurysm of anterior tibial artery
G723300	Aneurysm of dorsalis pedis artery
G723400	Aneurysm of posterior tibial artery
G723500	Ruptured popliteal artery aneurysm
G723600	Post radiological femoral false aneurysm
G723z00	Aneurysm of leg artery NOS
G72y.00	Aneurysm of other artery
G72y000	Aneurysm of common carotid art
G72y100	Aneurysm of external carotid artery
G72y200	Aneurysm of internal carotid artery
G72y400	Aneurysm of subclavian artery
G72y500	Aneurysm of splenic artery
G72y600	Aneurysm of axillary artery
G72y700	Aneurysm of coeliac artery
G72y800	Aneurysm of superior mesenteric artery
G72y900	Aneurysm of inferior mesenteric artery
G72yA00	Aneurysm of hepatic artery
G72yB00	Aneurysm of other visceral artery
G73..00	Other peripheral vascular disease
G73..11	Peripheral ischaemic vascular disease
G73..12	Ischaemia of legs
G73..13	Peripheral ischaemia
G730.00	Raynaud's syndrome
G730000	Raynaud's disease
G730100	Raynaud's phenomenon
G730z00	Raynaud's syndrome NOS
G731.00	Thromboangiitis obliterans
G731000	Buerger's disease
G731z00	Thromboangiitis obliterans NOS
G732.00	Peripheral gangrene
G732000	Gangrene of toe
G732100	Gangrene of foot
G733.00	Ischaemic foot
G73y.00	Other specified peripheral vascular disease
G73y100	Peripheral angiopathic disease EC NOS
G73y200	Acrocyanosis
G73y400	Acroparaesthesia - Schultze's type
G73y500	Acroparaesthesia - Nothnagel's type
G73y511	Nothnagel's vasomotor acroparaesthesia

G73y600	Acroparaesthesia - unspecified
G73y700	Erythrocyanosis
G73y800	Erythromelalgia
G73yz00	Other specified peripheral vascular disease NOS
G73z.00	Peripheral vascular disease NOS
G73z000	Intermittent claudication
G73z011	Claudication
G73zz00	Peripheral vascular disease NOS
G740.12	Aortoiliac obstruction
G742400	Embolism and thrombosis of the femoral artery
G742500	Embolism and thrombosis of the popliteal artery
G742600	Embolism and thrombosis of the anterior tibial artery
G742700	Embolism and thrombosis of the dorsalis pedis artery
G742900	Embolism and thrombosis of a leg artery NOS
G742z00	Peripheral arterial embolism and thrombosis NOS
G74y000	Embolism and/or thrombosis of the common iliac artery
G74y100	Embolism and/or thrombosis of the internal iliac artery
G74y200	Embolism and/or thrombosis of the external iliac artery
G74y300	Embolism and thrombosis of the iliac artery unspecified
G76z100	Femoral artery occlusion
G76z200	Popliteal artery occlusion
Gyu7300	[X]Aneurysm of other specified arteries
Gyu7400	[X]Other specified peripheral vascular diseases
M271.12	Ischaemic leg ulcer
M271300	Arterial leg ulcer
M271400	Mixed venous and arterial leg ulcer
P769000	Renal artery stenosis
R055000	[D]Failure of peripheral circulation
R055011	[D]Peripheral circulatory failure

Gastroduodenal Ulcer

Read code	Description
1956.00	Peptic ulcer symptoms
7627.00	Operations on duodenal ulcer
7612111	Balfour excision of gastric ulcer
7612500	Resection of gastric ulcer by cautery
7627000	Closure of perforated duodenal ulcer
7627100	Suture of duodenal ulcer not elsewhere classified
7627200	Oversew of blood vessel of duodenal ulcer
14C1.00	H/O: peptic ulcer
14C1.11	H/O: duodenal ulcer
14C1.12	H/O: gastric ulcer
761D500	Endoscopic injection haemostasis of duodenal ulcer
761D600	Endoscopic injection haemostasis of gastric ulcer
761J.00	Operations on gastric ulcer

761J.11	Stomach ulcer operations
761J000	Closure of perforated gastric ulcer
761J100	Closure of gastric ulcer NEC
761J111	Suture of ulcer of stomach NEC
761Jy00	Other specified operation on gastric ulcer
761Jz00	Operation on gastric ulcer NOS
7627y00	Other specified operation on duodenal ulcer
7627z00	Operation on duodenal ulcer NOS
J102000	Peptic ulcer of oesophagus
J11..00	Gastric ulcer - (GU)
J11..11	Prepyloric ulcer
J11..12	Pyloric ulcer
J110.00	Acute gastric ulcer
J110000	Acute gastric ulcer without mention of complication
J110100	Acute gastric ulcer with haemorrhage
J110111	Bleeding acute gastric ulcer
J110200	Acute gastric ulcer with perforation
J110300	Acute gastric ulcer with haemorrhage and perforation
J110400	Acute gastric ulcer with obstruction
J110y00	Acute gastric ulcer unspecified
J110z00	Acute gastric ulcer NOS
J111.00	Chronic gastric ulcer
J111000	Chronic gastric ulcer without mention of complication
J111100	Chronic gastric ulcer with haemorrhage
J111111	Bleeding chronic gastric ulcer
J111200	Chronic gastric ulcer with perforation
J111211	Perforated chronic gastric ulcer
J111300	Chronic gastric ulcer with haemorrhage and perforation
J111400	Chronic gastric ulcer with obstruction
J111y00	Chronic gastric ulcer unspecified
J111z00	Chronic gastric ulcer NOS
J112.00	Anti-platelet induced gastric ulcer
J112z00	Anti-platelet induced gastric ulcer NOS
J113.00	Non steroidal anti inflammatory drug induced gastric ulcer
J113z00	Non steroidal anti inflammatory drug induced gastric ulc NOS
J11y.00	Unspecified gastric ulcer
J11y000	Unspecified gastric ulcer without mention of complication
J11y100	Unspecified gastric ulcer with haemorrhage
J11y200	Unspecified gastric ulcer with perforation
J11y400	Unspecified gastric ulcer with obstruction
J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
J11yz00	Unspecified gastric ulcer NOS
J11z.00	Gastric ulcer NOS
J11z.11	Gastric erosions
J11z.12	Multiple gastric ulcers

J12..00	Duodenal ulcer - (DU)
J120.00	Acute duodenal ulcer
J120000	Acute duodenal ulcer without mention of complication
J120100	Acute duodenal ulcer with haemorrhage
J120200	Acute duodenal ulcer with perforation
J120300	Acute duodenal ulcer with haemorrhage and perforation
J120400	Acute duodenal ulcer with obstruction
J120y00	Acute duodenal ulcer unspecified
J120z00	Acute duodenal ulcer NOS
J121.00	Chronic duodenal ulcer
J121000	Chronic duodenal ulcer without mention of complication
J121100	Chronic duodenal ulcer with haemorrhage
J121111	Bleeding chronic duodenal ulcer
J121200	Chronic duodenal ulcer with perforation
J121211	Perforated chronic duodenal ulcer
J121300	Chronic duodenal ulcer with haemorrhage and perforation
J121400	Chronic duodenal ulcer with obstruction
J121y00	Chronic duodenal ulcer unspecified
J121z00	Chronic duodenal ulcer NOS
J122.00	Duodenal ulcer disease
J123.00	Duodenal erosion
J124.00	Recurrent duodenal ulcer
J125.00	Anti-platelet induced duodenal ulcer
J126.00	Non steroidal anti inflammatory drug induced duodenal ulcer
J12y.00	Unspecified duodenal ulcer
J12y000	Unspecified duodenal ulcer without mention of complication
J12y100	Unspecified duodenal ulcer with haemorrhage
J12y200	Unspecified duodenal ulcer with perforation
J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
J12y400	Unspecified duodenal ulcer with obstruction
J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
J12yz00	Unspecified duodenal ulcer NOS
J12z.00	Duodenal ulcer NOS
J13..00	Peptic ulcer - (PU) site unspecified
J13..11	Stress ulcer NOS
J130.00	Acute peptic ulcer
J130000	Acute peptic ulcer without mention of complication
J130100	Acute peptic ulcer with haemorrhage
J130200	Acute peptic ulcer with perforation
J130300	Acute peptic ulcer with haemorrhage and perforation
J130y00	Acute peptic ulcer unspecified
J130z00	Acute peptic ulcer NOS
J131.00	Chronic peptic ulcer
J131000	Chronic peptic ulcer without mention of complication
J131100	Chronic peptic ulcer with haemorrhage

J131200	Chronic peptic ulcer with perforation
J131400	Chronic peptic ulcer with obstruction
J131y00	Chronic peptic ulcer unspecified
J131z00	Chronic peptic ulcer NOS
J13y.00	Unspecified peptic ulcer
J13y000	Unspecified peptic ulcer without mention of complication
J13y100	Unspecified peptic ulcer with haemorrhage
J13y200	Unspecified peptic ulcer with perforation
J13y300	Unspecified peptic ulcer with haemorrhage and perforation
J13y400	Unspecified peptic ulcer with obstruction
J13yz00	Unspecified peptic ulcer NOS
J13z.00	Peptic ulcer NOS
J14..00	Gastrojejunal ulcer (GJU)
J14..11	Anastomotic ulcer
J14..12	Gastrocolic ulcer
J14..13	Jejunal ulcer
J14..14	Marginal ulcer
J14..15	Stomal ulcer
J140.00	Acute gastrojejunal ulcer
J140100	Acute gastrojejunal ulcer with haemorrhage
J140200	Acute gastrojejunal ulcer with perforation
J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
J140z00	Acute gastrojejunal ulcer NOS
J141.00	Chronic gastrojejunal ulcer
J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation
J14y.00	Unspecified gastrojejunal ulcer
J14y100	Unspecified gastrojejunal ulcer with haemorrhage
J14y200	Unspecified gastrojejunal ulcer with perforation
J14yz00	Unspecified gastrojejunal ulcer NOS
J14z.00	Gastrojejunal ulcer NOS
J173300	Duodenal scar
J17y700	Deformed duodenal cap (bulb)
J17y800	Healed gastric ulcer leaving a scar
ZV12700	[V]Personal history of digestive system disease
ZV12711	[V]Personal history of peptic ulcer
ZV12712	[V]Personal history of duodenal ulcer
ZV12C00	[V] Personal history of gastric ulcer

Chronic Obstructive Pulmonary Disease (COPD)

Read code	Description
14B3.11	H/O: bronchitis
14OJ.00	At risk of chronic obstructive pulmonary disease
1J71.00	Suspected chronic obstructive pulmonary disease
66YB.00	Chronic obstructive pulmonary disease monitoring
66YD.00	Chronic obstructive pulmonary disease monitoring due

66Ye.00	Emergency COPD admission since last appointment
66Yf.00	Number of COPD exacerbations in past year
66Yg.00	Chronic obstructive pulmonary disease disturbs sleep
66Yh.00	Chronic obstructive pulmonary disease does not disturb sleep
66YL.00	Chronic obstructive pulmonary disease follow-up
66YL.11	COPD follow-up
66YL.12	COAD follow-up
66YM.00	Chronic obstructive pulmonary disease annual review
66YS.00	Chronic obstructive pulmonary disease monitoring by nurse
66YT.00	Chronic obstructive pulmonary disease monitoring by doctor
679V.00	Health education - chronic obstructive pulmonary disease
8CE6.00	Chronic obstructive pulmonary disease leaflet given
8CR1.00	Chronic obstructive pulmonary disease clini management plan
8H2R.00	Admit COPD emergency
9Oi..00	Chronic obstructive pulmonary disease monitoring admin
9Oi0.00	Chronic obstructive pulmonary disease monitoring 1st letter
9Oi1.00	Chronic obstructive pulmonary disease monitoring 2nd letter
9Oi2.00	Chronic obstructive pulmonary disease monitoring 3rd letter
9Oi3.00	Chronic obstructive pulmonary disease monitoring verb invite
9Oi4.00	Chronic obstructive pulmonary disease monitor phone invite
H06..00	Acute bronchitis and bronchiolitis
H060.00	Acute bronchitis
H060.11	Acute wheezy bronchitis
H060000	Acute fibrinous bronchitis
H060200	Acute pseudomembranous bronchitis
H060300	Acute purulent bronchitis
H060400	Acute croupous bronchitis
H060500	Acute tracheobronchitis
H060600	Acute pneumococcal bronchitis
H060700	Acute streptococcal bronchitis
H060800	Acute haemophilus influenzae bronchitis
H060900	Acute neisseria catarrhalis bronchitis
H060A00	Acute bronchitis due to mycoplasma pneumoniae
H060B00	Acute bronchitis due to coxsackievirus
H060C00	Acute bronchitis due to parainfluenza virus
H060D00	Acute bronchitis due to respiratory syncytial virus
H060E00	Acute bronchitis due to rhinovirus
H060F00	Acute bronchitis due to echovirus
H060v00	Subacute bronchitis unspecified
H060w00	Acute viral bronchitis unspecified
H060x00	Acute bacterial bronchitis unspecified
H060z00	Acute bronchitis NOS
H06z.00	Acute bronchitis or bronchiolitis NOS
H06z000	Chest infection NOS
H06z011	Chest infection

H06z200	Recurrent chest infection
H20..11	Chest infection - viral pneumonia
H21..11	Chest infection - pneumococcal pneumonia
H22..11	Chest infection - other bacterial pneumonia
H23..11	Chest infection - pneumonia organism OS
H24..11	Chest infection with infectious disease EC
H25..11	Chest infection - unspecified bronchopneumonia
H26..11	Chest infection - pnemonia due to unspecified organism
H270.11	Chest infection - influenza with pneumonia
H3...00	Chronic obstructive pulmonary disease
H3...11	Chronic obstructive airways disease
H30..00	Bronchitis unspecified
H30..11	Chest infection - unspecified bronchitis
H30..12	Recurrent wheezy bronchitis
H300.00	Tracheobronchitis NOS
H301.00	Laryngotracheobronchitis
H302.00	Wheezy bronchitis
H30z.00	Bronchitis NOS
H31..00	Chronic bronchitis
H310.00	Simple chronic bronchitis
H310000	Chronic catarrhal bronchitis
H310100	Smokers' cough
H310z00	Simple chronic bronchitis NOS
H311.00	Mucopurulent chronic bronchitis
H311000	Purulent chronic bronchitis
H311100	Fetid chronic bronchitis
H311z00	Mucopurulent chronic bronchitis NOS
H312.00	Obstructive chronic bronchitis
H312000	Chronic asthmatic bronchitis
H312011	Chronic wheezy bronchitis
H312100	Emphysematous bronchitis
H312200	Acute exacerbation of chronic obstructive airways disease
H312300	Bronchiolitis obliterans
H312z00	Obstructive chronic bronchitis NOS
H313.00	Mixed simple and mucopurulent chronic bronchitis
H31y.00	Other chronic bronchitis
H31y000	Chronic tracheitis
H31y100	Chronic tracheobronchitis
H31yz00	Other chronic bronchitis NOS
H31z.00	Chronic bronchitis NOS
H32..00	Emphysema
H320.00	Chronic bullous emphysema
H320000	Segmental bullous emphysema
H320100	Zonal bullous emphysema
H320200	Giant bullous emphysema

H320300	Bullous emphysema with collapse
H320311	Tension pneumatocoele
H320z00	Chronic bullous emphysema NOS
H321.00	Panlobular emphysema
H322.00	Centrilobular emphysema
H32y.00	Other emphysema
H32y000	Acute vesicular emphysema
H32y100	Atrophic (senile) emphysema
H32y111	Acute interstitial emphysema
H32y200	MacLeod's unilateral emphysema
H32yz00	Other emphysema NOS
H32z.00	Emphysema NOS
H36..00	Mild chronic obstructive pulmonary disease
H37..00	Moderate chronic obstructive pulmonary disease
H38..00	Severe chronic obstructive pulmonary disease
H39..00	Very severe chronic obstructive pulmonary disease
H3A..00	End stage chronic obstructive airways disease
H3y..00	Other specified chronic obstructive airways disease
H3y..11	Other specified chronic obstructive pulmonary disease
H3y0.00	Chronic obstruct pulmonary dis with acute lower resp infectn
H3y1.00	Chron obstruct pulmonary dis wth acute exacerbation, unspec
H3z..00	Chronic obstructive airways disease NOS
H3z..11	Chronic obstructive pulmonary disease NOS
H581.00	Interstitial emphysema
H582.00	Compensatory emphysema
Hyu1000	[X]Acute bronchitis due to other specified organisms
Hyu3000	[X]Other emphysema
Hyu3100	[X]Other specified chronic obstructive pulmonary disease

Atrial Fibrillation

Read code	Description
3272.00	ECG: atrial fibrillation
3273.00	ECG: atrial flutter
14AN.00	H/O: atrial fibrillation
14AR.00	History of atrial flutter
212R.00	Atrial fibrillation resolved
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
7936A	Implantation of intravenous pacemaker for atrial fibrillation
9hF..00	Exception reporting: atrial fibrillation quality indicators
9hF0.00	Excepted from atrial fibrillation quality indicators: Patient unsuitable
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Atrial fibrillation monitoring second letter

9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
G573.00	Atrial fibrillation and flutter
G573000	Atrial fibrillation
G573100	Atrial flutter
G573200	Paroxysmal atrial fibrillation
G573300	Non-rheumatic atrial fibrillation
G573400	Permanent atrial fibrillation
G573500	Persistent atrial fibrillation
G573600	Paroxysmal atrial flutter
G573z00	Atrial fibrillation and flutter NOS

Cancer

Read code	Description
1429.00	H/O: * leukaemia
5135.00	Radiological tumour control
5136.00	X-ray metastasis control
5149.00	Radiotherapy-tumour palliation
1427000	H/O: prostate cancer
7008500	Insertion of carmustine wafers in cerebral neoplasm
7932400	Resection of heart tumour
142..00	H/O: malignant neoplasm (*)
142..11	H/O: cancer
142..12	H/O: carcinoma
142..13	H/O: malignancy
142..15	H/O: neoplasm
1D18.00	Pain from metastases
1I20.00	No evidence of recurrence of cancer
1O0..00	Cancer confirmed
4C53.00	Bone marrow: myeloma cells
4C54.00	Bone marrow: tumour cells
4K2M.00	Crv smr - hi grade dyskaryosis? invasive squamous carcinoma
4KJ0.00	Oestrogen receptor positive tumour
4KJ1.00	Progesterone receptor positive tumour
4KJ2.00	Oestrogen receptor negative tumour
4KJ3.00	Progesterone receptor negative tumour
4M...00	Tumour staging
4M0..00	Gleason grading of prostate cancer
4M00.00	Gleason prostate grade 2-4 (low)
4M01.00	Gleason prostate grade 5-7 (medium)
4M02.00	Gleason prostate grade 8-10 (high)
4M2..00	Lymphoma staging system
4M20.00	Lymphoma stage I
4M21.00	Lymphoma stage II

4M22.00	Lymphoma stage III
4M23.00	Lymphoma stage IV
4M5..00	TNM tumour staging
4M6..00	Recurrence of tumour
4M72.00	Clark melanoma level 3
5A12.00	Thyroid tumour/metast irradiat
5A15.00	Bone tumour/metast.irradiat.
677H.00	Cancer information offered
677K.00	Cancer home care pack given
67D2.00	Cancer information offered to patient
67G2.00	Cancer information offered to significant other
68W2.00	Bowel cancer screening programme
7B27.13	TURBT - transurethral resection of bladder tumour
7B27900	Endoscopic destruction of bladder tumour by laser
7G03J00	Excision of melanoma
7G03K00	Excision malignant skin tumour
7G05D00	Excision biopsy of basal cell carcinoma
7K13500	Curettage of tumour of bone and graft HFQ
7K13600	Curettage of tumour of bone NEC
7K13700	Excision of tumour of bone NEC
7K13900	Excision of tumour of bone
7L1b.00	Procurement drugs for chemotherapy for neoplasm in bands 1-5
7L1d.00	Delivery of chemotherapy for neoplasm
7L1dy00	Other specified delivery of chemotherapy for neoplasm
7L1dz00	Delivery of chemotherapy for neoplasm NOS
7L1e.00	Delivery of oral chemotherapy for neoplasm
7L1ez00	Delivery of oral chemotherapy for neoplasm NOS
7L1K300	Debulking of tumour of unspecified organ
8A9..00	Tumour marker monitoring
8B3p.00	Administration of cancer treatment
8BAD000	Cancer chemotherapy
8BAV.00	Cancer care review
8BC3.00	Cancer care plan given
8BC6.00	Cancer treatment started
8BCF.00	Cancer hospital treatment completed
8CEB.00	Cancer screening leaflet given
8CL0.00	Cancer diagnosis discussed
8CL1.00	Cancer diagnosis discussed with significant other
8CL2.00	Cancer diagnosis discussed with patient
8CM0.00	Cancer care plan
8CP0.00	Cancer care plan discussed with patient
8CP1.00	Cancer care plan discussed with significant other
8CR8.00	Cancer shared care medication card
8HH8.00	Referred to cancer primary healthcare multidisciplinary team
8HHt.00	Fast track cancer referral

8Hn..00	Priority cancer referral
8O83.00	Cancer emotional and psychosocial support and advice
9e00.00	GP out of hours service notified of cancer care plan
9h8..00	Exception reporting: cancer quality indicators
9h81.00	Excepted from cancer quality indicators: Patient unsuitable
9h82.00	Excepted from cancer quality indicators: Informed dissent
9N4S.00	DNA - Did not attend cancer clinic
9Nh1.00	Under care cancer primary healthcare multidisciplinary team
9NX0.00	Cancer primary healthcare multidisciplinary team
9NX1.00	Cancer supportive care worker
9Ok..00	Cancer monitoring administration
9Ok0.00	Cancer monitoring first letter
9Ok1.00	Cancer monitoring second letter
9Ok2.00	Cancer monitoring third letter
9Ok3.00	Date cancer diagnosis received in primary care
9Ok5.00	Cancer pain and symptom management
9Ok6.00	Cancer short term health assessment
9Ok7.00	Cancer rehabilitation and readaption
9Ok9.00	Cancer screening follow up
9OkA.00	Cancer monitoring verbal invitation
9OkB.00	Cancer monitoring telephone invitation
9OkC.00	Patient on regional cancer register
A788600	Human immunodeficiency virus with secondary cancers
A788W00	HIV disease resulting in unspecified malignant neoplasm
A789500	HIV disease resulting in Kaposi's sarcoma
A789600	HIV disease resulting in Burkitt's lymphoma
A789700	HIV dis resulting oth types of non-Hodgkin's lymphoma
AyuC600	[X]HIV disease resulting in other non-Hodgkin's lymphoma
B....00	Neoplasms
B....11	Cancers
B0...00	Malignant neoplasm of lip, oral cavity and pharynx
B0...11	Carcinoma of lip, oral cavity and pharynx
B00..00	Malignant neoplasm of lip
B00..11	Carcinoma of lip
B000.00	Malignant neoplasm of upper lip, vermilion border
B000000	Malignant neoplasm of upper lip, external
B000100	Malignant neoplasm of upper lip, lipstick area
B000z00	Malignant neoplasm of upper lip, vermilion border NOS
B001.00	Malignant neoplasm of lower lip, vermilion border
B001000	Malignant neoplasm of lower lip, external
B001100	Malignant neoplasm of lower lip, lipstick area
B001z00	Malignant neoplasm of lower lip, vermilion border NOS
B002.00	Malignant neoplasm of upper lip, inner aspect
B002100	Malignant neoplasm of upper lip, frenulum
B002200	Malignant neoplasm of upper lip, mucosa

B002300	Malignant neoplasm of upper lip, oral aspect
B002z00	Malignant neoplasm of upper lip, inner aspect NOS
B003.00	Malignant neoplasm of lower lip, inner aspect
B003000	Malignant neoplasm of lower lip, buccal aspect
B003100	Malignant neoplasm of lower lip, frenulum
B003200	Malignant neoplasm of lower lip, mucosa
B003300	Malignant neoplasm of lower lip, oral aspect
B003z00	Malignant neoplasm of lower lip, inner aspect NOS
B004.00	Malignant neoplasm of lip unspecified, inner aspect
B004000	Malignant neoplasm of lip unspecified, buccal aspect
B004200	Malignant neoplasm of lip unspecified, mucosa
B004300	Malignant neoplasm of lip, oral aspect
B005.00	Malignant neoplasm of commissure of lip
B006.00	Malignant neoplasm of overlapping lesion of lip
B007.00	Malignant neoplasm of lip, unspecified
B00z000	Malignant neoplasm of lip, unspecified, external
B00z100	Malignant neoplasm of lip, unspecified, lipstick area
B00zz00	Malignant neoplasm of lip, vermilion border NOS
B01..00	Malignant neoplasm of tongue
B010.00	Malignant neoplasm of base of tongue
B010.11	Malignant neoplasm of posterior third of tongue
B010000	Malignant neoplasm of base of tongue dorsal surface
B010z00	Malignant neoplasm of fixed part of tongue NOS
B011.00	Malignant neoplasm of dorsal surface of tongue
B011100	Malignant neoplasm of midline of tongue
B011z00	Malignant neoplasm of dorsum of tongue NOS
B012.00	Malignant neoplasm of tongue, tip and lateral border
B013.00	Malignant neoplasm of ventral surface of tongue
B013000	Malignant neoplasm of anterior 2/3 of tongue ventral surface
B013100	Malignant neoplasm of frenulum linguae
B013z00	Malignant neoplasm of ventral tongue surface NOS
B014.00	Malignant neoplasm of anterior 2/3 of tongue unspecified
B015.00	Malignant neoplasm of tongue, junctional zone
B016.00	Malignant neoplasm of lingual tonsil
B017.00	Malignant overlapping lesion of tongue
B01y.00	Malignant neoplasm of other sites of tongue
B01z.00	Malignant neoplasm of tongue NOS
B02..00	Malignant neoplasm of major salivary glands
B020.00	Malignant neoplasm of parotid gland
B021.00	Malignant neoplasm of submandibular gland
B022.00	Malignant neoplasm of sublingual gland
B02y.00	Malignant neoplasm of other major salivary glands
B02z.00	Malignant neoplasm of major salivary gland NOS
B03..00	Malignant neoplasm of gum
B030.00	Malignant neoplasm of upper gum

B031.00	Malignant neoplasm of lower gum
B03y.00	Malignant neoplasm of other sites of gum
B03z.00	Malignant neoplasm of gum NOS
B04..00	Malignant neoplasm of floor of mouth
B040.00	Malignant neoplasm of anterior portion of floor of mouth
B041.00	Malignant neoplasm of lateral portion of floor of mouth
B042.00	Malignant neoplasm, overlapping lesion of floor of mouth
B04y.00	Malignant neoplasm of other sites of floor of mouth
B04z.00	Malignant neoplasm of floor of mouth NOS
B05..00	Malignant neoplasm of other and unspecified parts of mouth
B050.00	Malignant neoplasm of cheek mucosa
B050.11	Malignant neoplasm of buccal mucosa
B051.00	Malignant neoplasm of vestibule of mouth
B051000	Malignant neoplasm of upper buccal sulcus
B051100	Malignant neoplasm of lower buccal sulcus
B052.00	Malignant neoplasm of hard palate
B053.00	Malignant neoplasm of soft palate
B054.00	Malignant neoplasm of uvula
B055.00	Malignant neoplasm of palate unspecified
B055000	Malignant neoplasm of junction of hard and soft palate
B055100	Malignant neoplasm of roof of mouth
B055z00	Malignant neoplasm of palate NOS
B056.00	Malignant neoplasm of retromolar area
B05y.00	Malignant neoplasm of other specified mouth parts
B05z.00	Malignant neoplasm of mouth NOS
B05z000	Kaposi's sarcoma of palate
B06..00	Malignant neoplasm of oropharynx
B060.00	Malignant neoplasm of tonsil
B060000	Malignant neoplasm of faucial tonsil
B060100	Malignant neoplasm of palatine tonsil
B060200	Malignant neoplasm of overlapping lesion of tonsil
B060z00	Malignant neoplasm tonsil NOS
B061.00	Malignant neoplasm of tonsillar fossa
B062.00	Malignant neoplasm of tonsillar pillar
B062000	Malignant neoplasm of faucial pillar
B062100	Malignant neoplasm of glossopalatine fold
B062200	Malignant neoplasm of palatoglossal arch
B062300	Malignant neoplasm of palatopharyngeal arch
B062z00	Malignant neoplasm of tonsillar fossa NOS
B063.00	Malignant neoplasm of vallecula
B064.00	Malignant neoplasm of anterior epiglottis
B064000	Malignant neoplasm of epiglottis, free border
B064100	Malignant neoplasm of glossoepiglottic fold
B064z00	Malignant neoplasm of anterior epiglottis NOS
B065.00	Malignant neoplasm of junctional region of epiglottis

B066.00	Malignant neoplasm of lateral wall of oropharynx
B067.00	Malignant neoplasm of posterior wall of oropharynx
B06y.00	Malignant neoplasm of oropharynx, other specified sites
B06yz00	Malignant neoplasm of other specified site of oropharynx NOS
B06z.00	Malignant neoplasm of oropharynx NOS
B07..00	Malignant neoplasm of nasopharynx
B070.00	Malignant neoplasm of roof of nasopharynx
B071.00	Malignant neoplasm of posterior wall of nasopharynx
B071000	Malignant neoplasm of adenoid
B071100	Malignant neoplasm of pharyngeal tonsil
B071z00	Malignant neoplasm of posterior wall of nasopharynx NOS
B072.00	Malignant neoplasm of lateral wall of nasopharynx
B072000	Malignant neoplasm of pharyngeal recess
B072z00	Malignant neoplasm of lateral wall of nasopharynx NOS
B073.00	Malignant neoplasm of anterior wall of nasopharynx
B073100	Malignant neoplasm of nasopharyngeal soft palate surface
B073200	Malignant neoplasm posterior margin nasal septum and choanae
B073z00	Malignant neoplasm of anterior wall of nasopharynx NOS
B074.00	Malignant neoplasm, overlapping lesion of nasopharynx
B07y.00	Malignant neoplasm of other specified site of nasopharynx
B07z.00	Malignant neoplasm of nasopharynx NOS
B08..00	Malignant neoplasm of hypopharynx
B080.00	Malignant neoplasm of postcricoid region
B081.00	Malignant neoplasm of pyriform sinus
B082.00	Malignant neoplasm aryepiglottic fold, hypopharyngeal aspect
B083.00	Malignant neoplasm of posterior pharynx
B08y.00	Malignant neoplasm of other specified hypopharyngeal site
B08z.00	Malignant neoplasm of hypopharynx NOS
B0z..00	Malig neop other/ill-defined sites lip, oral cavity, pharynx
B0z0.00	Malignant neoplasm of pharynx unspecified
B0z1.00	Malignant neoplasm of Waldeyer's ring
B0z2.00	Malignant neoplasm of laryngopharynx
B0zy.00	Malignant neoplasm of other sites lip, oral cavity, pharynx
B0zz.00	Malignant neoplasm of lip, oral cavity and pharynx NOS
B1...00	Malignant neoplasm of digestive organs and peritoneum
B1...11	Carcinoma of digestive organs and peritoneum
B10..00	Malignant neoplasm of oesophagus
B100.00	Malignant neoplasm of cervical oesophagus
B101.00	Malignant neoplasm of thoracic oesophagus
B102.00	Malignant neoplasm of abdominal oesophagus
B103.00	Malignant neoplasm of upper third of oesophagus
B104.00	Malignant neoplasm of middle third of oesophagus
B105.00	Malignant neoplasm of lower third of oesophagus
B106.00	Malignant neoplasm, overlapping lesion of oesophagus
B107.00	Siewert type I adenocarcinoma

B10y.00	Malignant neoplasm of other specified part of oesophagus
B10z.00	Malignant neoplasm of oesophagus NOS
B10z.11	Oesophageal cancer
B11..00	Malignant neoplasm of stomach
B11..11	Gastric neoplasm
B110.00	Malignant neoplasm of cardia of stomach
B110000	Malignant neoplasm of cardiac orifice of stomach
B110100	Malignant neoplasm of cardio-oesophageal junction of stomach
B110111	Malignant neoplasm of gastro-oesophageal junction
B110z00	Malignant neoplasm of cardia of stomach NOS
B111.00	Malignant neoplasm of pylorus of stomach
B111000	Malignant neoplasm of prepylorus of stomach
B111100	Malignant neoplasm of pyloric canal of stomach
B111z00	Malignant neoplasm of pylorus of stomach NOS
B112.00	Malignant neoplasm of pyloric antrum of stomach
B113.00	Malignant neoplasm of fundus of stomach
B114.00	Malignant neoplasm of body of stomach
B115.00	Malignant neoplasm of lesser curve of stomach unspecified
B116.00	Malignant neoplasm of greater curve of stomach unspecified
B117.00	Malignant neoplasm, overlapping lesion of stomach
B118.00	Siewert type II adenocarcinoma
B119.00	Siewert type III adenocarcinoma
B11y.00	Malignant neoplasm of other specified site of stomach
B11y000	Malignant neoplasm of anterior wall of stomach NEC
B11y100	Malignant neoplasm of posterior wall of stomach NEC
B11yz00	Malignant neoplasm of other specified site of stomach NOS
B11z.00	Malignant neoplasm of stomach NOS
B12..00	Malignant neoplasm of small intestine and duodenum
B120.00	Malignant neoplasm of duodenum
B121.00	Malignant neoplasm of jejunum
B122.00	Malignant neoplasm of ileum
B123.00	Malignant neoplasm of Meckel's diverticulum
B124.00	Malignant neoplasm, overlapping lesion of small intestine
B12y.00	Malignant neoplasm of other specified site small intestine
B12z.00	Malignant neoplasm of small intestine NOS
B13..00	Malignant neoplasm of colon
B130.00	Malignant neoplasm of hepatic flexure of colon
B131.00	Malignant neoplasm of transverse colon
B132.00	Malignant neoplasm of descending colon
B133.00	Malignant neoplasm of sigmoid colon
B134.00	Malignant neoplasm of caecum
B134.11	Carcinoma of caecum
B135.00	Malignant neoplasm of appendix
B136.00	Malignant neoplasm of ascending colon
B137.00	Malignant neoplasm of splenic flexure of colon

B138.00	Malignant neoplasm, overlapping lesion of colon
B139.00	Hereditary nonpolyposis colon cancer
B13y.00	Malignant neoplasm of other specified sites of colon
B13z.00	Malignant neoplasm of colon NOS
B13z.11	Colonic cancer
B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
B140.00	Malignant neoplasm of rectosigmoid junction
B141.00	Malignant neoplasm of rectum
B141.11	Carcinoma of rectum
B141.12	Rectal carcinoma
B142.00	Malignant neoplasm of anal canal
B142.11	Anal carcinoma
B142000	Malignant neoplasm of cloacogenic zone
B143.00	Malignant neoplasm of anus unspecified
B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
B15..00	Malignant neoplasm of liver and intrahepatic bile ducts
B150.00	Primary malignant neoplasm of liver
B150000	Primary carcinoma of liver
B150100	Hepatoblastoma of liver
B150200	Primary angiosarcoma of liver
B150300	Hepatocellular carcinoma
B150z00	Primary malignant neoplasm of liver NOS
B151.00	Malignant neoplasm of intrahepatic bile ducts
B151000	Malignant neoplasm of interlobular bile ducts
B151200	Malignant neoplasm of intrahepatic biliary passages
B151400	Malignant neoplasm of intrahepatic gall duct
B151z00	Malignant neoplasm of intrahepatic bile ducts NOS
B152.00	Malignant neoplasm of liver unspecified
B153.00	Secondary malignant neoplasm of liver
B15z.00	Malignant neoplasm of liver and intrahepatic bile ducts NOS
B16..00	Malignant neoplasm gallbladder and extrahepatic bile ducts
B160.00	Malignant neoplasm of gallbladder
B160.11	Carcinoma gallbladder
B161.00	Malignant neoplasm of extrahepatic bile ducts
B161000	Malignant neoplasm of cystic duct
B161100	Malignant neoplasm of hepatic duct
B161200	Malignant neoplasm of common bile duct
B161211	Carcinoma common bile duct
B161300	Malignant neoplasm of sphincter of Oddi
B161z00	Malignant neoplasm of extrahepatic bile ducts NOS
B162.00	Malignant neoplasm of ampulla of Vater
B163.00	Malignant neoplasm, overlapping lesion of biliary tract
B16y.00	Malignant neoplasm other gallbladder/extrahepatic bile duct
B16z.00	Malignant neoplasm gallbladder/extrahepatic bile ducts NOS

B17..00	Malignant neoplasm of pancreas
B170.00	Malignant neoplasm of head of pancreas
B171.00	Malignant neoplasm of body of pancreas
B172.00	Malignant neoplasm of tail of pancreas
B173.00	Malignant neoplasm of pancreatic duct
B174.00	Malignant neoplasm of Islets of Langerhans
B175.00	Malignant neoplasm, overlapping lesion of pancreas
B17y.00	Malignant neoplasm of other specified sites of pancreas
B17y000	Malignant neoplasm of ectopic pancreatic tissue
B17yz00	Malignant neoplasm of specified site of pancreas NOS
B17z.00	Malignant neoplasm of pancreas NOS
B18..00	Malignant neoplasm of retroperitoneum and peritoneum
B180.00	Malignant neoplasm of retroperitoneum
B180100	Malignant neoplasm of perinephric tissue
B180200	Malignant neoplasm of retrocaecal tissue
B180z00	Malignant neoplasm of retroperitoneum NOS
B181.00	Mesothelioma of peritoneum
B182.00	Overlapping malign lesion of retroperitoneum and peritoneum
B18y.00	Malignant neoplasm of specified parts of peritoneum
B18y100	Malignant neoplasm of mesocaecum
B18y200	Malignant neoplasm of mesorectum
B18y300	Malignant neoplasm of omentum
B18y400	Malignant neoplasm of parietal peritoneum
B18y500	Malignant neoplasm of pelvic peritoneum
B18y600	Malignant neoplasm of the pouch of Douglas
B18y700	Malignant neoplasm of mesentery
B18yz00	Malignant neoplasm of specified parts of peritoneum NOS
B18z.00	Malignant neoplasm of retroperitoneum and peritoneum NOS
B1z..00	Malig neop oth/ill-defined sites digestive tract/peritoneum
B1z0.00	Malignant neoplasm of intestinal tract, part unspecified
B1z0.11	Cancer of bowel
B1z1.00	Malignant neoplasm of spleen NEC
B1z1000	Angiosarcoma of spleen
B1z1100	Fibrosarcoma of spleen
B1z1z00	Malignant neoplasm of spleen NOS
B1z2.00	Malignant neoplasm, overlapping lesion of digestive system
B1zy.00	Malignant neoplasm other spec digestive tract and peritoneum
B1zz.00	Malignant neoplasm of digestive tract and peritoneum NOS
B2...00	Malig neop of respiratory tract and intrathoracic organs
B2...11	Carcinoma of respiratory tract and intrathoracic organs
B20..00	Malig neop nasal cavities, middle ear and accessory sinuses
B200.00	Malignant neoplasm of nasal cavities
B200000	Malignant neoplasm of cartilage of nose
B200100	Malignant neoplasm of nasal conchae
B200200	Malignant neoplasm of septum of nose

B200300	Malignant neoplasm of vestibule of nose
B200z00	Malignant neoplasm of nasal cavities NOS
B201.00	Malig neop auditory tube, middle ear and mastoid air cells
B201000	Malignant neoplasm of auditory (Eustachian) tube
B201100	Malignant neoplasm of tympanic cavity
B201200	Malignant neoplasm of tympanic antrum
B201300	Malignant neoplasm of mastoid air cells
B201z00	Malig neop auditory tube, middle ear, mastoid air cells NOS
B202.00	Malignant neoplasm of maxillary sinus
B203.00	Malignant neoplasm of ethmoid sinus
B204.00	Malignant neoplasm of frontal sinus
B205.00	Malignant neoplasm of sphenoidal sinus
B206.00	Malignant neoplasm, overlapping lesion of accessory sinuses
B20y.00	Malig neop other site nasal cavity, middle ear and sinuses
B20z.00	Malignant neoplasm of accessory sinus NOS
B21..00	Malignant neoplasm of larynx
B210.00	Malignant neoplasm of glottis
B211.00	Malignant neoplasm of supraglottis
B212.00	Malignant neoplasm of subglottis
B213.00	Malignant neoplasm of laryngeal cartilage
B213000	Malignant neoplasm of arytenoid cartilage
B213100	Malignant neoplasm of cricoid cartilage
B213200	Malignant neoplasm of cuneiform cartilage
B213300	Malignant neoplasm of thyroid cartilage
B213z00	Malignant neoplasm of laryngeal cartilage NOS
B214.00	Malignant neoplasm, overlapping lesion of larynx
B215.00	Malignant neoplasm of epiglottis NOS
B21y.00	Malignant neoplasm of larynx, other specified site
B21z.00	Malignant neoplasm of larynx NOS
B22..00	Malignant neoplasm of trachea, bronchus and lung
B220.00	Malignant neoplasm of trachea
B220100	Malignant neoplasm of mucosa of trachea
B220z00	Malignant neoplasm of trachea NOS
B221.00	Malignant neoplasm of main bronchus
B221000	Malignant neoplasm of carina of bronchus
B221100	Malignant neoplasm of hilus of lung
B221z00	Malignant neoplasm of main bronchus NOS
B222.00	Malignant neoplasm of upper lobe, bronchus or lung
B222.11	Pancoast's syndrome
B222000	Malignant neoplasm of upper lobe bronchus
B222100	Malignant neoplasm of upper lobe of lung
B222z00	Malignant neoplasm of upper lobe, bronchus or lung NOS
B223.00	Malignant neoplasm of middle lobe, bronchus or lung
B223000	Malignant neoplasm of middle lobe bronchus
B223100	Malignant neoplasm of middle lobe of lung

B223z00	Malignant neoplasm of middle lobe, bronchus or lung NOS
B224.00	Malignant neoplasm of lower lobe, bronchus or lung
B224000	Malignant neoplasm of lower lobe bronchus
B224100	Malignant neoplasm of lower lobe of lung
B224z00	Malignant neoplasm of lower lobe, bronchus or lung NOS
B225.00	Malignant neoplasm of overlapping lesion of bronchus & lung
B226.00	Mesothelioma
B22y.00	Malignant neoplasm of other sites of bronchus or lung
B22z.00	Malignant neoplasm of bronchus or lung NOS
B22z.11	Lung cancer
B23..00	Malignant neoplasm of pleura
B230.00	Malignant neoplasm of parietal pleura
B231.00	Malignant neoplasm of visceral pleura
B232.00	Mesothelioma of pleura
B23y.00	Malignant neoplasm of other specified pleura
B23z.00	Malignant neoplasm of pleura NOS
B24..00	Malignant neoplasm of thymus, heart and mediastinum
B240.00	Malignant neoplasm of thymus
B241.00	Malignant neoplasm of heart
B241000	Malignant neoplasm of endocardium
B241200	Malignant neoplasm of myocardium
B241300	Malignant neoplasm of pericardium
B241400	Mesothelioma of pericardium
B241z00	Malignant neoplasm of heart NOS
B242.00	Malignant neoplasm of anterior mediastinum
B243.00	Malignant neoplasm of posterior mediastinum
B24X.00	Malignant neoplasm of mediastinum, part unspecified
B24y.00	Malig neop of other site of heart, thymus and mediastinum
B24z.00	Malignant neoplasm of heart, thymus and mediastinum NOS
B25..00	Malig neo, overlapping lesion of heart, mediastinum & pleura
B26..00	Malignant neoplasm, overlap lesion of resp & intrathor orgs
B2z..00	Malig neop other/ill-defined sites resp/intrathoracic organs
B2z0.00	Malig neop of upper respiratory tract, part unspecified
B2zy.00	Malignant neoplasm of other site of respiratory tract
B2zz.00	Malignant neoplasm of respiratory tract NOS
B3...00	Malig neop of bone, connective tissue, skin and breast
B3...11	Carcinoma of bone, connective tissue, skin and breast
B3...12	Sarcoma of bone and connective tissue
B30..00	Malignant neoplasm of bone and articular cartilage
B30..11	Chondroma
B30..12	Osteoma
B300.00	Malignant neoplasm of bones of skull and face
B300000	Malignant neoplasm of ethmoid bone
B300100	Malignant neoplasm of frontal bone
B300200	Malignant neoplasm of malar bone

B300300	Malignant neoplasm of nasal bone
B300400	Malignant neoplasm of occipital bone
B300500	Malignant neoplasm of orbital bone
B300600	Malignant neoplasm of parietal bone
B300700	Malignant neoplasm of sphenoid bone
B300800	Malignant neoplasm of temporal bone
B300900	Malignant neoplasm of zygomatic bone
B300A00	Malignant neoplasm of maxilla
B300B00	Malignant neoplasm of turbinate
B300C00	Malignant neoplasm of vomer
B300z00	Malignant neoplasm of bones of skull and face NOS
B301.00	Malignant neoplasm of mandible
B302.00	Malignant neoplasm of vertebral column
B302000	Malignant neoplasm of cervical vertebra
B302100	Malignant neoplasm of thoracic vertebra
B302200	Malignant neoplasm of lumbar vertebra
B302z00	Malignant neoplasm of vertebral column NOS
B303.00	Malignant neoplasm of ribs, sternum and clavicle
B303000	Malignant neoplasm of rib
B303100	Malignant neoplasm of sternum
B303200	Malignant neoplasm of clavicle
B303300	Malignant neoplasm of costal cartilage
B303400	Malignant neoplasm of costo-vertebral joint
B303500	Malignant neoplasm of xiphoid process
B303z00	Malignant neoplasm of rib, sternum and clavicle NOS
B304.00	Malignant neoplasm of scapula and long bones of upper arm
B304000	Malignant neoplasm of scapula
B304100	Malignant neoplasm of acromion
B304200	Malignant neoplasm of humerus
B304300	Malignant neoplasm of radius
B304400	Malignant neoplasm of ulna
B304z00	Malig neop of scapula and long bones of upper arm NOS
B305.00	Malignant neoplasm of hand bones
B305.11	Malignant neoplasm of carpal bones
B305.12	Malignant neoplasm of metacarpal bones
B305000	Malignant neoplasm of carpal bone - scaphoid
B305100	Malignant neoplasm of carpal bone - lunate
B305A00	Malignant neoplasm of third metacarpal bone
B305C00	Malignant neoplasm of fifth metacarpal bone
B305D00	Malignant neoplasm of phalanges of hand
B305z00	Malignant neoplasm of hand bones NOS
B306.00	Malignant neoplasm of pelvic bones, sacrum and coccyx
B306000	Malignant neoplasm of ilium
B306100	Malignant neoplasm of ischium
B306200	Malignant neoplasm of pubis

B306300	Malignant neoplasm of sacral vertebra
B306400	Malignant neoplasm of coccygeal vertebra
B306500	Malignant sacral teratoma
B306z00	Malignant neoplasm of pelvis, sacrum or coccyx NOS
B307.00	Malignant neoplasm of long bones of leg
B307000	Malignant neoplasm of femur
B307100	Malignant neoplasm of fibula
B307200	Malignant neoplasm of tibia
B307z00	Malignant neoplasm of long bones of leg NOS
B308.00	Malignant neoplasm of short bones of leg
B308100	Malignant neoplasm of talus
B308200	Malignant neoplasm of calcaneum
B308300	Malignant neoplasm of medial cuneiform
B308800	Malignant neoplasm of first metatarsal bone
B308B00	Malignant neoplasm of fourth metatarsal bone
B308D00	Malignant neoplasm of phalanges of foot
B308z00	Malignant neoplasm of short bones of leg NOS
B30W.00	Malignant neoplasm/overlap lesion/bone+articulr cartilage
B30X.00	Malignant neoplasm/bones+articular cartilage/limb,unspfd
B30z.00	Malignant neoplasm of bone and articular cartilage NOS
B30z000	Osteosarcoma
B31..00	Malignant neoplasm of connective and other soft tissue
B310.00	Malig neop of connective and soft tissue head, face and neck
B310000	Malignant neoplasm of soft tissue of head
B310100	Malignant neoplasm of soft tissue of face
B310200	Malignant neoplasm of soft tissue of neck
B310300	Malignant neoplasm of cartilage of ear
B310400	Malignant neoplasm of tarsus of eyelid
B310500	Malignant neoplasm soft tissues of cervical spine
B310z00	Malig neop connective and soft tissue head, face, neck NOS
B311.00	Malig neop connective and soft tissue upper limb/shoulder
B311000	Malignant neoplasm of connective and soft tissue of shoulder
B311100	Malignant neoplasm of connective and soft tissue, upper arm
B311200	Malignant neoplasm of connective and soft tissue of fore-arm
B311300	Malignant neoplasm of connective and soft tissue of hand
B311400	Malignant neoplasm of connective and soft tissue of finger
B311500	Malignant neoplasm of connective and soft tissue of thumb
B311z00	Malig neop connective soft tissue upper limb/shoulder NOS
B312.00	Malig neop of connective and soft tissue of hip and leg
B312000	Malignant neoplasm of connective and soft tissue of hip
B312100	Malig neop of connective and soft tissue thigh and upper leg
B312200	Malig neop connective and soft tissue of popliteal space
B312300	Malig neop of connective and soft tissue of lower leg
B312400	Malignant neoplasm of connective and soft tissue of foot
B312500	Malignant neoplasm of connective and soft tissue of toe

B312z00	Malig neop connective and soft tissue hip and leg NOS
B313.00	Malignant neoplasm of connective and soft tissue of thorax
B313000	Malignant neoplasm of connective and soft tissue of axilla
B313100	Malignant neoplasm of diaphragm
B313200	Malignant neoplasm of great vessels
B313300	Malig neoplasm of connective and soft tissues of thor spine
B313z00	Malig neop of connective and soft tissue of thorax NOS
B314.00	Malignant neoplasm of connective and soft tissue of abdomen
B314000	Malig neop of connective and soft tissue of abdominal wall
B314100	Malig neoplasm of connective and soft tissues of lumb spine
B314z00	Malig neop of connective and soft tissue of abdomen NOS
B315.00	Malignant neoplasm of connective and soft tissue of pelvis
B315000	Malignant neoplasm of connective and soft tissue of buttock
B315100	Malig neop of connective and soft tissue of inguinal region
B315200	Malignant neoplasm of connective and soft tissue of perineum
B315z00	Malig neop of connective and soft tissue of pelvis NOS
B316.00	Malig neop of connective and soft tissue trunk unspecified
B31y.00	Malig neop connective and soft tissue other specified site
B31z.00	Malignant neoplasm of connective and soft tissue, site NOS
B31z000	Kaposi's sarcoma of soft tissue
B32..00	Malignant melanoma of skin
B320.00	Malignant melanoma of lip
B321.00	Malignant melanoma of eyelid including canthus
B322.00	Malignant melanoma of ear and external auricular canal
B322000	Malignant melanoma of auricle (ear)
B322100	Malignant melanoma of external auditory meatus
B322z00	Malignant melanoma of ear and external auricular canal NOS
B323.00	Malignant melanoma of other and unspecified parts of face
B323000	Malignant melanoma of external surface of cheek
B323100	Malignant melanoma of chin
B323200	Malignant melanoma of eyebrow
B323300	Malignant melanoma of forehead
B323400	Malignant melanoma of external surface of nose
B323500	Malignant melanoma of temple
B323z00	Malignant melanoma of face NOS
B324.00	Malignant melanoma of scalp and neck
B324000	Malignant melanoma of scalp
B324100	Malignant melanoma of neck
B324z00	Malignant melanoma of scalp and neck NOS
B325.00	Malignant melanoma of trunk (excluding scrotum)
B325000	Malignant melanoma of axilla
B325100	Malignant melanoma of breast
B325200	Malignant melanoma of buttock
B325300	Malignant melanoma of groin
B325500	Malignant melanoma of perineum

B325600	Malignant melanoma of umbilicus
B325700	Malignant melanoma of back
B325800	Malignant melanoma of chest wall
B325z00	Malignant melanoma of trunk, excluding scrotum, NOS
B326.00	Malignant melanoma of upper limb and shoulder
B326000	Malignant melanoma of shoulder
B326100	Malignant melanoma of upper arm
B326200	Malignant melanoma of fore-arm
B326300	Malignant melanoma of hand
B326400	Malignant melanoma of finger
B326500	Malignant melanoma of thumb
B326z00	Malignant melanoma of upper limb or shoulder NOS
B327.00	Malignant melanoma of lower limb and hip
B327000	Malignant melanoma of hip
B327100	Malignant melanoma of thigh
B327200	Malignant melanoma of knee
B327300	Malignant melanoma of popliteal fossa area
B327400	Malignant melanoma of lower leg
B327500	Malignant melanoma of ankle
B327600	Malignant melanoma of heel
B327700	Malignant melanoma of foot
B327800	Malignant melanoma of toe
B327900	Malignant melanoma of great toe
B327z00	Malignant melanoma of lower limb or hip NOS
B32y.00	Malignant melanoma of other specified skin site
B32y000	Overlapping malignant melanoma of skin
B32z.00	Malignant melanoma of skin NOS
B33..00	Other malignant neoplasm of skin
B33..11	Basal cell carcinoma
B33..12	Epithelioma
B33..13	Rodent ulcer
B33..14	Malignant neoplasm of sebaceous gland
B33..15	Malignant neoplasm of sweat gland
B33..16	Epithelioma basal cell
B330.00	Malignant neoplasm of skin of lip
B331.00	Malignant neoplasm of eyelid including canthus
B331000	Malignant neoplasm of canthus
B331100	Malignant neoplasm of upper eyelid
B331200	Malignant neoplasm of lower eyelid
B332.00	Malignant neoplasm skin of ear and external auricular canal
B332000	Malignant neoplasm of skin of auricle (ear)
B332100	Malignant neoplasm of skin of external auditory meatus
B332200	Malignant neoplasm of pinna NEC
B332z00	Malig neop skin of ear and external auricular canal NOS
B333.00	Malignant neoplasm skin of other and unspecified parts face

B333000	Malignant neoplasm of skin of cheek, external
B333100	Malignant neoplasm of skin of chin
B333200	Malignant neoplasm of skin of eyebrow
B333300	Malignant neoplasm of skin of forehead
B333400	Malignant neoplasm of skin of nose (external)
B333500	Malignant neoplasm of skin of temple
B333z00	Malignant neoplasm skin other and unspec part of face NOS
B334.00	Malignant neoplasm of scalp and skin of neck
B334000	Malignant neoplasm of scalp
B334100	Malignant neoplasm of skin of neck
B334z00	Malignant neoplasm of scalp or skin of neck NOS
B335.00	Malignant neoplasm of skin of trunk, excluding scrotum
B335000	Malignant neoplasm of skin of axillary fold
B335100	Malignant neoplasm of skin of chest, excluding breast
B335200	Malignant neoplasm of skin of breast
B335300	Malignant neoplasm of skin of abdominal wall
B335400	Malignant neoplasm of skin of umbilicus
B335500	Malignant neoplasm of skin of groin
B335600	Malignant neoplasm of skin of perineum
B335700	Malignant neoplasm of skin of back
B335800	Malignant neoplasm of skin of buttock
B335900	Malignant neoplasm of perianal skin
B335A00	Malignant neoplasm of skin of scapular region
B335z00	Malignant neoplasm of skin of trunk, excluding scrotum, NOS
B336.00	Malignant neoplasm of skin of upper limb and shoulder
B336000	Malignant neoplasm of skin of shoulder
B336100	Malignant neoplasm of skin of upper arm
B336200	Malignant neoplasm of skin of fore-arm
B336300	Malignant neoplasm of skin of hand
B336400	Malignant neoplasm of skin of finger
B336500	Malignant neoplasm of skin of thumb
B336z00	Malignant neoplasm of skin of upper limb or shoulder NOS
B337.00	Malignant neoplasm of skin of lower limb and hip
B337000	Malignant neoplasm of skin of hip
B337100	Malignant neoplasm of skin of thigh
B337200	Malignant neoplasm of skin of knee
B337300	Malignant neoplasm of skin of popliteal fossa area
B337400	Malignant neoplasm of skin of lower leg
B337500	Malignant neoplasm of skin of ankle
B337600	Malignant neoplasm of skin of heel
B337700	Malignant neoplasm of skin of foot
B337800	Malignant neoplasm of skin of toe
B337900	Malignant neoplasm of skin of great toe
B337z00	Malignant neoplasm of skin of lower limb or hip NOS
B338.00	Squamous cell carcinoma of skin

B339.00	Dermatofibrosarcoma protuberans
B33X.00	Malignant neoplasm overlapping lesion of skin
B33y.00	Malignant neoplasm of other specified skin sites
B33z.00	Malignant neoplasm of skin NOS
B33z.11	Squamous cell carcinoma of skin NOS
B33z000	Kaposi's sarcoma of skin
B33z100	Naevoid basal cell carcinoma syndrome
B34..00	Malignant neoplasm of female breast
B34..11	Ca female breast
B340.00	Malignant neoplasm of nipple and areola of female breast
B340000	Malignant neoplasm of nipple of female breast
B340100	Malignant neoplasm of areola of female breast
B340z00	Malignant neoplasm of nipple or areola of female breast NOS
B341.00	Malignant neoplasm of central part of female breast
B342.00	Malignant neoplasm of upper-inner quadrant of female breast
B343.00	Malignant neoplasm of lower-inner quadrant of female breast
B344.00	Malignant neoplasm of upper-outer quadrant of female breast
B345.00	Malignant neoplasm of lower-outer quadrant of female breast
B346.00	Malignant neoplasm of axillary tail of female breast
B347.00	Malignant neoplasm, overlapping lesion of breast
B34y.00	Malignant neoplasm of other site of female breast
B34y000	Malignant neoplasm of ectopic site of female breast
B34yz00	Malignant neoplasm of other site of female breast NOS
B34z.00	Malignant neoplasm of female breast NOS
B35..00	Malignant neoplasm of male breast
B350.00	Malignant neoplasm of nipple and areola of male breast
B350000	Malignant neoplasm of nipple of male breast
B350100	Malignant neoplasm of areola of male breast
B35z.00	Malignant neoplasm of other site of male breast
B35z000	Malignant neoplasm of ectopic site of male breast
B35zz00	Malignant neoplasm of male breast NOS
B36..00	Local recurrence of malignant tumour of breast
B3y..00	Malig neop of bone, connective tissue, skin and breast OS
B3z..00	Malig neop of bone, connective tissue, skin and breast NOS
B4...00	Malignant neoplasm of genitourinary organ
B4...11	Carcinoma of genitourinary organ
B40..00	Malignant neoplasm of uterus, part unspecified
B41..00	Malignant neoplasm of cervix uteri
B41..11	Cervical carcinoma (uterus)
B410.00	Malignant neoplasm of endocervix
B410000	Malignant neoplasm of endocervical canal
B410100	Malignant neoplasm of endocervical gland
B410z00	Malignant neoplasm of endocervix NOS
B411.00	Malignant neoplasm of exocervix
B412.00	Malignant neoplasm, overlapping lesion of cervix uteri

B41y.00	Malignant neoplasm of other site of cervix
B41y000	Malignant neoplasm of cervical stump
B41y100	Malignant neoplasm of squamocolumnar junction of cervix
B41yz00	Malignant neoplasm of other site of cervix NOS
B41z.00	Malignant neoplasm of cervix uteri NOS
B42..00	Malignant neoplasm of placenta
B420.00	Choriocarcinoma
B43..00	Malignant neoplasm of body of uterus
B430.00	Malignant neoplasm of corpus uteri, excluding isthmus
B430000	Malignant neoplasm of cornu of corpus uteri
B430100	Malignant neoplasm of fundus of corpus uteri
B430200	Malignant neoplasm of endometrium of corpus uteri
B430211	Malignant neoplasm of endometrium
B430300	Malignant neoplasm of myometrium of corpus uteri
B430z00	Malignant neoplasm of corpus uteri NOS
B431.00	Malignant neoplasm of isthmus of uterine body
B431000	Malignant neoplasm of lower uterine segment
B431z00	Malignant neoplasm of isthmus of uterine body NOS
B432.00	Malignant neoplasm of overlapping lesion of corpus uteri
B43y.00	Malignant neoplasm of other site of uterine body
B43z.00	Malignant neoplasm of body of uterus NOS
B44..00	Malignant neoplasm of ovary and other uterine adnexa
B440.00	Malignant neoplasm of ovary
B440.11	Cancer of ovary
B441.00	Malignant neoplasm of fallopian tube
B442.00	Malignant neoplasm of broad ligament
B443.00	Malignant neoplasm of parametrium
B44y.00	Malignant neoplasm of other site of uterine adnexa
B44z.00	Malignant neoplasm of uterine adnexa NOS
B45..00	Malig neop of other and unspecified female genital organs
B450.00	Malignant neoplasm of vagina
B450100	Malignant neoplasm of vaginal vault
B450z00	Malignant neoplasm of vagina NOS
B451.00	Malignant neoplasm of labia majora
B451000	Malignant neoplasm of greater vestibular (Bartholin's) gland
B451z00	Malignant neoplasm of labia majora NOS
B452.00	Malignant neoplasm of labia minora
B453.00	Malignant neoplasm of clitoris
B454.00	Malignant neoplasm of vulva unspecified
B454.11	Primary vulval cancer
B45X.00	Malignant neoplasm/overlapping lesion/feml genital organs
B45y.00	Malignant neoplasm of other specified female genital organ
B45y000	Malignant neoplasm of overlapping lesion of vulva
B45z.00	Malignant neoplasm of female genital organ NOS
B46..00	Malignant neoplasm of prostate

B47..00	Malignant neoplasm of testis
B470.00	Malignant neoplasm of undescended testis
B470200	Seminoma of undescended testis
B470300	Teratoma of undescended testis
B470z00	Malignant neoplasm of undescended testis NOS
B471.00	Malignant neoplasm of descended testis
B471000	Seminoma of descended testis
B471100	Teratoma of descended testis
B471z00	Malignant neoplasm of descended testis NOS
B47z.00	Malignant neoplasm of testis NOS
B47z.11	Seminoma of testis
B47z.12	Teratoma of testis
B48..00	Malignant neoplasm of penis and other male genital organs
B480.00	Malignant neoplasm of prepuce (foreskin)
B481.00	Malignant neoplasm of glans penis
B482.00	Malignant neoplasm of body of penis
B483.00	Malignant neoplasm of penis, part unspecified
B484.00	Malignant neoplasm of epididymis
B485.00	Malignant neoplasm of spermatic cord
B486.00	Malignant neoplasm of scrotum
B487.00	Malignant neoplasm, overlapping lesion of penis
B48y.00	Malignant neoplasm of other male genital organ
B48y000	Malignant neoplasm of seminal vesicle
B48y100	Malignant neoplasm of tunica vaginalis
B48y200	Malignant neoplasm, overlapping lesion male genital orgs
B48yz00	Malignant neoplasm of other male genital organ NOS
B48z.00	Malignant neoplasm of penis and other male genital organ NOS
B49..00	Malignant neoplasm of urinary bladder
B490.00	Malignant neoplasm of trigone of urinary bladder
B491.00	Malignant neoplasm of dome of urinary bladder
B492.00	Malignant neoplasm of lateral wall of urinary bladder
B493.00	Malignant neoplasm of anterior wall of urinary bladder
B494.00	Malignant neoplasm of posterior wall of urinary bladder
B495.00	Malignant neoplasm of bladder neck
B496.00	Malignant neoplasm of ureteric orifice
B497.00	Malignant neoplasm of urachus
B498.00	Local recurrence of malignant tumour of urinary bladder
B49y.00	Malignant neoplasm of other site of urinary bladder
B49y000	Malignant neoplasm, overlapping lesion of bladder
B49z.00	Malignant neoplasm of urinary bladder NOS
B4A..00	Malig neop of kidney and other unspecified urinary organs
B4A..11	Renal malignant neoplasm
B4A0.00	Malignant neoplasm of kidney parenchyma
B4A0000	Hypernephroma
B4A1.00	Malignant neoplasm of renal pelvis

B4A1000	Malignant neoplasm of renal calyces
B4A1100	Malignant neoplasm of ureteropelvic junction
B4A1z00	Malignant neoplasm of renal pelvis NOS
B4A2.00	Malignant neoplasm of ureter
B4A3.00	Malignant neoplasm of urethra
B4A4.00	Malignant neoplasm of paraurethral glands
B4Ay.00	Malignant neoplasm of other urinary organs
B4Ay000	Malignant neoplasm of overlapping lesion of urinary organs
B4Az.00	Malignant neoplasm of kidney or urinary organs NOS
B4y..00	Malignant neoplasm of genitourinary organ OS
B4z..00	Malignant neoplasm of genitourinary organ NOS
B5...00	Malignant neoplasm of other and unspecified sites
B5...11	Carcinoma of other and unspecified sites
B50..00	Malignant neoplasm of eye
B500.00	Malig neop eyeball excl conjunctiva, cornea, retina, choroid
B500000	Malignant neoplasm of ciliary body
B500100	Malignant neoplasm of iris
B500200	Malignant neoplasm of crystalline lens
B500z00	Malignant neoplasm of eyeball NOS
B501.00	Malignant neoplasm of orbit
B501000	Malignant neoplasm of connective tissue of orbit
B501z00	Malignant neoplasm of orbit NOS
B502.00	Malignant neoplasm of lacrimal gland
B503.00	Malignant neoplasm of conjunctiva
B504.00	Malignant neoplasm of cornea
B505.00	Malignant neoplasm of retina
B506.00	Malignant neoplasm of choroid
B507.00	Malignant neoplasm of lacrimal duct
B507000	Malignant neoplasm of lacrimal sac
B507100	Malignant neoplasm of nasolacrimal duct
B508.00	Malignant neoplasm, overlapping lesion of eye and adnexa
B50y.00	Malignant neoplasm of other specified site of eye
B50z.00	Malignant neoplasm of eye NOS
B51..00	Malignant neoplasm of brain
B51..11	Cerebral tumour - malignant
B510.00	Malignant neoplasm cerebrum (excluding lobes and ventricles)
B510000	Malignant neoplasm of basal ganglia
B510100	Malignant neoplasm of cerebral cortex
B510300	Malignant neoplasm of globus pallidus
B510400	Malignant neoplasm of hypothalamus
B510500	Malignant neoplasm of thalamus
B510z00	Malignant neoplasm of cerebrum NOS
B511.00	Malignant neoplasm of frontal lobe
B512.00	Malignant neoplasm of temporal lobe
B512000	Malignant neoplasm of hippocampus

B512z00	Malignant neoplasm of temporal lobe NOS
B513.00	Malignant neoplasm of parietal lobe
B514.00	Malignant neoplasm of occipital lobe
B515.00	Malignant neoplasm of cerebral ventricles
B515000	Malignant neoplasm of choroid plexus
B516.00	Malignant neoplasm of cerebellum
B517.00	Malignant neoplasm of brain stem
B517000	Malignant neoplasm of cerebral peduncle
B517100	Malignant neoplasm of medulla oblongata
B517200	Malignant neoplasm of midbrain
B517300	Malignant neoplasm of pons
B517z00	Malignant neoplasm of brain stem NOS
B51y.00	Malignant neoplasm of other parts of brain
B51y000	Malignant neoplasm of corpus callosum
B51y200	Malignant neoplasm, overlapping lesion of brain
B51yz00	Malignant neoplasm of other part of brain NOS
B51z.00	Malignant neoplasm of brain NOS
B52..00	Malig neop of other and unspecified parts of nervous system
B520.00	Malignant neoplasm of cranial nerves
B520000	Malignant neoplasm of olfactory bulb
B520100	Malignant neoplasm of optic nerve
B520200	Malignant neoplasm of acoustic nerve
B520z00	Malignant neoplasm of cranial nerves NOS
B521.00	Malignant neoplasm of cerebral meninges
B521z00	Malignant neoplasm of cerebral meninges NOS
B522.00	Malignant neoplasm of spinal cord
B523.00	Malignant neoplasm of spinal meninges
B523z00	Malignant neoplasm of spinal meninges NOS
B524.00	Malig neopl peripheral nerves and autonomic nervous system
B524000	Malignant neoplasm of peripheral nerves of head, face & neck
B524100	Malignant neoplasm of peripheral nerve,upp limb,incl should
B524200	Malignant neoplasm of peripheral nerve of low limb, incl hip
B524300	Malignant neoplasm of peripheral nerve of thorax
B524400	Malignant neoplasm of peripheral nerve of abdomen
B524500	Malignant neoplasm of peripheral nerve of pelvis
B524600	Malignant neoplasm,overlap lesion periph nerve & auton ns
B524W00	Mal neoplasm/periph nerves+autonomic nervous system,unspc
B525.00	Malignant neoplasm of cauda equina
B52W.00	Malig neopl, overlap lesion brain & other part of CNS
B52X.00	Malignant neoplasm of meninges, unspecified
B52y.00	Malignant neoplasm of other specified part of nervous system
B52z.00	Malignant neoplasm of nervous system NOS
B53..00	Malignant neoplasm of thyroid gland
B54..00	Malig neop of other endocrine glands and related structures
B540.00	Malignant neoplasm of adrenal gland

B540.11	Phaeochromocytoma
B540000	Malignant neoplasm of adrenal cortex
B540100	Malignant neoplasm of adrenal medulla
B540z00	Malignant neoplasm of adrenal gland NOS
B541.00	Malignant neoplasm of parathyroid gland
B542.00	Malignant neoplasm pituitary gland and craniopharyngeal duct
B542000	Malignant neoplasm of pituitary gland
B542100	Malignant neoplasm of craniopharyngeal duct
B542z00	Malig neop pituitary gland or craniopharyngeal duct NOS
B543.00	Malignant neoplasm of pineal gland
B544.00	Malignant neoplasm of carotid body
B545.00	Malignant neoplasm of aortic body and other paraganglia
B545000	Malignant neoplasm of glomus jugulare
B545100	Malignant neoplasm of aortic body
B545200	Malignant neoplasm of coccygeal body
B545z00	Malignant neoplasm of aortic body or paraganglia NOS
B546.00	Neuroblastoma
B54X.00	Malignant neoplasm-pluriglandular involvement,unspecified
B54y.00	Malignant neoplasm of other specified endocrine gland
B54z.00	Malig neop of endocrine gland or related structure NOS
B55..00	Malignant neoplasm of other and ill-defined sites
B550.00	Malignant neoplasm of head, neck and face
B550000	Malignant neoplasm of head NOS
B550100	Malignant neoplasm of cheek NOS
B550200	Malignant neoplasm of nose NOS
B550300	Malignant neoplasm of jaw NOS
B550400	Malignant neoplasm of neck NOS
B550500	Malignant neoplasm of supraclavicular fossa NOS
B550z00	Malignant neoplasm of head, neck and face NOS
B551.00	Malignant neoplasm of thorax
B551000	Malignant neoplasm of axilla NOS
B551100	Malignant neoplasm of chest wall NOS
B551200	Malignant neoplasm of intrathoracic site NOS
B551z00	Malignant neoplasm of thorax NOS
B552.00	Malignant neoplasm of abdomen
B553.00	Malignant neoplasm of pelvis
B553000	Malignant neoplasm of inguinal region NOS
B553100	Malignant neoplasm of presacral region
B553200	Malignant neoplasm of sacrococcygeal region
B553z00	Malignant neoplasm of pelvis NOS
B554.00	Malignant neoplasm of upper limb NOS
B555.00	Malignant neoplasm of lower limb NOS
B55y.00	Malignant neoplasm of other specified sites
B55y000	Malignant neoplasm of back NOS
B55y100	Malignant neoplasm of trunk NOS

B55y200	Malignant neoplasm of flank NOS
B55yz00	Malignant neoplasm of specified site NOS
B55z.00	Malignant neoplasm of other and ill defined site NOS
B56..00	Secondary and unspecified malignant neoplasm of lymph nodes
B56..11	Lymph node metastases
B560.00	Secondary and unspec malig neop lymph nodes head/face/neck
B560000	Secondary and unspec malig neop of superficial parotid LN
B560100	Secondary and unspec malignant neoplasm mastoid lymph nodes
B560200	Secondary and unspec malig neop superficial cervical LN
B560300	Secondary and unspec malignant neoplasm occipital lymph node
B560400	Secondary and unspec malig neop deep parotid lymph nodes
B560500	Secondary and unspec malig neop submandibular lymph nodes
B560600	Secondary and unspec malig neop of facial lymph nodes
B560700	Secondary and unspec malig neop submental lymph nodes
B560800	Secondary and unspec malig neop anterior cervical LN
B560900	Secondary and unspec malig neop deep cervical LN
B560z00	Secondary unspec malig neop lymph nodes head/face/neck NOS
B561.00	Secondary and unspec malig neop intrathoracic lymph nodes
B561000	Secondary and unspec malig neop internal mammary lymph nodes
B561200	Secondary and unspec malig neop diaphragmatic lymph nodes
B561300	Secondary and unspec malig neop ant mediastinal lymph nodes
B561400	Secondary and unspec malig neop post mediastinal lymph nodes
B561500	Secondary and unspec malig neop paratracheal lymph nodes
B561600	Secondary and unspec malig neop superfic tracheobronchial LN
B561700	Secondary and unspec malig neop inferior tracheobronchial LN
B561800	Secondary and unspec malig neop bronchopulmonary lymph nodes
B561900	Secondary and unspec malig neop pulmonary lymph nodes
B561z00	Secondary and unspec malig neop intrathoracic LN NOS
B562.00	Secondary and unspec malig neop intra-abdominal lymph nodes
B562000	Secondary and unspec malig neop coeliac lymph nodes
B562100	Secondary and unspec malig neop superficial mesenteric LN
B562200	Secondary and unspec malig neop inferior mesenteric LN
B562300	Secondary and unspec malig neop common iliac lymph nodes
B562400	Secondary and unspec malig neop external iliac lymph nodes
B562z00	Secondary and unspec malig neop intra-abdominal LN NOS
B563.00	Secondary and unspec malig neop axilla and upper limb LN
B563000	Secondary and unspec malig neop axillary lymph nodes
B563100	Secondary and unspec malig neop supratrochlear lymph nodes
B563200	Secondary and unspec malig neop infraclavicular lymph nodes
B563300	Secondary and unspec malig neop pectoral lymph nodes
B563z00	Secondary and unspec malig neop axilla and upper limb LN NOS
B564.00	Secondary and unspec malig neop inguinal and lower limb LN
B564000	Secondary and unspec malig neop superficial inguinal LN
B564100	Secondary and unspec malig neop deep inguinal lymph nodes
B564z00	Secondary and unspec malig neop of inguinal and leg LN NOS

B565.00	Secondary and unspec malig neop intrapelvic lymph nodes
B565000	Secondary and unspec malig neop internal iliac lymph nodes
B565200	Secondary and unspec malig neop circumflex iliac LN
B565300	Secondary and unspec malig neop sacral lymph nodes
B565z00	Secondary and unspec malig neop intrapelvic LN NOS
B56y.00	Secondary and unspec malig neop lymph nodes multiple sites
B56z.00	Secondary and unspec malig neop lymph nodes NOS
B57..00	Secondary malig neop of respiratory and digestive systems
B57..11	Metastases of respiratory and/or digestive systems
B57..12	Secondary carcinoma of respiratory and/or digestive systems
B570.00	Secondary malignant neoplasm of lung
B571.00	Secondary malignant neoplasm of mediastinum
B572.00	Secondary malignant neoplasm of pleura
B573.00	Secondary malignant neoplasm of other respiratory organs
B574.00	Secondary malignant neoplasm of small intestine and duodenum
B574000	Secondary malignant neoplasm of duodenum
B574200	Secondary malignant neoplasm of ileum
B574z00	Secondary malig neop of small intestine or duodenum NOS
B575.00	Secondary malignant neoplasm of large intestine and rectum
B575000	Secondary malignant neoplasm of colon
B575100	Secondary malignant neoplasm of rectum
B575z00	Secondary malig neop of large intestine or rectum NOS
B576.00	Secondary malig neop of retroperitoneum and peritoneum
B576000	Secondary malignant neoplasm of retroperitoneum
B576100	Secondary malignant neoplasm of peritoneum
B576200	Malignant ascites
B576z00	Secondary malig neop of retroperitoneum or peritoneum NOS
B577.00	Secondary malignant neoplasm of liver
B577.11	Liver metastases
B57y.00	Secondary malignant neoplasm of other digestive organ
B57z.00	Secondary malig neop of respiratory or digestive system NOS
B58..00	Secondary malignant neoplasm of other specified sites
B58..11	Secondary carcinoma of other specified sites
B580.00	Secondary malignant neoplasm of kidney
B581.00	Secondary malignant neoplasm of other urinary organs
B581000	Secondary malignant neoplasm of ureter
B581100	Secondary malignant neoplasm of bladder
B581200	Secondary malignant neoplasm of urethra
B581z00	Secondary malignant neoplasm of other urinary organ NOS
B582.00	Secondary malignant neoplasm of skin
B582000	Secondary malignant neoplasm of skin of head
B582100	Secondary malignant neoplasm of skin of face
B582200	Secondary malignant neoplasm of skin of neck
B582300	Secondary malignant neoplasm of skin of trunk
B582400	Secondary malignant neoplasm of skin of shoulder and arm

B582500	Secondary malignant neoplasm of skin of hip and leg
B582600	Secondary malignant neoplasm of skin of breast
B582z00	Secondary malignant neoplasm of skin NOS
B583.00	Secondary malignant neoplasm of brain and spinal cord
B583000	Secondary malignant neoplasm of brain
B583100	Secondary malignant neoplasm of spinal cord
B583200	Cerebral metastasis
B583z00	Secondary malignant neoplasm of brain or spinal cord NOS
B584.00	Secondary malignant neoplasm of other part of nervous system
B585.00	Secondary malignant neoplasm of bone and bone marrow
B585000	Pathological fracture due to metastatic bone disease
B586.00	Secondary malignant neoplasm of ovary
B587.00	Secondary malignant neoplasm of adrenal gland
B58y.00	Secondary malignant neoplasm of other specified sites
B58y000	Secondary malignant neoplasm of breast
B58y100	Secondary malignant neoplasm of uterus
B58y200	Secondary malignant neoplasm of cervix uteri
B58y211	Secondary cancer of the cervix
B58y300	Secondary malignant neoplasm of vagina
B58y400	Secondary malignant neoplasm of vulva
B58y411	Secondary cancer of the vulva
B58y500	Secondary malignant neoplasm of prostate
B58y600	Secondary malignant neoplasm of testis
B58y700	Secondary malignant neoplasm of penis
B58y800	Secondary malignant neoplasm of epididymis and vas deferens
B58y900	Secondary malignant neoplasm of tongue
B58yz00	Secondary malignant neoplasm of other specified site NOS
B58z.00	Secondary malignant neoplasm of other specified site NOS
B59..00	Malignant neoplasm of unspecified site
B590.00	Disseminated malignancy NOS
B590.11	Carcinomatosis
B591.00	Other malignant neoplasm NOS
B592.00	Malignant neoplasms of independent (primary) multiple sites
B592X00	Kaposi's sarcoma of multiple organs
B593.00	Primary malignant neoplasm of unknown site
B594.00	Secondary malignant neoplasm of unknown site
B595.00	Malignant tumour of unknown origin
B59z.00	Malignant neoplasm of unspecified site NOS
B59zX00	Kaposi's sarcoma, unspecified
B5y..00	Malignant neoplasm of other and unspecified site OS
B5z..00	Malignant neoplasm of other and unspecified site NOS
B6...00	Malignant neoplasm of lymphatic and haemopoietic tissue
B6...11	Malignant neoplasm of histiocytic tissue
B60..00	Lymphosarcoma and reticulosarcoma
B600.00	Reticulosarcoma

B600000	Reticulosarcoma of unspecified site
B600100	Reticulosarcoma of lymph nodes of head, face and neck
B600300	Reticulosarcoma of intra-abdominal lymph nodes
B600700	Reticulosarcoma of spleen
B600z00	Reticulosarcoma NOS
B601.00	Lymphosarcoma
B601000	Lymphosarcoma of unspecified site
B601100	Lymphosarcoma of lymph nodes of head, face and neck
B601200	Lymphosarcoma of intrathoracic lymph nodes
B601300	Lymphosarcoma of intra-abdominal lymph nodes
B601500	Lymphosarcoma of lymph nodes of inguinal region and leg
B601700	Lymphosarcoma of spleen
B601800	Lymphosarcoma of lymph nodes of multiple sites
B601z00	Lymphosarcoma NOS
B602.00	Burkitt's lymphoma
B602100	Burkitt's lymphoma of lymph nodes of head, face and neck
B602200	Burkitt's lymphoma of intrathoracic lymph nodes
B602300	Burkitt's lymphoma of intra-abdominal lymph nodes
B602500	Burkitt's lymphoma of lymph nodes of inguinal region and leg
B602z00	Burkitt's lymphoma NOS
B60y.00	Other specified reticulosarcoma or lymphosarcoma
B60z.00	Reticulosarcoma or lymphosarcoma NOS
B61..00	Hodgkin's disease
B61..11	Hodgkin lymphoma
B610.00	Hodgkin's paragranuloma
B610100	Hodgkin's paragranuloma of lymph nodes of head, face, neck
B610300	Hodgkin's paragranuloma of intra-abdominal lymph nodes
B611.00	Hodgkin's granuloma
B611100	Hodgkin's granuloma of lymph nodes of head, face and neck
B612.00	Hodgkin's sarcoma
B612400	Hodgkin's sarcoma of lymph nodes of axilla and upper limb
B613.00	Hodgkin's disease, lymphocytic-histiocytic predominance
B613000	Hodgkin's, lymphocytic-histiocytic predominance unspec site
B613100	Hodgkin's, lymphocytic-histiocytic pred of head, face, neck
B613200	Hodgkin's, lymphocytic-histiocytic pred intrathoracic nodes
B613300	Hodgkin's, lymphocytic-histiocytic pred intra-abdominal node
B613500	Hodgkin's, lymphocytic-histiocytic pred inguinal and leg
B613600	Hodgkin's, lymphocytic-histiocytic pred intrapelvic nodes
B613700	Hodgkin's, lymphocytic-histiocytic predominance of spleen
B613800	Hodgkin's, lymphocytic-histiocytic pred of multiple sites
B613z00	Hodgkin's, lymphocytic-histiocytic predominance NOS
B614.00	Hodgkin's disease, nodular sclerosis
B614000	Hodgkin's disease, nodular sclerosis of unspecified site
B614100	Hodgkin's nodular sclerosis of head, face and neck
B614200	Hodgkin's nodular sclerosis of intrathoracic lymph nodes

B614300	Hodgkin's nodular sclerosis of intra-abdominal lymph nodes
B614400	Hodgkin's nodular sclerosis of lymph nodes of axilla and arm
B614700	Hodgkin's disease, nodular sclerosis of spleen
B614800	Hodgkin's nodular sclerosis of lymph nodes of multiple sites
B614z00	Hodgkin's disease, nodular sclerosis NOS
B615.00	Hodgkin's disease, mixed cellularity
B615000	Hodgkin's disease, mixed cellularity of unspecified site
B615100	Hodgkin's mixed cellularity of lymph nodes head, face, neck
B615200	Hodgkin's mixed cellularity of intrathoracic lymph nodes
B615500	Hodgkin's mixed cellularity of lymph nodes inguinal and leg
B615z00	Hodgkin's disease, mixed cellularity NOS
B616.00	Hodgkin's disease, lymphocytic depletion
B616000	Hodgkin's lymphocytic depletion of unspecified site
B616100	Hodgkin's lymphocytic depletion of head, face and neck
B616400	Hodgkin's lymphocytic depletion lymph nodes axilla and arm
B616500	Hodgkin's lymphocytic depletion lymph nodes inguinal and leg
B616700	Hodgkin's disease, lymphocytic depletion of spleen
B616800	Hodgkin's lymphocytic depletion lymph nodes multiple sites
B616z00	Hodgkin's disease, lymphocytic depletion NOS
B617.00	Nodular lymphocyte predominant Hodgkin lymphoma
B618.00	Nodular sclerosis classical Hodgkin lymphoma
B619.00	Mixed cellularity classical Hodgkin lymphoma
B61B.00	Lymphocyte-rich classical Hodgkin lymphoma
B61C.00	Other classical Hodgkin lymphoma
B61z.00	Hodgkin's disease NOS
B61z.11	Hodgkin lymphoma NOS
B61z000	Hodgkin's disease NOS, unspecified site
B61z100	Hodgkin's disease NOS of lymph nodes of head, face and neck
B61z200	Hodgkin's disease NOS of intrathoracic lymph nodes
B61z300	Hodgkin's disease NOS of intra-abdominal lymph nodes
B61z400	Hodgkin's disease NOS of lymph nodes of axilla and arm
B61z500	Hodgkin's disease NOS of lymph nodes inguinal region and leg
B61z700	Hodgkin's disease NOS of spleen
B61z800	Hodgkin's disease NOS of lymph nodes of multiple sites
B61zz00	Hodgkin's disease NOS
B62..00	Other malignant neoplasm of lymphoid and histiocytic tissue
B620.00	Nodular lymphoma (Brill - Symmers disease)
B620000	Nodular lymphoma of unspecified site
B620100	Nodular lymphoma of lymph nodes of head, face and neck
B620200	Nodular lymphoma of intrathoracic lymph nodes
B620300	Nodular lymphoma of intra-abdominal lymph nodes
B620400	Nodular lymphoma of lymph nodes of axilla and upper limb
B620500	Nodular lymphoma of lymph nodes of inguinal region and leg
B620800	Nodular lymphoma of lymph nodes of multiple sites
B620z00	Nodular lymphoma NOS

B621.00	Mycosis fungoides
B621000	Mycosis fungoides of unspecified site
B621300	Mycosis fungoides of intra-abdominal lymph nodes
B621400	Mycosis fungoides of lymph nodes of axilla and upper limb
B621500	Mycosis fungoides of lymph nodes of inguinal region and leg
B621800	Mycosis fungoides of lymph nodes of multiple sites
B621z00	Mycosis fungoides NOS
B622.00	Sezary's disease
B622z00	Sezary's disease NOS
B623.00	Malignant histiocytosis
B623000	Malignant histiocytosis of unspecified site
B623100	Malignant histiocytosis of lymph nodes head, face and neck
B623300	Malignant histiocytosis of intra-abdominal lymph nodes
B623z00	Malignant histiocytosis NOS
B624.00	Leukaemic reticuloendotheliosis
B624.11	Leukaemic reticuloendotheliosis
B624.12	Hairy cell leukaemia
B624000	Leukaemic reticuloendotheliosis of unspecified sites
B624300	Leukaemic reticuloend of intra-abdominal lymph nodes
B624z00	Leukaemic reticuloendotheliosis NOS
B625.00	Letterer-Siwe disease
B625.11	Histiocytosis X (acute, progressive)
B625000	Letterer-Siwe disease of unspecified sites
B625200	Letterer-Siwe disease of intrathoracic lymph nodes
B625800	Letterer-Siwe disease of lymph nodes of multiple sites
B625z00	Letterer-Siwe disease NOS
B626.00	Malignant mast cell tumours
B626000	Mast cell malignancy of unspecified site
B626500	Mast cell malignancy of lymph nodes inguinal region and leg
B626800	Mast cell malignancy of lymph nodes of multiple sites
B626z00	Malignant mast cell tumour NOS
B627.00	Non - Hodgkin's lymphoma
B627.11	Non-Hodgkin lymphoma
B627000	Follicular non-Hodgkin's small cleaved cell lymphoma
B627100	Follicular non-Hodg mixed sml cleavd & lge cell lymphoma
B627200	Follicular non-Hodgkin's large cell lymphoma
B627300	Diffuse non-Hodgkin's small cell (diffuse) lymphoma
B627400	Diffuse non-Hodgkin's small cleaved cell (diffuse) lymphoma
B627500	Diffuse non-Hodgkin mixed sml & lge cell (diffuse) lymphoma
B627600	Diffuse non-Hodgkin's immunoblastic (diffuse) lymphoma
B627700	Diffuse non-Hodgkin's lymphoblastic (diffuse) lymphoma
B627800	Diffuse non-Hodgkin's lymphoma undifferentiated (diffuse)
B627900	Mucosa-associated lymphoma
B627911	Maltoma
B627A00	Diffuse non-Hodgkin's large cell lymphoma

B627B00	Other types of follicular non-Hodgkin's lymphoma
B627C00	Follicular non-Hodgkin's lymphoma
B627C11	Follicular lymphoma NOS
B627D00	Diffuse non-Hodgkin's centroblastic lymphoma
B627E00	Diffuse large B-cell lymphoma
B627G00	Mediastinal (thymic) large B-cell lymphoma
B627W00	Unspecified B-cell non-Hodgkin's lymphoma
B627X00	Diffuse non-Hodgkin's lymphoma, unspecified
B628.00	Follicular lymphoma
B628000	Follicular lymphoma grade 1
B628100	Follicular lymphoma grade 2
B628200	Follicular lymphoma grade 3
B628300	Follicular lymphoma grade 3a
B628400	Follicular lymphoma grade 3b
B628500	Diffuse follicle centre lymphoma
B628600	Cutaneous follicle centre lymphoma
B628700	Other types of follicular lymphoma
B62A.00	Sarcoma of dendritic cells
B62D.00	Histiocytic sarcoma
B62E.00	T/NK-cell lymphoma
B62E100	Anaplastic large cell lymphoma, ALK-positive
B62E200	Anaplastic large cell lymphoma, ALK-negative
B62E300	Cutaneous T-cell lymphoma
B62E500	Hepatosplenic T-cell lymphoma
B62E600	Enteropathy-associated T-cell lymphoma
B62E700	Subcutaneous panniculitic T-cell lymphoma
B62E800	Blastic NK-cell lymphoma
B62E900	Angioimmunoblastic T-cell lymphoma
B62Ew00	Other mature T/NK-cell lymphoma
B62F.00	Nonfollicular lymphoma
B62F.11	Non-follicular lymphoma
B62F000	Small cell B-cell lymphoma
B62F100	Mantle cell lymphoma
B62F200	Lymphoblastic (diffuse) lymphoma
B62x.00	Malignant lymphoma otherwise specified
B62x000	T-zone lymphoma
B62x100	Lymphoepithelioid lymphoma
B62x200	Peripheral T-cell lymphoma
B62x400	Malignant reticulosis
B62x500	Malignant immunoproliferative small intestinal disease
B62x600	True histiocytic lymphoma
B62xX00	Oth and unspecif peripheral & cutaneous T-cell lymphomas
B62y.00	Malignant lymphoma NOS
B62y000	Malignant lymphoma NOS of unspecified site
B62y100	Malignant lymphoma NOS of lymph nodes of head, face and neck

B62y200	Malignant lymphoma NOS of intrathoracic lymph nodes
B62y300	Malignant lymphoma NOS of intra-abdominal lymph nodes
B62y400	Malignant lymphoma NOS of lymph nodes of axilla and arm
B62y500	Malignant lymphoma NOS of lymph node inguinal region and leg
B62y600	Malignant lymphoma NOS of intrapelvic lymph nodes
B62y700	Malignant lymphoma NOS of spleen
B62y800	Malignant lymphoma NOS of lymph nodes of multiple sites
B62yz00	Malignant lymphoma NOS
B62z.00	Malignant neoplasms of lymphoid and histiocytic tissue NOS
B62z000	Unspec malig neop lymphoid/histiocytic of unspecified site
B62z100	Unspec malig neop lymphoid/histiocytic lymph node head/neck
B62z200	Unspec malig neop lymphoid/histiocytic of intrathoracic node
B62z300	Unspec malig neop lymphoid/histiocytic intra-abdominal nodes
B62z400	Unspec malig neop lymphoid/histiocytic lymph node axilla/arm
B62z500	Unspec malig neop lymphoid/histiocytic nodes inguinal/leg
B62z800	Unspec malig neop lymphoid/histiocytic of multiple sites
B62zz00	Lymphoid and histiocytic malignancy NOS
B62zz11	Immunoproliferative neoplasm
B63..00	Multiple myeloma and immunoproliferative neoplasms
B630.00	Multiple myeloma
B630.11	Kahler's disease
B630.12	Myelomatosis
B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
B630100	Solitary myeloma
B630200	Plasmacytoma NOS
B630300	Lambda light chain myeloma
B630400	Solitary plasmacytoma
B631.00	Plasma cell leukaemia
B63y.00	Other immunoproliferative neoplasms
B63z.00	Immunoproliferative neoplasm or myeloma NOS
B64..00	Lymphoid leukaemia
B64..11	Lymphatic leukaemia
B640.00	Acute lymphoid leukaemia
B640000	B-cell acute lymphoblastic leukaemia
B641.00	Chronic lymphoid leukaemia
B641.11	Chronic lymphatic leukaemia
B641000	B-cell chronic lymphocytic leukaemia
B641011	Chronic lymphocytic leukaemia of B-cell type
B641100	Clinical stage A chronic lymphocytic leukaemia
B641200	Clinical stage B chronic lymphocytic leukaemia
B641300	Clinical stage C chronic lymphocytic leukaemia
B642.00	Subacute lymphoid leukaemia
B64y.00	Other lymphoid leukaemia
B64y100	Prolymphocytic leukaemia
B64y200	Adult T-cell leukaemia

B64y300	B-cell prolymphocytic leukaemia
B64y400	T-cell prolymphocytic leukaemia
B64y500	Adult T-cell lymphoma/leukaemia (HTLV-1-associated)
B64yz00	Other lymphoid leukaemia NOS
B64z.00	Lymphoid leukaemia NOS
B65..00	Myeloid leukaemia
B650.00	Acute myeloid leukaemia
B651.00	Chronic myeloid leukaemia
B651.11	Chronic granulocytic leukaemia
B651000	Chronic eosinophilic leukaemia
B651100	Chronic myeloid leukaemia, BCR/ABL positive
B651200	Chronic neutrophilic leukaemia
B651300	Atypical chronic myeloid leukaemia, BCR/ABL negative
B651z00	Chronic myeloid leukaemia NOS
B652.00	Subacute myeloid leukaemia
B653.00	Myeloid sarcoma
B653000	Chloroma
B653100	Granulocytic sarcoma
B654.00	Acute myeloblastic leukaemia
B65y100	Acute promyelocytic leukaemia
B65yz00	Other myeloid leukaemia NOS
B65z.00	Myeloid leukaemia NOS
B66..00	Monocytic leukaemia
B66..11	Histiocytic leukaemia
B66..12	Monoblastic leukaemia
B660.00	Acute monocytic leukaemia
B661.00	Chronic monocytic leukaemia
B662.00	Subacute monocytic leukaemia
B663.00	Acute monoblastic leukaemia
B66y.00	Other monocytic leukaemia
B66yz00	Other monocytic leukaemia NOS
B66z.00	Monocytic leukaemia NOS
B67..00	Other specified leukaemia
B670.00	Acute erythraemia and erythroleukaemia
B670.11	Di Guglielmo's disease
B671.11	Heilmeyer - Schoner disease
B672.00	Megakaryocytic leukaemia
B672.11	Thrombocytic leukaemia
B673.00	Mast cell leukaemia
B674.00	Acute panmyelosis
B675.00	Acute myelofibrosis
B677.00	Myelodysplastic and myeloproliferative disease
B67y.00	Other and unspecified leukaemia
B67y000	Lymphosarcoma cell leukaemia
B67yz00	Other and unspecified leukaemia NOS

B67z.00	Other specified leukaemia NOS
B68..00	Leukaemia of unspecified cell type
B680.00	Acute leukaemia NOS
B681.00	Chronic leukaemia NOS
B682.00	Subacute leukaemia NOS
B68y.00	Other leukaemia of unspecified cell type
B68z.00	Leukaemia NOS
B69..00	Myelomonocytic leukaemia
B690.00	Acute myelomonocytic leukaemia
B691.00	Chronic myelomonocytic leukaemia
B692.00	Subacute myelomonocytic leukaemia
B693.00	Juvenile myelomonocytic leukaemia
B6y..00	Malignant neoplasm lymphatic or haematopoietic tissue OS
B6y0.00	Myeloproliferative disorder
B6y0.11	Myeloproliferative disease
B6y1.00	Myelosclerosis with myeloid metaplasia
B6z..00	Malignant neoplasm lymphatic or haematopoietic tissue NOS
B6z0.00	Kaposi's sarcoma of lymph nodes
B702300	Warthin's tumour
B717011	Endocrine tumour of pancreas
B7C2000	Adenoma of prostate
B7F1000	Acoustic neuroma
B7F2000	Cerebral meningioma
B7F4000	Spinal meningioma
B8...00	Carcinoma in situ
B80..00	Carcinoma in situ of digestive organs
B800.00	Carcinoma in situ of lip, oral cavity and pharynx
B800.11	Carcinoma in situ of oral cavity
B800.12	Carcinoma in situ of pharynx
B800000	Carcinoma in situ of lip
B800100	Carcinoma in situ of tongue
B800200	Carcinoma in situ of salivary glands
B800300	Carcinoma in situ of gums
B800400	Carcinoma in situ of floor of mouth
B800500	Carcinoma in situ of cheek
B800600	Carcinoma in situ of palate
B800700	Carcinoma in situ of nasopharynx
B800800	Carcinoma in situ of oropharynx
B800900	Carcinoma in situ of hypopharynx
B800z00	Carcinoma in situ of lip, oral cavity and pharynx NOS
B801.00	Carcinoma in situ of oesophagus
B801000	Carcinoma in situ of upper 1/3 oesophagus
B801100	Carcinoma in situ of middle 1/3 oesophagus
B801200	Carcinoma in situ of lower 1/3 oesophagus
B801z00	Carcinoma in situ of oesophagus NOS

B802.00	Carcinoma in situ of stomach
B802000	Carcinoma in situ of cardia of stomach
B802100	Carcinoma in situ of fundus of stomach
B802200	Carcinoma in situ of body of stomach
B802300	Carcinoma in situ of pyloric antrum
B802400	Carcinoma in situ of pyloric canal
B802z00	Carcinoma in situ of stomach NOS
B803.00	Carcinoma in situ of colon
B803000	Carcinoma in situ of hepatic flexure of colon
B803100	Carcinoma in situ of transverse colon
B803200	Carcinoma in situ of descending colon
B803300	Carcinoma in situ of sigmoid colon
B803400	Carcinoma in situ of caecum
B803500	Carcinoma in situ of appendix
B803600	Carcinoma in situ of ascending colon
B803700	Carcinoma in situ of splenic flexure of colon
B803800	High grade dysplasia of colon
B803z00	Carcinoma in situ of colon NOS
B804.00	Carcinoma in situ of rectum and rectosigmoid junction
B804000	Carcinoma in situ of rectosigmoid junction
B804100	Carcinoma in situ of rectum
B804z00	Carcinoma in situ of rectum or rectosigmoid junction NOS
B805.00	Carcinoma in situ of anal canal
B806.00	Carcinoma in situ of anus NOS
B807.00	Carcinoma in situ of other and unspecified small intestine
B807000	Carcinoma in situ of duodenum
B807100	Carcinoma in situ of jejunum
B807200	Carcinoma in situ of ileum
B807300	Carcinoma in situ of Meckel's diverticulum
B807z00	Carcinoma in situ other and unspecified small intestine NOS
B808.00	Carcinoma in situ of liver and biliary system
B808.11	Carcinoma in situ of biliary system
B808000	Carcinoma in situ of liver
B808100	Carcinoma in situ of intrahepatic bile ducts
B808200	Carcinoma in situ of hepatic duct
B808300	Carcinoma in situ of gall bladder
B808400	Carcinoma in situ of cystic duct
B808500	Carcinoma in situ of common bile duct
B808600	Carcinoma in situ of ampulla of Vater
B808z00	Carcinoma in situ of liver or biliary system NOS
B80z.00	Carcinoma in situ of other and unspecified digestive organs
B80z000	Carcinoma in situ of pancreas
B80z100	Carcinoma in situ of spleen
B81..00	Carcinoma in situ of respiratory system
B810.00	Carcinoma in situ of larynx

B810000	Carcinoma in situ of thyroid cartilage
B810100	Carcinoma in situ of cricoid cartilage
B810200	Carcinoma in situ of epiglottis
B810300	Carcinoma in situ of arytenoid cartilage
B810600	Carcinoma in situ of aryepiglottic fold
B810700	Carcinoma in situ of vestibular fold
B810800	Carcinoma in situ of vocal fold - glottis
B810811	Carcinoma in situ of glottis
B810z00	Carcinoma in situ of larynx NOS
B811.00	Carcinoma in situ of trachea
B812.00	Carcinoma in situ of bronchus and lung
B812000	Carcinoma in situ of carina of bronchus
B812100	Carcinoma in situ of main bronchus
B812200	Carcinoma in situ of upper lobe bronchus and lung
B812300	Carcinoma in situ of middle lobe bronchus and lung
B812400	Carcinoma in situ of lower lobe bronchus and lung
B812z00	Carcinoma in situ of bronchus or lung NOS
B81y.00	Carcinoma in situ of other specified part respiratory system
B81y.11	Carcinoma in situ of nasal sinuses
B81y000	Carcinoma in situ of pleura
B81y100	Carcinoma in situ of nasal cavity
B81y400	Carcinoma in situ of Eustachian tube
B81y500	Carcinoma in situ of mastoid air cells
B81y600	Carcinoma in situ of maxillary sinus
B81y700	Carcinoma in situ of ethmoidal sinus
B81y900	Carcinoma in situ of sphenoidal sinus
B81yz00	Carcinoma in situ of specified parts respiratory system NOS
B81z.00	Carcinoma in situ of respiratory organ NOS
B82..00	Carcinoma in situ of skin
B820.00	Carcinoma in situ of skin of lip
B821.00	Carcinoma in situ of skin of eyelid including canthus
B822.00	Carcinoma in situ skin of ear and external auricular canal
B822.11	Carcinoma in situ of ear
B822000	Carcinoma in situ of skin of auricle
B822z00	Carcinoma in situ skin of ear/external auricular canal NOS
B823.00	Carcinoma in situ of skin of other parts of face
B823000	Carcinoma in situ of skin of forehead skin
B823100	Carcinoma in situ of skin of eyebrow
B823300	Carcinoma in situ of skin of cheek
B823400	Carcinoma in situ of skin of nose
B823500	Carcinoma in situ of skin of temple
B823600	Carcinoma in situ of skin of jaw
B824.00	Carcinoma in situ of scalp and skin of neck
B824000	Carcinoma in situ of scalp
B824100	Carcinoma in situ of skin of neck

B825.00	Carcinoma in situ of skin of trunk, excluding scrotum
B825000	Carcinoma in situ of skin of breast
B825100	Carcinoma in situ of skin of chest wall NOS
B825200	Carcinoma in situ of skin of axilla
B825300	Carcinoma in situ of skin of back
B825400	Carcinoma in situ of skin of abdominal wall
B825500	Carcinoma in situ of skin of groin
B825600	Carcinoma in situ of skin of perineum
B825700	Carcinoma in situ of skin of buttock
B825800	Carcinoma in situ of perianal skin
B825z00	Carcinoma in situ of skin of trunk NOS
B826.00	Carcinoma in situ of skin of upper limb and shoulder
B826000	Carcinoma in situ of skin of shoulder
B826100	Carcinoma in situ of skin of upper arm
B826200	Carcinoma in situ of skin of lower arm
B826300	Carcinoma in situ of skin of hand
B826z00	Carcinoma in situ of skin of upper limb or shoulder NOS
B827.00	Carcinoma in situ of skin of lower limb and hip
B827.11	Carcinoma in situ of skin of leg
B827000	Carcinoma in situ of skin of hip
B827100	Carcinoma in situ of skin of thigh
B827200	Carcinoma in situ of skin of knee
B827300	Carcinoma in situ of skin of lower leg
B827400	Carcinoma in situ of skin of foot
B827z00	Carcinoma in situ of skin of lower limb or hip NOS
B82y.00	Carcinoma in situ of other specified sites of skin
B82z.00	Carcinoma in situ of skin NOS
B83..00	Carcinoma in situ of breast and genitourinary system
B830.00	Carcinoma in situ of breast
B830000	Lobular carcinoma in situ of breast
B830100	Intraductal carcinoma in situ of breast
B831.00	Carcinoma in situ of cervix uteri
B831.11	CIN III - carcinoma in situ of cervix
B831000	Carcinoma in situ of endocervix
B831100	Carcinoma in situ of exocervix
B832.00	Carcinoma in situ of other and unspecified parts of uterus
B832.11	Carcinoma in situ of body of uterus
B832000	Carcinoma in situ of endometrium
B833.00	Carcinoma in situ other and unspecified female genital organ
B833000	Carcinoma in situ of ovary
B833100	Carcinoma in situ of fallopian tube
B833200	Carcinoma in situ of vagina
B833300	Carcinoma in situ of vulva
B833z00	Carcinoma in situ of female genital organs NOS
B834.00	Carcinoma in situ of prostate

B834000	High grade prostatic intraepithelial neoplasia
B834100	Prostatic intraepithelial neoplasia
B835.00	Carcinoma in situ of penis
B836.00	Carcinoma in situ other and unspecified male genital organs
B836000	Carcinoma in situ of testis
B836300	Carcinoma in situ of scrotum
B837.00	Carcinoma in situ of bladder
B83z.00	Carcinoma in situ of urinary organs NOS
B8y..00	Carcinoma in situ of other and unspecified sites
B8y0.00	Carcinoma in situ of eye
B8yy.00	Carcinoma in situ of other specified site
B8yy000	Carcinoma in situ of thyroid gland
B8yy100	Carcinoma in situ of adrenal gland
B8yy200	Carcinoma in situ of parathyroid gland
B8yy300	Carcinoma in situ of pituitary gland
B8yyz00	Carcinoma in situ of other specified site NOS
B8z..00	Carcinoma in situ NOS
B9...00	Neoplasms of uncertain behaviour
B900011	Mixed parotid tumour
B902000	Neoplasm of uncertain behaviour of stomach
B902400	Neoplasm of uncertain behaviour of colon
B902500	Neoplasm of uncertain behaviour of rectum
B902z00	Neop of uncertain behaviour stomach, intestine or rectum NOS
B905400	Gastrointestinal stromal tumour
B911013	Choriocarcinoma
B911100	Epithelioid trophoblastic tumour
B915.00	Neoplasm of uncertain behaviour of prostate
B91z111	Renal neoplasm of uncertain behaviour
B91z200	Uncertain neoplasm ureter
B91zz00	Uncertain neoplasm of urinary organ NOS
B933.00	Neoplasm of uncertain behaviour of breast
B933.11	Cystosarcoma phyllodes
B935.11	Histiocytic tumour NOS
B936.11	Myeloma - solitary
B936.12	Plasmacytoma NOS
BA...00	Unspecified nature neoplasm
BA03.00	Neoplasm of unspecified nature of breast
BA04.00	Neoplasm of unspecified nature of bladder
BB...00	[M]Morphology of neoplasms
BB...11	[M]Tumour morphology
BB0..00	[M]Neoplasms NOS
BB02.00	[M]Neoplasm, malignant
BB03.00	[M]Neoplasm, metastatic
BB03.11	[M]Secondary neoplasm
BB03.12	[M]Tumour embolus

BB03.13	[M]Tumour embolism
BB04.00	[M]Neoplasm, malig, uncertain whether primary or metastatic
BB07.00	[M]Tumour cells, malignant
BB08.00	[M]Malignant tumour, small cell type
BB09.00	[M]Malignant tumour, giant cell type
BB0A.00	[M]Malignant tumour, fusiform cell type
BB0z.00	[M]Unspecified tumour cell NOS
BB1..00	[M]Epithelial neoplasms NOS
BB10.00	[M]Epithelial tumour, benign
BB11.00	[M]Carcinoma in situ NOS
BB11.11	[M]Intraepithelial carcinoma NOS
BB12.00	[M]Carcinoma NOS
BB13.00	[M]Carcinoma, metastatic, NOS
BB13.11	[M]Secondary carcinoma
BB14.00	[M]Carcinomatosis
BB16.00	[M]Epithelioma, malignant
BB17.00	[M]Large cell carcinoma NOS
BB18.00	[M]Carcinoma, undifferentiated type, NOS
BB19.00	[M]Carcinoma, anaplastic type, NOS
BB1A.00	[M]Pleomorphic carcinoma
BB1B.00	[M]Giant cell and spindle cell carcinoma
BB1C.00	[M]Giant cell carcinoma
BB1D.00	[M]Spindle cell carcinoma
BB1E.00	[M]Pseudosarcomatous carcinoma
BB1F.00	[M]Polygonal cell carcinoma
BB1G.00	[M]Spheroidal cell carcinoma
BB1H.00	[M]Tumourlet
BB1J.00	[M]Small cell carcinoma NOS
BB1J.12	[M]Round cell carcinoma
BB1K.00	[M]Oat cell carcinoma
BB1L.00	[M]Small cell carcinoma, fusiform cell type
BB1M.00	[M]Small cell carcinoma, intermediate cell
BB1N.00	[M]Small cell-large cell carcinoma
BB1P.00	[M]Non-small cell carcinoma
BB1z.00	[M]Unspecified epithelial neoplasm
BB2..00	[M]Papillary and squamous cell neoplasms
BB2..11	[M]Papillary neoplasms
BB2..12	[M]Squamous cell neoplasms
BB21.00	[M]Papillary carcinoma in situ
BB22.00	[M]Papillary carcinoma NOS
BB24.00	[M]Verrucous carcinoma NOS
BB24.11	[M]Verrucous epidermoid carcinoma
BB24.12	[M]Verrucous squamous cell carcinoma
BB26.00	[M]Papillary squamous cell carcinoma
BB26.11	[M]Papillary epidermoid carcinoma

BB29.00	[M]Squamous cell carcinoma in situ NOS
BB29.11	[M]Epidermoid carcinoma in situ
BB29.12	[M]Intraepidermal carcinoma NOS
BB29.13	[M]Intraepithelial squamous cell carcinoma
BB2A.00	[M]Squamous cell carcinoma NOS
BB2A.11	[M]Epidermoid carcinoma NOS
BB2A.12	[M]Spinous cell carcinoma
BB2A.13	[M]Squamous cell carcinoma of skin NOS
BB2B.00	[M]Squamous cell carcinoma, metastatic NOS
BB2C.00	[M]Squamous cell carcinoma, keratinising type NOS
BB2C.11	[M]Epidermoid carcinoma, keratinising type
BB2D.00	[M]Squamous cell carcinoma, large cell, non-keratinising
BB2E.00	[M]Squamous cell carcinoma, small cell, non-keratinising
BB2F.00	[M]Squamous cell carcinoma, spindle cell type
BB2G.00	[M]Adenoid squamous cell carcinoma
BB2J.00	[M]Squamous cell carcinoma, microinvasive
BB2M.00	[M]Lymphoepithelial carcinoma
BB2N.00	[M]Intraepit neop,grade III,of cervix, vulva and vagina
BB2z.00	[M]Papillary or squamous cell neoplasm NOS
BB3..00	[M]Basal cell neoplasms
BB30.00	[M]Basal cell tumour
BB31.00	[M]Basal cell carcinoma NOS
BB32.00	[M]Multicentric basal cell carcinoma
BB33.00	[M]Basal cell carcinoma, morphoea type
BB34.00	[M]Basal cell carcinoma, fibroepithelial type
BB35.00	[M]Basosquamous carcinoma
BB36.00	[M]Metatypical carcinoma
BB37.00	[M]Intraepidermal epithelioma of Jadassohn
BB38.00	[M]Trichoepithelioma
BB38.12	[M]Epithelioma adenoides cyst
BB3B.11	[M]Malherbe's calcified epithelioma
BB3C.00	[M]Superficial basal cell carcinoma
BB3D.00	[M]Basal cell carcinoma, nodular
BB3E.00	[M]Basal cell carcinoma, micronodular
BB3F.00	[M]Basal cell carcinoma, infiltrative
BB3G.00	[M]Pigmented basal cell carcinoma
BB3z.00	[M]Basal cell neoplasm NOS
BB4..00	[M]Transitional cell papillomas and carcinomas
BB42.00	[M]Transitional cell carcinoma in situ
BB43.00	[M]Transitional cell carcinoma NOS
BB43.11	[M]Urothelial carcinoma
BB46.00	[M]Schneiderian carcinoma
BB47.00	[M]Transitional cell carcinoma, spindle cell type
BB48.00	[M]Basaloid carcinoma
BB49.00	[M]Cloacogenic carcinoma

BB4A.00	[M]Papillary transitional cell carcinoma
BB4z.00	[M]Transitional cell papilloma or carcinoma NOS
BB5..00	[M]Adenomas and adenocarcinomas
BB5..11	[M]Adenocarcinomas
BB51.00	[M]Adenocarcinoma in situ
BB51000	[M]Adenocarcinoma in situ in villous adenoma
BB51100	[M]Adenocarcinoma in situ in tubulovillous adenoma
BB52.00	[M]Adenocarcinoma NOS
BB52000	[M]Adenocarcinoma in tubulovillous adenoma
BB53.00	[M]Adenocarcinoma, metastatic, NOS
BB54.00	[M]Scirrhous adenocarcinoma
BB55.00	[M]Linitis plastica
BB56.00	[M]Superficial spreading adenocarcinoma
BB57.00	[M]Adenocarcinoma, intestinal type
BB58.00	[M]Carcinoma, diffuse type
BB5a.00	[M]Renal adenoma and carcinoma
BB5a000	[M]Renal cell carcinoma
BB5a011	[M]Grawitz tumour
BB5a012	[M]Hypernephroma
BB5az00	[M]Renal adenoma or carcinoma NOS
BB5b.00	[M]Granular cell carcinoma
BB5B.00	[M]Pancreatic adenomas and carcinomas
BB5B011	[M]Nesidioblastoma
BB5B100	[M]Islet cell carcinoma
BB5B200	[M]Insulinoma NOS
BB5B300	[M]Insulinoma, malignant
BB5B400	[M]Glucagonoma NOS
BB5B500	[M]Glucagonoma, malignant
BB5B600	[M]Mixed islet cell and exocrine adenocarcinoma
BB5Bz00	[M]Pancreatic adenoma or carcinoma NOS
BB5c.00	[M]Parathyroid adenomas and adenocarcinomas
BB5C.00	[M]Gastrinoma and carcinomas
BB5C000	[M]Gastrinoma NOS
BB5C011	[M]G cell tumour NOS
BB5C100	[M]Gastrinoma, malignant
BB5cz00	[M]Parathyroid adenoma or adenocarcinoma NOS
BB5Cz00	[M]Gastrinoma or carcinoma NOS
BB5D.00	[M]Hepatobiliary tract adenomas and carcinomas
BB5D.11	[M]Biliary tract adenomas and adenocarcinomas
BB5D100	[M]Cholangiocarcinoma
BB5D111	[M]Bile duct carcinoma
BB5D300	[M]Bile duct cystadenocarcinoma
BB5D500	[M]Hepatocellular carcinoma NOS
BB5D513	[M]Liver cell carcinoma
BB5D700	[M]Combined hepatocellular carcinoma and cholangiocarcinoma

BB5D800	[M]Hepatocellular carcinoma, fibrolamellar
BB5Dz00	[M]Hepatobiliary adenoma or carcinoma NOS
BB5f.00	[M]Thyroid adenoma and adenocarcinoma
BB5F.00	[M]Trabecular adenocarcinoma
BB5f100	[M]Follicular adenocarcinoma NOS
BB5f111	[M]Follicular carcinoma
BB5f200	[M]Follicular adenocarcinoma, well differentiated type
BB5f300	[M]Follicular adenocarcinoma, trabecular type
BB5f600	[M]Papillary and follicular adenocarcinoma
BB5f700	[M]Nonencapsulated sclerosing carcinoma
BB5fz00	[M]Thyroid adenoma or adenocarcinoma NOS
BB5h.00	[M]Adrenal cortical tumours
BB5H.11	[M]Turban tumour
BB5h100	[M]Adrenal cortical carcinoma
BB5hz00	[M]Adrenal cortical tumours NOS
BB5j.00	[M]Endometrioid adenomas and carcinomas
BB5J.00	[M]Adenoid cystic carcinoma
BB5J.11	[M]Cylindroid adenocarcinoma
BB5j200	[M]Endometrioid carcinoma
BB5jz00	[M]Endometrioid adenoma or carcinoma NOS
BB5K.00	[M]Cribriform carcinoma
BB5L.00	[M]Adenomatous and adenocarcinomatous polyps
BB5L100	[M]Adenocarcinoma in adenomatous polyp
BB5L200	[M]Adenocarcinoma in situ in adenomatous polyp
BB5L300	[M]Adenocarcinoma in multiple adenomatous polyps
BB5Lz00	[M]Adenomatous or adenocarcinomatous polyp NOS
BB5M.00	[M]Tubular adenomas and adenocarcinomas
BB5M100	[M]Tubular adenocarcinoma
BB5Mz00	[M]Tubular adenoma or adenocarcinoma NOS
BB5N.00	[M]Adenomatous and adenocarcinomatous polyps of colon
BB5N.11	[M]Adenoma or or adenocarcinoma in polyposis coli
BB5N100	[M]Adenocarcinoma in adenomatous polposis coli
BB5Nz00	[M]Adenomatous or adenocarcinomatous polyps of the colon NOS
BB5P.00	[M]Solid carcinoma NOS
BB5R.00	[M]Carcinoid tumours
BB5R000	[M]Carcinoid tumour NOS
BB5R100	[M]Carcinoid tumour, malignant
BB5R200	[M]Carcinoid tumour, argentaffin, NOS
BB5R400	[M]Carcinoid tumour, nonargentaffin, NOS
BB5R500	[M]Carcinoid tumour, nonargentaffin, malignant
BB5R600	[M]Mucocarcinoid tumour, malignant
BB5R611	[M]Goblet cell tumour
BB5R800	[M]Adenocarcinoid tumour
BB5R900	[M]Neuroendocrine carcinoma
BB5RA00	[M]Merkel cell carcinoma

BB5Rz00	[M]Carcinoid tumours NOS
BB5S.00	[M]Respiratory tract adenomas and adenocarcinomas
BB5S200	[M]Bronchiolo-alveolar adenocarcinoma
BB5S211	[M]Alveolar cell carcinoma
BB5S212	[M]Bronchiolar carcinoma
BB5S400	[M]Alveolar adenocarcinoma
BB5Sz00	[M]Respiratory tract adenoma or adenocarcinoma NOS
BB5T.00	[M]Papillary adenomas and adenocarcinomas
BB5T100	[M]Papillary adenocarcinoma NOS
BB5Tz00	[M]Papillary adenoma or adenocarcinoma NOS
BB5U.00	[M]Villous adenomas and adenocarcinomas
BB5U100	[M]Adenocarcinoma in villous adenoma
BB5U200	[M]Villous adenocarcinoma
BB5Uz00	[M]Villous adenoma or adenocarcinoma NOS
BB5V.00	[M]Pituitary adenomas and carcinomas
BB5V100	[M]Chromophobe carcinoma
BB5V311	[M]Eosinophil carcinoma
BB5V700	[M]Basophil carcinoma
BB5V711	[M]Mucoid cell carcinoma
BB5Vz00	[M]Pituitary adenoma or carcinoma NOS
BB5W.00	[M]Oxyphilic adenomas and adenocarcinomas
BB5W100	[M]Oxyphilic adenocarcinoma
BB5W111	[M]Hurthle cell adenocarcinoma
BB5W112	[M]Oncytic adenocarcinoma
BB5Wz00	[M]Oxyphilic adenoma or adenocarcinoma NOS
BB5X.00	[M]Clear cell adenomas and adenocarcinomas
BB5X100	[M]Clear cell adenocarcinoma NOS
BB5Xz00	[M]Clear cell adenoma or adenocarcinoma NOS
BB5Y.00	[M]Hypernephroid tumour
BB5y000	[M]Basal cell adenocarcinoma
BB5y200	[M]Klatskin's tumour
BB5y300	[M]Apudoma
BB5z.00	[M]Adenoma or adenocarcinoma NOS
BB6..00	[M]Adnexal and skin appendage neoplasms
BB60.00	[M]Skin appendage adenoma and carcinoma
BB60100	[M]Skin appendage carcinoma
BB61.00	[M]Sweat gland adenoma and adenocarcinomas
BB61100	[M]Sweat gland tumour NOS
BB61200	[M]Sweat gland adenocarcinoma
BB62.00	[M]Apocrine adenoma and adenocarcinomas
BB62100	[M]Apocrine adenocarcinoma
BB62z00	[M]Apocrine adenoma or adenocarcinoma NOS
BB69.00	[M]Sebaceous adenoma and adenocarcinoma
BB69100	[M]Sebaceous adenocarcinoma
BB69z00	[M]Sebaceous adenoma or adenocarcinoma NOS

BB6A.00	[M]Ceruminous adenoma and adenocarcinoma
BB6z.00	[M]Adnexal and skin appendage neoplasm NOS
BB7..00	[M]Mucoepidermoid neoplasms
BB70.00	[M]Mucoepidermoid tumour
BB71.00	[M]Mucoepidermoid carcinoma
BB7z.00	[M]Mucoepidermoid neoplasm NOS
BB8..00	[M]Cystic, mucinous and serous neoplasms
BB80.00	[M]Cystadenoma and carcinoma
BB80100	[M]Cystadenocarcinoma NOS
BB80z00	[M]Cystadenoma or carcinoma NOS
BB81.00	[M]Ovarian cystic, mucinous and serous neoplasms
BB81.11	[M]Ovarian cystadenoma or carcinoma
BB81.12	[M]Ovarian mucinous tumour
BB81.13	[M]Ovarian papillary tumour
BB81.14	[M]Ovarian serous tumour
BB81200	[M]Serous cystadenocarcinoma, NOS
BB81500	[M]Papillary cystadenocarcinoma, NOS
BB81800	[M]Papillary serous cystadenocarcinoma
BB81B00	[M]Serous surface papillary carcinoma
BB81E00	[M]Mucinous cystadenocarcinoma NOS
BB81E11	[M]Pseudomucinous adenocarcinoma
BB81H00	[M]Papillary mucinous cystadenocarcinoma
BB81L00	[M]Papillary cystic tumour
BB81z00	[M]Ovarian cystic, mucinous or serous neoplasm NOS
BB82.00	[M]Mucinous adenoma and adenocarcinoma
BB82100	[M]Mucinous adenocarcinoma
BB82111	[M]Colloid adenocarcinoma
BB82112	[M]Gelatinous adenocarcinoma
BB82114	[M]Mucous adenocarcinoma
BB82z00	[M]Mucinous adenoma or adenocarcinoma NOS
BB84.00	[M]Mucin-producing adenocarcinoma
BB85.00	[M]Signet ring carcinoma
BB85000	[M]Signet ring cell carcinoma
BB85100	[M]Metastatic signet ring cell carcinoma
BB85111	[M]Krukenberg tumour
BB85z00	[M]Signet ring carcinoma NOS
BB8z.00	[M]Cystic, mucinous or serous neoplasm NOS
BB9..00	[M]Ductal, lobular and medullary neoplasms
BB90.00	[M]Intraductal carcinoma, noninfiltrating NOS
BB91.00	[M]Infiltrating duct carcinoma
BB91.11	[M]Duct carcinoma NOS
BB91000	[M]Intraductal papillary adenocarcinoma with invasion
BB91100	[M]Infiltrating duct and lobular carcinoma
BB92.00	[M]Comedocarcinoma, noninfiltrating
BB93.00	[M]Comedocarcinoma NOS

BB94.00	[M]Juvenile breast carcinoma
BB94.11	[M]Secretory breast carcinoma
BB96.00	[M]Noninfiltrating intraductal papillary adenocarcinoma
BB9B.00	[M]Medullary carcinoma NOS
BB9B.11	[M]C cell carcinoma
BB9C.00	[M]Medullary carcinoma with amyloid stroma
BB9D.00	[M]Medullary carcinoma with lymphoid stroma
BB9E.00	[M]Lobular carcinoma in situ
BB9E000	[M]Intraductal carcinoma and lobular carcinoma in situ
BB9F.00	[M]Lobular carcinoma NOS
BB9G.00	[M]Infiltrating ductular carcinoma
BB9H.00	[M]Inflammatory carcinoma
BB9K.00	[M]Paget's disease and infiltrating breast duct carcinoma
BB9K000	[M]Paget's disease and intraductal carcinoma of breast
BB9M.00	[M]Intracystic carcinoma NOS
BB9z.00	[M]Ductal, lobular or medullary neoplasm NOS
BBa..00	[M]Miscellaneous tumours
BBA..00	[M]Acinar cell neoplasms
BBa0.11	[M]Rathke's pouch tumour
BBA1.00	[M]Acinar cell tumour
BBA2.00	[M]Acinar cell carcinoma
BBa4.00	[M]Melanotic neuroectodermal tumour
BBa4.13	[M]Retinal angle tumour
BBaz.00	[M]Miscellaneous tumour NOS
BBAz.00	[M]Acinar cell neoplasm NOS
BBB..00	[M]Complex epithelial neoplasms
BBB0.00	[M]Adenosquamous carcinoma
BBb0.11	[M]Glioma NOS
BBb0.12	[M]Gliosarcoma
BBB1.00	[M]Adenolymphoma
BBB1.11	[M]Warthin's tumour
BBB2.00	[M]Adenocarcinoma with squamous metaplasia
BBB3.00	[M]Adenocarcinoma with cartilaginous and osseous metaplasia
BBB4.00	[M]Adenocarcinoma with spindle cell metaplasia
BBB5.00	[M]Adenocarcinoma with apocrine metaplasia
BBB7.00	[M]Epithelial-myoepithelial carcinoma
BBba.00	[M]Primitive neuroectodermal tumour
BBba000	[M]Peripheral neuroectodermal tumour
BBbW.00	[M]Cerebellar sarcoma NOS
BBBz.00	[M]Complex epithelial neoplasm NOS
BBc..00	[M]Neuroepitheliomatous neoplasms
BBC..00	[M]Specialised gonadal neoplasms
BBc0.00	[M]Ganglioneuromatous neoplasms
BBC0.00	[M]Sex cord-stromal tumour
BBC0.11	[M]Gonadal stromal tumour

BBC0.12	[M]Ovarian stromal tumour
BBC0.13	[M]Testicular stromal tumour
BBC0000	[M]Sex cord tumour with annular tubules
BBC1.00	[M]Thecal cell neoplasms
BBc2.00	[M]Medulloepithelioma NOS
BBc3.00	[M]Teratoid medulloepithelioma
BBC3.00	[M]Granulosa cell tumour NOS
BBC3000	[M]Juvenile granulosa cell tumour
BBc4.00	[M]Neuroepithelioma NOS
BBC4.00	[M]Granulosa cell tumour, malignant
BBC5.00	[M]Granulosa cell-theca cell tumour
BBC7.00	[M]Sertoli-Leydig cell tumour
BBc8.00	[M]Pacinian tumour
BBC9.13	[M]Sertoli cell tumour
BBcA.00	[M]Olfactory neurogenic tumour
BBCA.00	[M]Sertoli cell carcinoma
BBCC.00	[M]Leydig cell tumour
BBcC.11	[M]Olfactory neuroblastoma
BBCC000	[M]Leydig cell tumour, benign
BBCC011	[M]Interstitial cell tumour, benign
BBCC100	[M]Leydig cell tumour, malignant
BBCCz00	[M]Leydig cell tumour NOS
BBCCz11	[M]Interstitial cell tumour NOS
BBCD.00	[M]Hilar cell tumour
BBcD.11	[M]Olfactory neuroepithelioma
BBCE.00	[M]Lipid cell tumour of ovary
BBCF.00	[M]Adrenal rest tumour
BBCG.00	[M]Sclerosing stromal tumour
BBcz.00	[M]Neuroepitheliomatous neoplasm NOS
BBD..00	[M]Paragangliomas and glomus tumours
BBD1.00	[M]Paraganglioma, malignant
BBd2.11	[M]Leptomeningeal sarcoma
BBd2.12	[M]Meningothelial sarcoma
BBD4.00	[M]Glomus jugulare tumour
BBD5.00	[M]Aortic body tumour
BBD6.00	[M]Carotid body tumour
BBdB.00	[M]Meningeal sarcomatosis
BBDB.00	[M]Glomangiosarcoma
BBDB.11	[M]Glomoid sarcoma
BBDC.00	[M]Glomus tumour
BBDz.00	[M]Paraganglioma or glomus tumour NOS
BBe..00	[M]Nerve sheath tumour
BBE1.00	[M]Malignant melanoma NOS
BBE1.11	[M]Melanocarcinoma
BBE1.12	[M]Melanoma NOS

BBE1.13	[M]Melanosarcoma NOS
BBE1.14	[M]Naevocarcinoma
BBE1000	[M]Malignant melanoma, regressing
BBE1100	[M]Desmoplastic melanoma, malignant
BBe2.00	[M]Neurofibrosarcoma
BBE4.00	[M]Balloon cell melanoma
BBe9.00	[M]Triton tumour, malignant
BBEA.00	[M]Amelanotic melanoma
BBEC.00	[M]Malignant melanoma in junctional naevus
BBED.00	[M]Precancerous melanosis NOS
BBEG.00	[M]Malignant melanoma in Hutchinson's melanotic freckle
BBEG.11	[M]Lentigo maligna melanoma
BBEG000	[M]Acral lentiginous melanoma, malignant
BBEH.00	[M]Superficial spreading melanoma
BBEM.00	[M]Malignant melanoma in giant pigmented naevus
BBEN.11	[M]Juvenila melanoma
BBEP.00	[M]Epithelioid cell melanoma
BBEQ.00	[M]Spindle cell melanoma NOS
BBES.00	[M]Spindle cell melanoma, type B
BBET.00	[M]Mixed epithelioid and spindle melanoma
BBez.00	[M]Nerve sheath tumour NOS
BBf..00	[M]Granular cell tumours and alveolar soft part sarcoma
BBF..00	[M]Soft tissue tumours and sarcomas NOS
BBf0.00	[M]Granular cell tumour NOS
BBF0.00	[M]Soft tissue tumour, benign
BBF1.00	[M]Sarcoma NOS
BBf2.00	[M]Alveolar soft part sarcoma
BBF2.00	[M]Sarcomatosis NOS
BBF3.00	[M]Spindle cell sarcoma
BBF4.00	[M]Giant cell sarcoma (except of bone)
BBF4.11	[M]Pleomorphic cell sarcoma
BBF5.00	[M]Small cell sarcoma
BBF5.11	[M]Round cell sarcoma
BBF6.00	[M]Epithelioid cell sarcoma
BBFz.00	[M]Soft tissue tumour or sarcoma NOS
BBg..00	[M]Lymphomas, NOS or diffuse
BBG..00	[M]Fibromatous neoplasms
BBg0.00	[M]Lymphomatous tumour, benign
BBg1.00	[M]Malignant lymphoma NOS
BBG1.00	[M]Fibrosarcoma NOS
BBg1.11	[M]Lymphoma NOS
BBg1000	[M]Malignant lymphoma, diffuse NOS
BBg2.00	[M]Malignant lymphoma, non Hodgkin's type
BBg2.11	[M]Non Hodgkins lymphoma
BBg3.00	[M]Malignant lymphoma, undifferentiated cell type NOS

BBG3.00	[M]Fibromyxosarcoma
BBg4.00	[M]Malignant lymphoma, stem cell type
BBg5.00	[M]Malignant lymphoma, convoluted cell type NOS
BBg6.00	[M]Lymphosarcoma NOS
BBg7.00	[M]Malignant lymphoma, lymphoplasmacytoid type
BBg8.00	[M]Malignant lymphoma, immunoblastic type
BBG9.00	[M]Elastofibroma
BBgA.00	[M]Malignant lymphoma, centroblastic-centrocytic, diffuse
BBgB.00	[M]Malignant lymphoma, follicular centre cell NOS
BBgC.00	[M]Malignant lymphoma, lymphocytic, well differentiated NOS
BBgC.11	[M]Lymphocytic lymphoma NOS
BBgC.12	[M]Lymphocytic lymphosarcoma NOS
BBgD.00	[M]Malig lymphoma, lymphocytic, intermediate different NOS
BBgE.00	[M]Malignant lymphoma, centrocytic
BBGF.00	[M]Fibrous histiocytoma, malignant
BBgG.00	[M]Malignant lymphoma, lymphocytic, poorly different NOS
BBgG.11	[M]Lymphoblastic lymphosarcoma NOS
BBgG.12	[M]Lymphoblastic lymphoma NOS
BBgH.00	[M]Prolymphocytic lymphosarcoma
BBgJ.00	[M]Malignant lymphoma, centroblastic type NOS
BBgJ.11	[M]Germinoblastic sarcoma NOS
BBGJ.11	[M]Fibroxanthosarcoma
BBgK.00	[M]Malig lymphoma, follicular centre cell, non-cleaved NOS
BBgL.00	[M]Malignant lymphoma, small lymphocytic NOS
BBgM.00	[M]Malignant lymphoma, small cleaved cell, diffuse
BBGM.00	[M]Dermatofibrosarcoma NOS
BBgN.00	[M]Malign lymphoma,lymphocytic,intermediate differn, diffuse
BBgP.00	[M]Malignant lymphoma, mixed small and large cell, diffuse
BBGP.00	[M]Pigmented dermatofibrosarcoma protuberans
BBgQ.00	[M]Malignant lymphomatous polyposis
BBgR.00	[M]Malignant lymphoma, large cell, diffuse NOS
BBgS.00	[M]Malignant lymphoma, large cell, cleaved, diffuse
BBgT.00	[M]Malignant lymphoma, large cell, noncleaved, diffuse
BBgV.00	[M]Malignant lymphoma, small cell, noncleaved, diffuse
BBgz.00	[M]Lymphoma, diffuse or NOS
BBGz.00	[M]Fibromatous neoplasm NOS
BBh..00	[M]Reticulosarcomas
BBH..00	[M]Myxomatous neoplasms
BBh0.00	[M]Reticulosarcoma NOS
BBh0.11	[M]Reticulum cell sarcoma NOS
BBH1.00	[M]Myxosarcoma
BBh2.00	[M]Reticulosarcoma, nodular
BBHz.00	[M]Myxomatous neoplasm NOS
BBj..00	[M]Hodgkin's disease
BBJ..00	[M]Lipomatous neoplasms

BBj0.00	[M]Hodgkin's disease NOS
BBj1.00	[M]Hodgkin's disease, lymphocytic predominance
BBJ1.00	[M]Liposarcoma NOS
BBJ1.11	[M]Fibroliposarcoma
BBj1000	[M]Hodgkin,s disease, lymphocytic predominance, diffuse
BBj1100	[M]Hodgkin,s disease, lymphocytic predominance, nodular
BBj2.00	[M]Hodgkin's disease, mixed cellularity
BBJ3.00	[M]Liposarcoma, well differentiated type
BBj4.00	[M]Hodgkin's disease,lymphocytic depletion,diffuse fibrosis
BBJ5.00	[M]Myxoid liposarcoma
BBJ5.12	[M]Myxoliposarcoma
BBj6.00	[M]Hodgkin's disease, nodular sclerosis NOS
BBJ6.00	[M]Round cell liposarcoma
BBj6000	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic predom
BBj6100	[M]Hodgkin,s disease, nodular sclerosis, mixed cellularity
BBj6200	[M]Hodgkin,s disease, nodular sclerosis, lymphocytic deplet
BBj7.00	[M]Hodgkin's disease, nodular sclerosis, cellular phase
BBJ7.00	[M]Pleomorphic liposarcoma
BBJ8.00	[M]Mixed type liposarcoma
BBj9.00	[M]Hodgkin's granuloma
BBJA.00	[M]Spindle cell lipoma
BBJB.00	[M]Angiolipomatous neoplasms
BBJBz00	[M]Angiolipomatous neoplasm NOS
BBJD.11	[M]Brown fat tumour
BBJH.00	[M]Dedifferentiated liposarcoma
BBjz.00	[M]Hodgkin's disease NOS
BBJz.00	[M]Lipomatous neoplasms NOS
BBk..00	[M]Lymphomas, nodular or follicular
BBK..00	[M]Myomatous neoplasms
BBk0.00	[M]Malignant lymphoma, nodular NOS
BBK0.00	[M]Leiomyomatous neoplasms
BBk0.11	[M]Brill - Symmers' disease
BBk0.12	[M]Follicular lymphosarcoma NOS
BBk0.13	[M]Giant follicular lymphoma
BBK0200	[M]Leiomyosarcoma NOS
BBK0311	[M]Leiomyoblastoma
BBK0400	[M]Epithelioid leiomyosarcoma
BBK0700	[M]Myxoid leiomyosarcoma
BBK0z00	[M]Leiomyomatous neoplasm NOS
BBK1.00	[M]Angiomyomatous neoplasms
BBK1100	[M]Angiomyosarcoma
BBK1z00	[M]Angiomyomatous neoplasm NOS
BBk2.00	[M]Malignant lymphoma, centroblastic-centrocytic, follicular
BBK2.00	[M]Myoma and myosarcoma
BBK2100	[M]Myosarcoma

BBK2z00	[M]Myoma or myosarcoma NOS
BBk3.00	[M]Malig lymphoma, lymphocytic, well differentiated,nodular
BBK3.00	[M]Rhabdomyomatous neoplasms
BBK3100	[M]Rhabdomyosarcoma NOS
BBK3200	[M]Pleomorphic rhabdomyosarcoma
BBK3300	[M]Mixed cell rhabdomyosarcoma
BBK3600	[M]Embryonal rhabdomyosarcoma
BBK3611	[M]Sarcoma botryoides
BBK3700	[M]Alveolar rhabdomyosarcoma
BBK3800	[M]Smooth muscle tumour NOS
BBK3z00	[M]Rhabdomyomatous neoplasm NOS
BBk7.00	[M]Malignant lymphoma, centroblastic type, follicular
BBkz.00	[M]Lymphoma, nodular or follicular NOS
BBKz.00	[M]Myomatous neoplasm NOS
BBl..00	[M]Mycosis fungoides
BBL..00	[M]Complex mixed and stromal neoplasms
BBl0.00	[M]Mycosis fungoides
BBL0.00	[M]Endometrial stromal sarcoma
BBl1.00	[M]Sezary's disease
BBL3.12	[M]Mixed tumour NOS
BBL4.00	[M]Mixed tumour, malignant, NOS
BBL5.00	[M]Mullerian mixed tumour
BBL6.00	[M]Mesodermal mixed tumour
BBL7.00	[M]Mixed and stromal renal neoplasms
BBL7.11	[M]Nephromas and nephroblastomas
BBL7000	[M]Mesoblastic nephroma
BBL7100	[M]Nephroblastoma NOS
BBL7111	[M]Adenosarcoma
BBL7112	[M]Wilms' tumour
BBL7200	[M]Epithelial nephroblastoma
BBL7300	[M]Mesenchymal nephroblastoma
BBL7z00	[M]Mixed or stromal renal neoplasm NOS
BBL8.00	[M]Hepatoblastoma
BBL9.00	[M]Carcinosarcoma NOS
BBLA.00	[M]Carcinosarcoma, embryonal type
BBLB.00	[M]Myoepithelioma
BBLD.00	[M]Embryonal sarcoma
BBLE.00	[M]Adenosarcoma
BBLG.00	[M]Carcinoma in pleomorphic adenoma
BBLH.00	[M]Rhabdoid sarcoma
BBLJ.00	[M]Clear cell sarcoma of kidney
BBlz.00	[M]Mycosis fungoides NOS
BBLz.00	[M]Complex mixed or stromal neoplasm NOS
BBm..00	[M]Miscellaneous reticuloendothelial neoplasms
BBM..00	[M]Fibroepithelial neoplasms

BBM0.00	[M]Brenner tumours
BBM0000	[M]Brenner tumour, borderline malignancy
BBM0100	[M]Brenner tumour, malignant
BBM0z00	[M]Brenner tumour NOS
BBm1.00	[M]Malignant histiocytosis
BBm1.11	[M]Malignant reticulosis
BBm3.12	[M]Acute progressive histiocytosis X
BBm4.00	[M]True histiocytic lymphoma
BBm5.00	[M] Peripheral T-cell lymphoma NOS
BBM7.11	[M]Cystosarcoma phyllodes, benign
BBM8.00	[M]Cystosarcoma phyllodes NOS
BBm9.00	[M] Monocytoid B-cell lymphoma
BBM9.00	[M]Cystosarcoma phyllodes, malignant
BBmD.00	[M] Cutaneous lymphoma
BBmH.00	[M] Large cell lymphoma
BBmK.00	[M]Waldenstrom's macroglobulinaemia
BBMz.00	[M]Fibroepithelial neoplasm NOS
BBn..00	[M]Plasma cell tumours
BBN..00	[M]Synovial neoplasms
BBn0.00	[M]Plasma cell myeloma
BBn0.11	[M]Multiple myeloma
BBn0.12	[M]Myeloma NOS
BBn0.13	[M]Myelomatosis
BBn0.14	[M]Plasmacytic myeloma
BBn1.00	[M]Plasma cell tumour, benign
BBN1.00	[M]Synovial sarcoma NOS
BBn1.11	[M]Plasmacytoma, benign
BBn2.00	[M]Plasmacytoma NOS
BBN2.00	[M]Synovial sarcoma, spindle cell type
BBn2.11	[M]Monostotic myeloma
BBn2.12	[M]Solitary myeloma
BBn3.00	[M]Plasma cell tumour, malignant
BBN4.00	[M]Synovial sarcoma, biphasic type
BBN5.00	[M]Clear cell sarcoma of tendons and aponeuroses
BBnz.00	[M]Plasma cell tumour NOS
BBNz.00	[M]Synovial neoplasm NOS
BBp..00	[M]Mast cell tumours
BBP..00	[M]Mesothelial neoplasms
BBP0.00	[M]Mesothelioma, benign
BBp1.00	[M]Mast cell sarcoma
BBP1.00	[M]Mesothelioma, malignant
BBP2.00	[M]Fibrous mesothelioma, benign
BBP3.11	[M]Sarcomatoid mesothelioma
BBP4.00	[M]Epithelioid mesothelioma, benign
BBP5.00	[M]Epithelioid mesothelioma, malignant

BBP7.00	[M]Mesothelioma, biphasic type, malignant
BBP8.00	[M]Adenomatoid tumour NOS
BBP9.00	[M]Cystic mesothelioma
BBPX.00	[M]Mesothelioma, unspecified
BBpz.00	[M]Mast cell tumour NOS
BBPz.00	[M]Mesothelial neoplasm NOS
BBQ..00	[M]Germ cell neoplasms
BBQ0.00	[M]Dysgerminoma
BBQ1.00	[M]Seminomas
BBQ1000	[M]Seminoma, anaplastic type
BBQ1100	[M]Spermatocytic seminoma
BBQ1z00	[M]Seminoma NOS
BBQ3.00	[M]Embryonal carcinoma NOS
BBQ4.00	[M]Endodermal sinus tumour
BBQ4.11	[M]Infantile embryonal carcinoma
BBQ4.14	[M]Yolk sac tumour
BBQ7.00	[M]Teratomas
BBQ7000	[M]Teratoma, benign
BBQ7011	[M]Adult cystic teratoma
BBQ7012	[M]Mature teratoma
BBQ7100	[M]Teratoma NOS
BBQ7200	[M]Teratoma, malignant, NOS
BBQ7211	[M]Embryonal teratoma
BBQ7212	[M]Immature teratoma
BBQ7300	[M]Teratocarcinoma
BBQ7400	[M]Malignant teratoma, undifferentiated type
BBQ7500	[M]Malignant teratoma, intermediate type
BBQ7z00	[M]Teratoma NOS
BBQA.00	[M]Strumal neoplasms
BBQB.00	[M]Mixed germ cell tumour
BBQz.00	[M]Germ cell neoplasm NOS
BBr..00	[M]Leukaemias
BBR..00	[M]Trophoblastic neoplasms
BBr0.00	[M]Leukaemias unspecified
BBr0000	[M]Leukaemia NOS
BBr0100	[M]Acute leukaemia NOS
BBr0111	[M]Blast cell leukaemia
BBr0112	[M]Blastic leukaemia
BBr0113	[M]Stem cell leukaemia
BBr0200	[M]Subacute leukaemia NOS
BBr0300	[M]Chronic leukaemia NOS
BBr0400	[M]Aleukaemic leukaemia NOS
BBr0z00	[M]Leukaemia unspecified, NOS
BBr2.00	[M]Lymphoid leukaemias
BBR2.00	[M]Choriocarcinoma

BBr2000	[M]Lymphoid leukaemia NOS
BBr2011	[M]Lymphatic leukaemia
BBr2100	[M]Acute lymphoid leukaemia
BBr2300	[M]Chronic lymphoid leukaemia
BBr2500	[M]Prolymphocytic leukaemia
BBr2600	[M]Burkitt's cell leukaemia
BBr2700	[M]Adult T-cell leukaemia/lymphoma
BBr3.00	[M]Plasma cell leukaemias
BBR3.00	[M]Choriocarcinoma combined with teratoma
BBr3z00	[M]Plasma cell leukaemia NOS
BBr4.00	[M]Erythroleukaemias
BBR4.00	[M]Malignant teratoma, trophoblastic
BBr4000	[M]Erythroleukaemia
BBr4z00	[M]Erythroleukaemia NOS
BBr6.00	[M]Myeloid leukaemias
BBR6.00	[M]Placental site trophoblastic tumour
BBr6000	[M]Myeloid leukaemia NOS
BBr6011	[M]Granulocytic leukaemia NOS
BBr6100	[M]Acute myeloid leukaemia
BBr6200	[M]Subacute myeloid leukaemia
BBr6300	[M]Chronic myeloid leukaemia
BBr6311	[M]Naegeli-type monocytic leukaemia
BBr6600	[M]Acute promyelocytic leukaemia
BBr6700	[M]Acute myelomonocytic leukaemia
BBr6800	[M]Chronic myelomonocytic leukaemia
BBr6900	[M]Juvenile myelomonocytic leukaemia
BBr6z00	[M]Other myeloid leukaemia NOS
BBr7000	[M]Basophilic leukaemia
BBr8.00	[M]Eosinophilic leukaemias
BBr8000	[M]Eosinophilic leukaemia
BBr8z00	[M]Eosinophilic leukaemia NOS
BBr9000	[M]Monocytic leukaemia NOS
BBrA.00	[M]Miscellaneous leukaemias
BBrA100	[M]Megakaryocytic leukaemia
BBrA111	[M]Thrombocytic leukaemia
BBrA300	[M]Myeloid sarcoma
BBrA311	[M]Chloroma
BBrA312	[M]Granulocytic sarcoma
BBrA400	[M]Hairy cell leukaemia
BBrA500	[M]Acute megakaryoblastic leukaemia
BBrA600	[M]Acute panmyelosis
BBrA700	[M]Acute myelofibrosis
BBrAz00	[M]Miscellaneous leukaemia NOS
BBrz.00	[M]Leukaemia NOS
BBRz.00	[M]Trophoblastic neoplasm NOS

BBs..00	[M]Misc myeloproliferative and lymphoproliferative disorders
BBs1.00	[M]Acute panmyelosis
BBs2.00	[M]Chronic myeloproliferative disease
BBsz.00	[M]Misc myeloproliferative or lymphoproliferative dis NOS
BBT..00	[M]Blood vessel tumours
BBT..11	[M]Haemangiomatous tumours
BBT1.00	[M]Haemangiosarcoma
BBT1.11	[M]Angiosarcoma
BBTA.00	[M]Kaposi's sarcoma
BBTDz00	[M]Haemangiopericytic neoplasm NOS
BBTL.00	[M]Intravascular bronchial alveolar tumour
BBTz.00	[M]Blood vessel tumour NOS
BBU..00	[M]Lymphatic vessel tumours
BBU..11	[M]Lymphangiomatous tumours
BBU1.00	[M]Lymphangiosarcoma
BBUz.00	[M]Lymphatic vessel tumour NOS
BBV..00	[M]Osteomas and osteosarcomas
BBV..11	[M]Juxtacortical osteogenic sarcoma
BBV..12	[M]Parosteal osteosarcoma
BBV..13	[M]Periosteal osteogenic sarcoma
BBv0.00	[M]Monocytoid B-cell lymphoma
BBV0.00	[M]Osteoma NOS
BBV1.00	[M]Osteosarcoma NOS
BBV1.11	[M]Osteoblastic sarcoma
BBV1.12	[M]Osteochondrosarcoma
BBV1.13	[M]Osteogenic sarcoma NOS
BBv2.00	[M]AngiocentricT-cell lymphoma
BBV2.00	[M]Chondroblastic osteosarcoma
BBV3.00	[M]Fibroblastic osteosarcoma
BBV4.00	[M]Telangiectatic osteosarcoma
BBV5.00	[M]Osteosarcoma in Paget's disease of bone
BBV7.00	[M]Osteoid osteoma NOS
BBV8.11	[M]Giant osteoid osteoma
BBV9.00	[M]Myxoid chondrosarcoma
BBVA.00	[M] Small cell osteosarcoma
BBVz.00	[M]Osteoma or osteosarcoma NOS
BBW..00	[M]Chondromatous neoplasms
BBW0.00	[M]Osteochondroma
BBW0.12	[M]Ecchondroma
BBW1.00	[M]Osteochondromatosis NOS
BBW2.00	[M]Chondroma NOS
BBW2.11	[M]Enchondroma
BBW3.00	[M]Chondromatosis NOS
BBW4.00	[M]Chondrosarcoma NOS
BBW4.11	[M]Fibrochondrosarcoma

BBW5.00	[M]Juxtacortical chondroma
BBW5.11	[M]Periosteal chondroma
BBW6.00	[M]Juxtacortical chondrosarcoma
BBW7.11	[M]Chondromatous giant cell tumour
BBW9.00	[M]Mesenchymal chondrosarcoma
BBWz.00	[M]Chondromatous neoplasm NOS
BBX..00	[M]Giant cell tumours
BBX0.00	[M]Giant cell tumour of bone NOS
BBX1.00	[M]Giant cell tumour of bone, malignant
BBX1.11	[M]Giant cell bone sarcoma
BBX2.00	[M]Giant cell tumour of soft parts NOS
BBX3.00	[M]Malignant giant cell tumour of soft parts
BBXz.00	[M]Giant cell tumour NOS
BBy..00	[M]No microscopic confirmation of tumour
BBY..00	[M]Miscellaneous bone tumours
BBy0.00	[M]No microscopic confirmation of tumour, clinically benign
BBY0.00	[M]Ewing's sarcoma
BBY0.11	[M]Endothelial bone sarcoma
BBy2.00	[M]No microscopic confirmation tumour, clinically metastatic
BByz.00	[M]No microscopic confirmation of tumour, clinically NOS
BBYz.00	[M]Miscellaneous bone tumour NOS
BBZ..00	[M]Odontogenic tumours
BBz0.00	[M]Neuroendocrine neoplasm
BBZ0.00	[M]Odontogenic tumour, benign
BBZ1.00	[M]Odontogenic tumour NOS
BBZ2.00	[M]Odontogenic tumour, malignant
BBZ2.11	[M]Intraosseous carcinoma
BBZC.00	[M]Ameloblastic odontosarcoma
BBZD.00	[M]Adenomatoid odontogenic tumour
BBZJ.00	[M]Squamous odontogenic tumour
BBZN.00	[M]Ameloblastic fibrosarcoma
BBZN.11	[M]Odontogenic fibrosarcoma
BBZP.00	[M]Calcifying epithelial odontogenic tumour
BBZz.00	[M]Odontogenic tumour NOS
By...00	Neoplasms otherwise specified
Byu..00	[X]Additional neoplasm classification terms
Byu0.00	[X]Malignant neoplasm of lip, oral cavity and pharynx
Byu1.00	[X]Malignant neoplasm of digestive organs
Byu1100	[X]Other specified carcinomas of liver
Byu1200	[X]Malignant neoplasm of intestinal tract, part unspecified
Byu1300	[X]Malignant neoplsm/ill-defin sites within digestive system
Byu2.00	[X]Malignant neoplasm of respiratory and intrathoracic orga
Byu2000	[X]Malignant neoplasm of bronchus or lung, unspecified
Byu2100	[X]Malignant neoplasm/overlap lesion/heart,mediastinm+pleura
Byu2300	[X]Malignant neopl/overlapping les/resp+intrathoracic organs

Byu2400	[X]Malignant neoplasm/ill-defined sites within resp system
Byu2500	[X]Malignant neoplasm of mediastinum, part unspecified
Byu3.00	[X]Malignant neoplasm of bone and articular cartilage
Byu3100	[X]Malignant neoplasm/bones+articular cartilage/limb,unspfd
Byu3200	[X]Malignant neoplasm/overlap lesion/bone+articulr cartilage
Byu3300	[X]Malignant neoplasm/bone+articular cartilage, unspecified
Byu4.00	[X]Melanoma and other malignant neoplasms of skin
Byu4000	[X]Malignant melanoma of other+unspecified parts of face
Byu4100	[X]Malignant melanoma of skin, unspecified
Byu4200	[X]Oth malignant neoplasm/skin of oth+unspecfd parts of face
Byu4300	[X]Malignant neoplasm of skin, unspecified
Byu5.00	[X]Malignant neoplasm of mesothelial and soft tissue
Byu5000	[X]Mesothelioma of other sites
Byu5011	[X]Mesothelioma of lung
Byu5100	[X]Mesothelioma, unspecified
Byu5300	[X]Kaposi's sarcoma, unspecified
Byu5400	[X]Malignant neoplasm/peripheral nerves of trunk,unspecified
Byu5500	[X]Mal neoplasm/overlap les/periph nerv+autonomic nerv systm
Byu5700	[X]Malignant neoplasm of peritoneum, unspecified
Byu5800	[X]Mal neoplasm/connective+soft tissue of trunk,unspecified
Byu5900	[X]Malignant neoplasm/connective + soft tissue,unspecified
Byu5A00	[X]Malignant neoplasm overlapping lesion of skin
Byu5B00	[X]Kaposi's sarcoma of other sites
Byu6.00	[X]Malignant neoplasm of breast
Byu7.00	[X]Malignant neoplasm of female genital organs
Byu7000	[X]Malignant neoplasm of uterine adnexa, unspecified
Byu7100	[X]Malignant neoplasm/other specified female genital organs
Byu7300	[X]Malignant neoplasm of female genital organ, unspecified
Byu8.00	[X]Malignant neoplasm of male genital organs
Byu8000	[X]Malignant neoplasm/other specified male genital organs
Byu8200	[X]Malignant neoplasm of male genital organ, unspecified
Byu9.00	[X]Malignant neoplasm of urinary tract
Byu9000	[X]Malignant neoplasm of urinary organ, unspecified
ByuA.00	[X]Malignant neoplasm of eye, brain and other parts of cent
ByuA000	[X]Malignant neoplasm/other and unspecified cranial nerves
ByuA100	[X]Malignant neoplasm/central nervous system, unspecified
ByuA200	[X]Malignant neoplasm of meninges, unspecified
ByuA300	[X]Malig neopl, overlap lesion brain & other part of CNS
ByuB.00	[X]Malignant neoplasm of thyroid and other endocrine glands
ByuB100	[X]Malignant neoplasm of endocrine gland, unspecified
ByuC.00	[X]Malignant neoplasm of ill-defined, secondary and unspeci
ByuC000	[X]Malignant neoplasm of other specified sites
ByuC100	[X]Malignant neoplasm/overlap lesion/other+ill-defined sites
ByuC200	[X]2ndry+unspcf malignant neoplasm lymph nodes/multi regions
ByuC300	[X]Secondary malignant neoplasm/oth+unspc respiratory organs

ByuC400	[X]Secondary malignant neoplasm/oth+unspcfd digestive organs
ByuC500	[X]2ndry malignant neoplasm/bladder+oth+unsp urinary organs
ByuC600	[X]2ndry malignant neoplasm/oth+unspec parts/nervous system
ByuC700	[X]Secondary malignant neoplasm of other specified sites
ByuC800	[X]Malignant neoplasm without specification of site
ByuD.00	[X]Malignant neoplasms of lymphoid, haematopoietic and rela
ByuD000	[X]Other Hodgkin's disease
ByuD100	[X]Other types of follicular non-Hodgkin's lymphoma
ByuD200	[X]Other types of diffuse non-Hodgkin's lymphoma
ByuD300	[X]Other specified types of non-Hodgkin's lymphoma
ByuD400	[X]Other malignant immunoproliferative diseases
ByuD500	[X]Other lymphoid leukaemia
ByuD600	[X]Other myeloid leukaemia
ByuD700	[X]Other monocytic leukaemia
ByuD800	[X]Other specified leukaemias
ByuD900	[X]Other leukaemia of unspecified cell type
ByuDB00	[X]Mal neoplasm/lymphoid,haematopoietic+related tissu,unspcf
ByuDC00	[X]Diffuse non-Hodgkin's lymphoma, unspecified
ByuDD00	[X]Oth and unspecif peripheral & cutaneous T-cell lymphomas
ByuDE00	[X]Unspecified B-cell non-Hodgkin's lymphoma
ByuDF00	[X]Non-Hodgkin's lymphoma, unspecified type
ByuDF11	[X]Non-Hodgkin's lymphoma NOS
ByuE.00	[X]Malignant neoplasms/independent (primary) multiple sites
ByuE000	[X]Malignant neoplasms/independent(primary)multiple sites
ByuF.00	[X]In situ neoplasms
ByuF100	[X]Carcinoma in situ of other specified digestive organs
ByuF300	[X]Carcinoma in situ of other parts of respiratory system
ByuF600	[X]Melanoma in situ of other sites
ByuF900	[X]Carcinoma in situ of skin, unspecified
ByuFA00	[X]Carcinoma in situ of other parts of cervix
ByuFC00	[X]Carcinoma in situ of oth+unspecified male genital organs
ByuFF00	[X]Melanoma in situ, unspecified
ByuFG00	[X]Other carcinoma in situ of breast
ByuG.00	[X]Benign neoplasms
ByuG000	[X]Benign neoplasm of other and unspecified parts of mouth
ByuG100	[X]Benign neoplasm of other parts of oropharynx
ByuG600	[X]Ben lipomatous neoplsm/skin+subcut tissu/oth+unspcf sites
ByuG700	[X]Benign lipomatous neoplasm of other sites
ByuGA00	[X]Benign neoplasm/skin of other+unspecified parts of face
ByuGB00	[X]Benign neoplasm of other parts of uterus
ByuGC00	[X]Benign neoplasm of other specified female genital organs
ByuGD00	[X]Benign neoplasm of other male genital organs
ByuGH00	[X]Benign neoplasm of other specified sites
ByuGJ00	[X]Benign neoplasm of pharynx, unspecified
ByuH.00	[X]Neoplasms of uncertain and unknown behaviour

ByuH000	[X]Neoplasm/uncertain+unknown behaviour/oth digestive organs
ByuHD00	[X]Myelodysplastic syndrome, unspecified
Bz...00	Neoplasms NOS
C13y300	Diencephalic syndrome secondary to tumour
C330000	Waldenstrom's hypergammaglobulinaemic purpura
C333.00	Macroglobulinaemia
C333000	Waldenstrom's macroglobulinaemia
C333z00	Macroglobulinaemia NOS
C37y000	Hand - Schuller - Christian disease
C37y100	Eosinophilic granuloma
C37y500	Histiocytosis X , chronic
C37y600	Histiocytosis X , unspecified
C37yB00	Langerhans' cell histiocytosis
C37yD00	Tumour lysis syndrome
D212000	Anaemia in ovarian carcinoma
D41y100	Myelofibrosis
F1539C	
F1991MC	
F282.11	Pseudotumour cerebri
F456400	Glaucoma due to ocular tumour or cyst
F4G1111	Pseudotumour of orbit
F4H5100	Disorder of optic chiasm due to non-pituitary neoplasm
K01w112	Wilms' tumour + nephrotic syndrome + pseudohermaphroditism
K217	
K9611	
L241.00	Tumour of uterine body in pregnancy/childbirth/puerperium
L241000	Tumour of uterine body affecting obstetric care
L241100	Tumour of uterine body - baby delivered
L241200	Tumour of uterine body - baby delivered + p/n complication
L241300	Tumour of uterine body complicating a/n care, baby not deliv
L241z00	Uterine body tumour in pregnancy/childbirth/puerperium NOS
N237300	Pseudosarcomatous fibromatosis
N330900	Osteoporosis in multiple myelomatosis
N332500	Brown tumour of hyperparathyroidism
PE1..12	Sternomastoid tumour
PG42.00	Multiple enchondromata
PG42.11	Enchondromatosis
PG42000	Multiple enchondromata with haemangioma
PG4A.00	Metachondromatosis
Z4B3.00	Cancer counselling
ZG42.00	Advice on cancer
ZG42200	Advice on testicular cancer
ZG42300	Advice for other tumours affecting genital function
ZRVy.00	Mental adjustment to cancer scale
ZV10.00	[V]Personal history of malignant neoplasm

ZV10000	[V]Personal history of malig neop of gastrointestinal tract
ZV10011	[V]Personal history of malignant neoplasm of anus
ZV10012	[V]Personal history of malig neop of gastrointestinal tract
ZV10014	[V]Personal history of malignant neoplasm of large intestine
ZV10015	[V]Personal history of malignant neoplasm of liver
ZV10016	[V]Personal history of malignant neoplasm of oesophagus
ZV10017	[V]Personal history of malignant neoplasm of rectum
ZV10018	[V]Personal history of malignant neoplasm of stomach
ZV10019	[V]Personal history of malignant neoplasm of tongue
ZV10100	[V]Personal history of malig neop of trachea/bronchus/lung
ZV10111	[V]Personal history of malignant neoplasm of bronchus
ZV10112	[V]Personal history of malignant neoplasm of lung
ZV10200	[V]Personal history of malig neop other intrathoracic organ
ZV10211	[V]Personal history of malignant neoplasm - accessory sinus
ZV10212	[V]Personal history of malignant neoplasm of larynx
ZV10214	[V]Personal history of malignant neoplasm of nose
ZV10300	[V]Personal history of malignant neoplasm of breast
ZV10400	[V]Personal history of malignant neoplasm of genital organ
ZV10411	[V]Personal history of malignant neoplasm of cervix uteri
ZV10414	[V]Personal history of malignant neoplasm of ovary
ZV10415	[V]Personal history of malignant neoplasm of prostate
ZV10416	[V]Personal history of malignant neoplasm of testis
ZV10417	[V]Personal history of malignant neoplasm of uterine body
ZV10500	[V]Personal history of malignant neoplasm of urinary organ
ZV10511	[V]Personal history of malignant neoplasm of bladder
ZV10512	[V]Personal history of malignant neoplasm of kidney
ZV10513	[V]Personal history of malignant neoplasm of kidney
ZV10600	[V]Personal history of leukaemia
ZV10611	[V]Personal history of lymphoid leukaemia
ZV10700	[V]Personal history other lymphatic/haematopoietic neoplasm
ZV10711	[V]Personal history of Hodgkin's disease
ZV10y00	[V]Personal history of other specified malignant neoplasm
ZV10y11	[V]Personal history of malignant neoplasm of bone
ZV10y12	[V]Personal history of malignant neoplasm of brain
ZV10y13	[V]Personal history of malignant neoplasm of eye
ZV10y14	[V]Personal history of malignant neoplasm of skin
ZV10y15	[V]Personal history of malignant neoplasm of thyroid
ZV10y16	[V]Personal history of malignant neoplasm of tongue
ZV10z00	[V]Personal history of unspecified malignant neoplasm
ZV58800	[V]Chemotherapy session for neoplasm
ZV67600	[V]Follow-up examination aft surgery for malignant neoplasm
ZV67700	[V]Follow-up exam after radiotherapy for malignant neoplasm
ZV67800	[V]Follow-up examin after chemotherapy for malign neoplasm
ZV67811	[V]Follow-up examination after chemotherapy for leukaemia
ZV67900	[V]Follow-up exam aft combined treatment for malig neoplasm

ZV67A00	[V]Folow-up exam aft other treatment for malignant neoplasm
ZV67B00	[V]Folow-up exam aft unspec treatment for malignant neoplasm
ZVu6J00	[X]Personal history of other neoplasms

Diabetes

Read code	Description
1434.00	H/O: diabetes mellitus
1435.00	H/O: Admission in last year for hyperglycaemic disorder
3881.00	Education score - diabetes
3882.00	Diabetes well being questionnaire
3883.00	Diabetes treatment satisfaction questionnaire
6761.00	Diabetic pre-pregnancy counselling
7276.00	Pan retinal photocoagulation for diabetes
9360.00	Patient held diabetic record issued
2126300	Diabetes resolved
13AB.00	Diabetic lipid lowering diet
13AC.00	Diabetic weight reducing diet
13B1.00	Diabetic diet
13L4.11	Diabetic child
14F4.00	H/O: Admission in last year for diabetes foot problem
14P3.00	H/O: insulin therapy
212H.00	Diabetes resolved
2BBF.00	Retinal abnormality - diabetes related
2BBJ.00	O/E - no right diabetic retinopathy
2BBk.00	O/E - right eye stable treated prolif diabetic retinopathy
2BBK.00	O/E - no left diabetic retinopathy
2BBl.00	O/E - left eye stable treated prolif diabetic retinopathy
2BBL.00	O/E - diabetic maculopathy present both eyes
2BBM.00	O/E - diabetic maculopathy absent both eyes
2BBo.00	O/E - sight threatening diabetic retinopathy
2BBP.00	O/E - right eye background diabetic retinopathy
2BBQ.00	O/E - left eye background diabetic retinopathy
2BBr.00	Impaired vision due to diabetic retinopathy
2BBR.00	O/E - right eye preproliferative diabetic retinopathy
2BBS.00	O/E - left eye preproliferative diabetic retinopathy
2BBT.00	O/E - right eye proliferative diabetic retinopathy
2BBV.00	O/E - left eye proliferative diabetic retinopathy
2BBW.00	O/E - right eye diabetic maculopathy
2BBX.00	O/E - left eye diabetic maculopathy
2G51000	Foot abnormality - diabetes related
2G5A.00	O/E - Right diabetic foot at risk
2G5B.00	O/E - Left diabetic foot at risk
2G5C.00	Foot abnormality - diabetes related
2G5d.00	O/E - Left diabetic foot at increased risk
2G5e.00	O/E - Right diabetic foot at increased risk

2G5E.00	O/E - Right diabetic foot at low risk
2G5F.00	O/E - Right diabetic foot at moderate risk
2G5G.00	O/E - Right diabetic foot at high risk
2G5H.00	O/E - Right diabetic foot - ulcerated
2G5I.00	O/E - Left diabetic foot at low risk
2G5J.00	O/E - Left diabetic foot at moderate risk
2G5K.00	O/E - Left diabetic foot at high risk
2G5L.00	O/E - Left diabetic foot - ulcerated
2G5V.00	O/E - right chronic diabetic foot ulcer
2G5W.00	O/E - left chronic diabetic foot ulcer
38DK.00	Finnish diabetes risk score
42c..00	HbA1 - diabetic control
42c0.00	HbA1 < 7% - good control
42c1.00	HbA1 7 - 10% - borderline control
42c2.00	HbA1 > 10% - bad control
42W..00	Hb. A1C - diabetic control
42W1.00	Hb. A1C < 7% - good control
42W2.00	Hb. A1C 7-10% - borderline
42W3.00	Hb. A1C > 10% - bad control
42WZ.00	Hb. A1C - diabetic control NOS
44qE.00	Urine MDMA screening test
44T9.00	Glucometer blood sugar
44UZ.00	Blood glucose 14+ mmol/L
44Uz.11	Blood hyperglycaemia NOS
44V3.00	Glucose tol. test diabetic
661N400	Diabetes self-management plan review
66A..00	Diabetic monitoring
66A1.00	Initial diabetic assessment
66A2.00	Follow-up diabetic assessment
66A3.00	Diabetic on diet only
66A4.00	Diabetic on oral treatment
66A5.00	Diabetic on insulin
66A6.00	Last hypo. attack
66A7.00	Frequency of hypo. attacks
66A7000	Frequency of hospital treated hypoglycaemia
66A7100	Frequency of GP or paramedic treated hypoglycaemia
66A8.00	Has seen dietician - diabetes
66A9.00	Understands diet - diabetes
66Aa.00	Diabetic diet - poor compliance
66AA.11	Injection sites - diabetic
66Ab.00	Diabetic foot examination
66Ac.00	Diabetic peripheral neuropathy screening
66AC.00	Blood sugar charts
66AD.00	Fundoscopy - diabetic check
66Ae.00	HbA1c target

66AE.00	Feet examination
66Af.00	Patient diabetes education review
66Ag.00	Insulin needles changed daily
66AG.00	Diabetic drug side effects
66Ah.00	Insulin needles changed for each injection
66AH.00	Diabetic treatment changed
66AH000	Conversion to insulin
66AH100	Conversion to insulin in secondary care
66AH200	Conversion to insulin by diabetes specialist nurse
66Ai.00	Diabetic 6 month review
66AI.00	Diabetic - good control
66Aj.00	Insulin needles changed less than once a day
66AJ.00	Diabetic - poor control
66AJ.11	Unstable diabetes
66AJ000	Chronic hyperglycaemia
66AJ100	Brittle diabetes
66AJ200	Loss of hypoglycaemic warning
66AJ300	Recurrent severe hypos
66AJz00	Diabetic - poor control NOS
66Ak.00	Diabetic monitoring - lower risk albumin excretion
66AK.00	Diabetic - cooperative patient
66Al.00	Diabetic monitoring - higher risk albumin excretion
66AL.00	Diabetic-uncooperative patient
66Am.00	Insulin dose changed
66AM.00	Diabetic - follow-up default
66An.00	Diabetes type 1 review
66AN.00	Date diabetic treatment start
66Ao.00	Diabetes type 2 review
66Ap.00	Insulin treatment initiated
66AP.00	Diabetes: practice programme
66Aq.00	Diabetic foot screen
66AQ.00	Diabetes: shared care programme
66AQ000	Unsuitable for diabetes year of care programme
66AQ100	Declined consent for diabetes year of care programme
66AR.00	Diabetes management plan given
66As.00	Diabetic on subcutaneous treatment
66AS.00	Diabetic annual review
66AS000	Diabetes Year of Care annual review
66At.00	Diabetic dietary review
66AT.00	Annual diabetic blood test
66At000	Type I diabetic dietary review
66At011	Type 1 diabetic dietary review
66At100	Type II diabetic dietary review
66At111	Type 2 diabetic dietary review
66Au.00	Diabetic erectile dysfunction review

66AU.00	Diabetes care by hospital only
66Av.00	Diabetic assessment of erectile dysfunction
66AV.00	Diabetic on insulin and oral treatment
66Aw.00	Insulin dose
66AW.00	Diabetic foot risk assessment
66AX.00	Diabetes: shared care in pregnancy - diabetol and obstet
66AY.00	Diabetic diet - good compliance
66AZ.00	Diabetic monitoring NOS
66b1.00	Diabetic monitoring not required
66o..00	Further diabetic monitoring
679c.00	Insulin administration education
679L.00	Health education - diabetes
679L000	Education in self management of diabetes
679L200	Education about diabetes and driving
679L211	Advice about diabetes and driving
679R.00	Patient offered diabetes structured education programme
67D8.00	Provision of diabetes clinical summary
67IJ100	Pre-conception advice for diabetes mellitus
68A7.00	Diabetic retinopathy screening
68A9.00	Diabetic retinopathy screening offered
68AB.00	Diabetic digital retinopathy screening offered
7L10000	Continuous subcutaneous infusion of insulin
7L10011	Subcutaneous infusion with insulin pump
7L19800	Subcutaneous injection of insulin
7L19J00	Subcutaneous injection of exenatide
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
8A12.00	Diabetic crisis monitoring
8A13.00	Diabetic stabilisation
8A17.00	Self monitoring of blood glucose
8A18.00	Self monitoring of urine glucose
8A19.00	Self monitoring of blood and urine glucose
8A1A.00	Self monitoring urine ketones
8B3l.00	Diabetes medication review
8BAi.00	Insulin passport completed
8BAj.00	Informed dissent not to carry insulin passport
8BAm.00	Insulin passport checked
8BL2.00	Patient on maximal tolerated therapy for diabetes
8CA4100	Pt advised re diabetic diet
8CAQ.00	Advice about blood glucose control
8CE0100	Insulin alert patient information booklet given
8CE0200	Insulin passport given
8CMW700	Diabetes clinical pathway
8CP2.00	Transition of diabetes care options discussed
8CR2.00	Diabetes clinical management plan
8CS0.00	Diabetes care plan agreed

8H2J.00	Admit diabetic emergency
8H3O.00	Non-urgent diabetic admission
8H4e.00	Referral to diabetes special interest general practitioner
8H4F.00	Referral to diabetologist
8H7C.00	Refer, diabetic liaison nurse
8H7f.00	Referral to diabetes nurse
8H7r.00	Refer to diabetic foot screener
8HBG.00	Diabetic retinopathy 12 month review
8HBH.00	Diabetic retinopathy 6 month review
8Hg4.00	Discharged from care of diabetes specialist nurse
8HgC.00	Discharged from diabetes shared care programme
8HHy.00	Referral to diabetic register
8Hj0.00	Referral to diabetes structured education programme
8Hj3.00	Referral to DAFNE diabetes structured education programme
8Hj4.00	Referral to DESMOND diabetes structured education programme
8Hj5.00	Referral to XPERT diabetes structured education programme
8HKE.00	Diabetology D.V. requested
8Hl1.00	Referral for diabetic retinopathy screening
8Hl4.00	Referral to community diabetes specialist nurse
8Hlc.00	Referral to community diabetes service
8HLE.00	Diabetology D.V. done
8HME.00	Listed for Diabetology admissn
8HTe.00	Referral to diabetes preconception counselling clinic
8HTE100	Referral to community diabetes clinic
8HTi.00	Referral to multidisciplinary diabetic clinic
8HTk.00	Referral to diabetic eye clinic
8HVU.00	Private referral to diabetologist
8I2P.00	Sulphonylureas contraindicated
8I2S.00	Glitazones contraindicated
8I3k.00	Insulin therapy declined
8I3W.00	Diabetic foot examination declined
8I3X.00	Diabetic retinopathy screening refused
8I57.00	Patient held diabetic record declined
8I6F.00	Diabetic retinopathy screening not indicated
8I6G.00	Diabetic foot examination not indicated
8I7B.00	Metformin not tolerated
8I7C.00	Sulphonylureas not tolerated
8I81.00	Did not complete diabetes structured education programme
8I82.00	Did not complete DAFNE diabetes structured education program
8I83.00	Did not complete DESMOND diabetes structured educat program
8I84.00	Did not complete XPERT diabetes structured education program
8IAs.00	Diabetic dietary review declined
8IE2.00	Diabetes care plan declined
8IEa.00	Referral to DAFNE diabetes structured educn prog declined
8IEQ.00	Referral to community diabetes specialist nurse declined

8OA3.00	Provision of written information about diabetes and driving
918T.00	Diabetes key contact
93C4.00	Patient consent given for addition to diabetic register
9b92000	Diabetic medicine
9h4..00	Exception reporting: diabetes quality indicators
9h41.00	Excepted from diabetes qual indicators: Patient unsuitable
9h42.00	Excepted from diabetes quality indicators: Informed dissent
9kL..00	Insulin initiation - enhanced services administration
9m00.00	Eligible for diabetic retinopathy screening
9M00.00	Informed consent for diabetes national audit
9m0A.00	Declined diabetic retinopathy screening
9M10.00	Informed dissent for diabetes national audit
9N0m.00	Seen in diabetic nurse consultant clinic
9N0n.00	Seen in community diabetes specialist clinic
9N0o.00	Seen in community diabetic specialist nurse clinic
9N1i.00	Seen in diabetic foot clinic
9N1o.00	Seen in multidisciplinary diabetic clinic
9N1Q.00	Seen in diabetic clinic
9N1v.00	Seen in diabetic eye clinic
9N2d.00	Seen by diabetologist
9N2i.00	Seen by diabetic liaison nurse
9N4I.00	DNA - Did not attend diabetic clinic
9N4p.00	Did not attend diabetic retinopathy clinic
9NiA.00	Did not attend diabetes structured education programme
9NiC.00	Did not attend DAFNE diabetes structured education programme
9NiD.00	Did not attend DESMOND diabetes structured education program
9NiE.00	Did not attend XPERT diabetes structured education programme
9NiZ.00	Did not attend diabetes foot screening
9Nl4.00	Seen by general practitioner special interest in diabetes
9NM0.00	Attending diabetes clinic
9NN8.00	Under care of diabetologist
9NN9.00	Under care of diabetes specialist nurse
9NND.00	Under care of diabetic foot screener
9OL..00	Diabetes monitoring admin.
9OL..11	Diabetes clinic administration
9OL1.00	Attends diabetes monitoring
9OL2.00	Refuses diabetes monitoring
9OL3.00	Diabetes monitoring default
9OL4.00	Diabetes monitoring 1st letter
9OL5.00	Diabetes monitoring 2nd letter
9OL6.00	Diabetes monitoring 3rd letter
9OL7.00	Diabetes monitor.verbal invite
9OL8.00	Diabetes monitor.phone invite
9OL9.00	Diabetes monitoring deleted
9OLA.00	Diabetes monitor. check done

9OLA.11	Diabetes monitored
9OLB.00	Attended diabetes structured education programme
9OLD.00	Diabetic patient unsuitable for digital retinal photography
9OLE.00	Attended DESMOND structured programme
9OLF.00	Diabetes structured education programme completed
9OLG.00	Attended XPERT diabetes structured education programme
9OLH.00	Attended DAFNE diabetes structured education programme
9OLJ.00	DAFNE diabetes structured education programme completed
9OLK.00	DESMOND diabetes structured education programme completed
9OLL.00	XPERT diabetes structured education programme completed
9OLM.00	Diabetes structured education programme declined
9OLN.00	Diabetes monitor invitation by SMS (short message service)
9OLZ.00	Diabetes monitoring admin.NOS
9Oy..00	Diabetes screening administration
9Oy0000	Diabetic foot screening invitation
9Oy0200	Diabetic foot screening invitation first letter
9Oy0300	Diabetic foot screening invitation second letter
9Oy0400	Diabetic foot screening invitation third letter
C10..00	Diabetes mellitus
C100.00	Diabetes mellitus with no mention of complication
C100000	Diabetes mellitus, juvenile type, no mention of complication
C100011	Insulin dependent diabetes mellitus
C100100	Diabetes mellitus, adult onset, no mention of complication
C100111	Maturity onset diabetes
C100112	Non-insulin dependent diabetes mellitus
C100z00	Diabetes mellitus NOS with no mention of complication
C101.00	Diabetes mellitus with ketoacidosis
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C101y00	Other specified diabetes mellitus with ketoacidosis
C101z00	Diabetes mellitus NOS with ketoacidosis
C102.00	Diabetes mellitus with hyperosmolar coma
C102000	Diabetes mellitus, juvenile type, with hyperosmolar coma
C102100	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C103.00	Diabetes mellitus with ketoacidotic coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic coma
C103100	Diabetes mellitus, adult onset, with ketoacidotic coma
C103y00	Other specified diabetes mellitus with coma
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C104.00	Diabetes mellitus with renal manifestation
C104.11	Diabetic nephropathy
C104000	Diabetes mellitus, juvenile type, with renal manifestation
C104100	Diabetes mellitus, adult onset, with renal manifestation
C104y00	Other specified diabetes mellitus with renal complications

C104z00	Diabetes mellitus with nephropathy NOS
C105.00	Diabetes mellitus with ophthalmic manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifestation
C105y00	Other specified diabetes mellitus with ophthalmic complicatn
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C106.00	Diabetes mellitus with neurological manifestation
C106.11	Diabetic amyotrophy
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C106y00	Other specified diabetes mellitus with neurological comps
C106z00	Diabetes mellitus NOS with neurological manifestation
C107.00	Diabetes mellitus with peripheral circulatory disorder
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107300	IDDM with peripheral circulatory disorder
C107400	NIDDM with peripheral circulatory disorder
C107z00	Diabetes mellitus NOS with peripheral circulatory disorder
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complications
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic comps
C108112	Type 1 diabetes mellitus with ophthalmic complications
C108200	Insulin-dependent diabetes mellitus with neurological comps
C108211	Type I diabetes mellitus with neurological complications
C108212	Type 1 diabetes mellitus with neurological complications
C108300	Insulin dependent diabetes mellitus with multiple complicatn
C108311	Type I diabetes mellitus with multiple complications
C108400	Unstable insulin dependent diabetes mellitus
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108600	Insulin dependent diabetes mellitus with gangrene
C108700	Insulin dependent diabetes mellitus with retinopathy

C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A00	Insulin-dependent diabetes without complication
C108A11	Type I diabetes mellitus without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108D11	Type I diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E11	Type I diabetes mellitus with hypoglycaemic coma
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108F11	Type I diabetes mellitus with diabetic cataract
C108G00	Insulin dependent diab mell with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108H11	Type I diabetes mellitus with arthropathy
C108J00	Insulin dependent diab mell with neuropathic arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C108y00	Other specified diabetes mellitus with multiple comps
C108z00	Unspecified diabetes mellitus with multiple complications
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal comps
C109011	Type II diabetes mellitus with renal complications
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalm comps
C109111	Type II diabetes mellitus with ophthalmic complications
C109112	Type 2 diabetes mellitus with ophthalmic complications
C109200	Non-insulin-dependent diabetes mellitus with neuro comps
C109211	Type II diabetes mellitus with neurological complications
C109212	Type 2 diabetes mellitus with neurological complications
C109300	Non-insulin-dependent diabetes mellitus with multiple comps
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer

C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109800	Reaven's syndrome
C109900	Non-insulin-dependent diabetes mellitus without complication
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglyca coma
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F00	Non-insulin-dependent d m with peripheral angiopath
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C10A000	Malnutrition-related diabetes mellitus with coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
C10A500	Malnutritn-relat diabetes melitus wth periph circul complctn
C10B.00	Diabetes mellitus induced by steroids

C10B000	Steroid induced diabetes mellitus without complication
C10C.00	Diabetes mellitus autosomal dominant
C10C.11	Maturity onset diabetes in youth
C10C.12	Maturity onset diabetes in youth type 1
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complications
C10E100	Type 1 diabetes mellitus with ophthalmic complications
C10E111	Type I diabetes mellitus with ophthalmic complications
C10E112	Insulin-dependent diabetes mellitus with ophthalmic comps
C10E200	Type 1 diabetes mellitus with neurological complications
C10E212	Insulin-dependent diabetes mellitus with neurological comps
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple complicat
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E612	Insulin dependent diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy

C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cataract
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbuminuria
C10EL11	Type I diabetes mellitus with persistent microalbuminuria
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10EQ11	Type I diabetes mellitus with gastroparesis
C10ER00	Latent autoimmune diabetes mellitus in adult
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complications
C10F111	Type II diabetes mellitus with ophthalmic complications
C10F200	Type 2 diabetes mellitus with neurological complications
C10F211	Type II diabetes mellitus with neurological complications
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F800	Reaven's syndrome
C10F811	Metabolic syndrome X
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy

C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FK11	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbuminuria
C10FM11	Type II diabetes mellitus with persistent microalbuminuria
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10FS00	Maternally inherited diabetes mellitus
C10G.00	Secondary pancreatic diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication
C10H.00	Diabetes mellitus induced by non-steroid drugs
C10H000	DM induced by non-steroid drugs without complication
C10J.00	Insulin autoimmune syndrome
C10K.00	Type A insulin resistance
C10K000	Type A insulin resistance without complication
C10M.00	Lipoatrophic diabetes mellitus
C10N.00	Secondary diabetes mellitus
C10N000	Secondary diabetes mellitus without complication
C10N100	Cystic fibrosis related diabetes mellitus
C10P000	Type I diabetes mellitus in remission
C10P100	Type II diabetes mellitus in remission
C10y.00	Diabetes mellitus with other specified manifestation
C10y000	Diabetes mellitus, juvenile, + other specified manifestation
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10yy00	Other specified diabetes mellitus with other spec comps

C10yz00	Diabetes mellitus NOS with other specified manifestation
C10z.00	Diabetes mellitus with unspecified complication
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10zy00	Other specified diabetes mellitus with unspecified comps
C10zz00	Diabetes mellitus NOS with unspecified complication
C110.11	Insulin coma
C110000	Iatrogenic hyperinsulinism
C11y000	Steroid induced diabetes
C11y300	Impaired fasting glycaemia
C1A..00	Insulin resistance
C314.00	Renal glycosuria
C314.11	Renal diabetes
C321.00	Pure hyperglyceridaemia
C350011	Bronzed diabetes
Cyu2.00	[X]Diabetes mellitus
Cyu2000	[X]Other specified diabetes mellitus
Cyu2300	[X]Unspecified diabetes mellitus with renal complications
F171100	Autonomic neuropathy due to diabetes
F345000	Diabetic mononeuritis multiplex
F35z000	Diabetic mononeuritis NOS
F372.00	Polyneuropathy in diabetes
F372.11	Diabetic polyneuropathy
F372.12	Diabetic neuropathy
F372000	Acute painful diabetic neuropathy
F372100	Chronic painful diabetic neuropathy
F372200	Asymptomatic diabetic neuropathy
F381300	Myasthenic syndrome due to diabetic amyotrophy
F381311	Diabetic amyotrophy
F3y0.00	Diabetic mononeuropathy
F420.00	Diabetic retinopathy
F420000	Background diabetic retinopathy
F420100	Proliferative diabetic retinopathy
F420200	Preproliferative diabetic retinopathy
F420300	Advanced diabetic maculopathy
F420400	Diabetic maculopathy
F420500	Advanced diabetic retinal disease
F420600	Non proliferative diabetic retinopathy
F420700	High risk proliferative diabetic retinopathy
F420800	High risk non proliferative diabetic retinopathy
F420z00	Diabetic retinopathy NOS
F440700	Diabetic iritis
F464000	Diabetic cataract
G73y000	Diabetic peripheral angiopathy
K01x100	Nephrotic syndrome in diabetes mellitus

K01x111	Kimmelstiel - Wilson disease
K08yA00	Proteinuric diabetic nephropathy
K08yA11	Clinical diabetic nephropathy
K27y700	Erectile dysfunction due to diabetes mellitus
Kyu0300	[X]Glomerular disorders in diabetes mellitus
L0010AI	
L0010EI	
L180.00	Diabetes mellitus during pregnancy/childbirth/puerperium
L180000	Diabetes mellitus - unspec whether in pregnancy/puerperium
L180100	Diabetes mellitus during pregnancy - baby delivered
L180300	Diabetes mellitus during pregnancy - baby not yet delivered
L180500	Pre-existing diabetes mellitus, insulin-dependent
L180600	Pre-existing diabetes mellitus, non-insulin-dependent
L180800	Diabetes mellitus arising in pregnancy
L180811	Gestational diabetes mellitus
L180900	Gestational diabetes mellitus
L180X00	Pre-existing diabetes mellitus, unspecified
L180z00	Diabetes mellitus in pregnancy/childbirth/puerperium NOS
L2500GC	
L2500PC	
L2501CU	
M037200	Cellulitis in diabetic foot
M21yC00	Insulin lipohypertrophy
M21yC11	Insulin site lipohypertrophy
M271000	Ischaemic ulcer diabetic foot
M271100	Neuropathic diabetic ulcer - foot
M271200	Mixed diabetic ulcer - foot
N030000	Diabetic cheiroarthropathy
N030011	Diabetic cheiropathy
N030100	Diabetic Charcot arthropathy
Q441.00	Neonatal diabetes mellitus
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
R102.00	[D]Glucose tolerance test abnormal
R102.12	[D]Impaired glucose tolerance test
R105711	[D]Drug induced hyperglycaemia
R105712	[D]Hyperglycaemia
R10C.00	[D]Drug induced hyperglycaemia
R10D.00	[D]Elevated blood glucose level
R10D000	[D]Impaired fasting glycaemia
R10D011	[D]Impaired fasting glucose
R10E.00	[D]Impaired glucose tolerance
Ryu8A00	[X]Hyperglycaemia, unspecified
SL23.00	Insulins and antidiabetic poisoning
SL23400	Insulin poisoning

TJ23.00	Adverse reaction to insulins and antidiabetic agents
TJ23000	Adverse reaction to insulins
TJ23200	Adverse reaction to chlorpropamide
TJ23300	Adverse reaction to glibenclamide
TJ23400	Adverse reaction to gliclazide
TJ23500	Adverse reaction to glipizide
TJ23800	Adverse reaction to tolazamide
TJ23900	Adverse reaction to tolbutamide
TJ23A00	Adverse reaction to metformin hydrochloride
TJ23B00	Adverse reaction to glucagon
TJ23z00	Adverse reaction to insulins and antidiabetic agents NOS
U602300	[X]Insul/oral hypoglyc drugs caus adverse eff therapeut use
U602311	[X] Adverse reaction to insulins and antidiabetic agents
U602312	[X] Adverse reaction to insulins
U602315	[X] Adverse reaction to glibenclamide
U602316	[X] Adverse reaction to gliclazide
U602317	[X] Adverse reaction to glipzide
U602318	[X] Adverse reaction to gliquidone
U60231A	[X] Adverse reaction to tolazamide
U60231B	[X] Adverse reaction to tolbutamide
U60231C	[X] Adverse reaction to metformin hydrochloride
U60231E	[X] Adverse reaction to insulins and antidiabetic agents NOS
ZC2C800	Dietary advice for diabetes mellitus
ZC2C900	Dietary advice for type I diabetes
ZC2CA00	Dietary advice for type II diabetes
ZL22500	Under care of diabetic liaison nurse
ZL62500	Referral to diabetes nurse
ZL62600	Referral to diabetic liaison nurse
ZLA2500	Seen by diabetic liaison nurse
ZLD7500	Discharge by diabetic liaison nurse
ZRB4.00	Diabetes clinic satisfaction questionnaire
ZRB4.11	CSQ - Diabetes clinic satisfaction questionnaire
ZRB5.00	Diabetes treatment satisfaction questionnaire
ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire
ZRB6.00	Diabetes wellbeing questionnaire
ZRB6.11	DWBQ - Diabetes wellbeing questionnaire
ZRBa.00	Education score - diabetes
ZRbH.00	Perceived control of insulin-dependent diabetes
ZV13F00	[V]Personal history of gestational diabetes mellitus
ZV65312	[V]Dietary counselling in diabetes mellitus
ZV6DA00	[V]Admitted for commencement of insulin
ZV6DB00	[V]Admitted for conversion to insulin

Chronic Kidney Disease (CKD)

Read code	Description	Category
1Z10.00	Chronic kidney disease stage 1	Stage 1
1Z11.00	Chronic kidney disease stage 2	Stage 2
1Z12.00	Chronic kidney disease stage 3	Stage 3
1Z13.00	Chronic kidney disease stage 4	Stage 4
1Z14.00	Chronic kidney disease stage 5	Stage 5
1Z15.00	Chronic kidney disease stage 3A	Stage 3
1Z16.00	Chronic kidney disease stage 3B	Stage 3
1Z17.00	Chronic kidney disease stage 1 with proteinuria	Stage 1
1Z17.11	CKD stage 1 with proteinuria	Stage 1
1Z18.00	Chronic kidney disease stage 1 without proteinuria	Stage 1
1Z18.11	CKD stage 1 without proteinuria	Stage 1
1Z19.00	Chronic kidney disease stage 2 with proteinuria	Stage 2
1Z19.11	CKD stage 2 with proteinuria	Stage 2
1Z1A.00	Chronic kidney disease stage 2 without proteinuria	Stage 2
1Z1a.00	CKD with GFR category G4 & albuminuria category A1	Stage 4
1Z1A.11	CKD stage 2 without proteinuria	Stage 2
1Z1B.00	Chronic kidney disease stage 3 with proteinuria	Stage 3
1Z1b.00	CKD with GFR category G4 & albuminuria category A2	Stage 4
1Z1B.11	CKD stage 3 with proteinuria	Stage 3
1Z1C.00	Chronic kidney disease stage 3 without proteinuria	Stage 3
1Z1c.00	CKD with GFR category G4 & albuminuria category A3	Stage 4
1Z1C.11	CKD stage 3 without proteinuria	Stage 3
1Z1D.00	Chronic kidney disease stage 3A with proteinuria	Stage 3
1Z1d.00	CKD with GFR category G5 & albuminuria category A1	Stage 5
1Z1D.11	CKD stage 3A with proteinuria	Stage 3
1Z1E.00	Chronic kidney disease stage 3A without proteinuria	Stage 3
1Z1e.00	CKD with GFR category G5 & albuminuria category A2	Stage 5
1Z1E.11	CKD stage 3A without proteinuria	Stage 3
1Z1F.00	Chronic kidney disease stage 3B with proteinuria	Stage 3
1Z1f.00	CKD with GFR category G5 & albuminuria category A3	Stage 5
1Z1F.11	CKD stage 3B with proteinuria	Stage 3
1Z1G.00	Chronic kidney disease stage 3B without proteinuria	Stage 3
1Z1G.11	CKD stage 3B without proteinuria	Stage 3
1Z1H.00	Chronic kidney disease stage 4 with proteinuria	Stage 4
1Z1H.11	CKD stage 4 with proteinuria	Stage 4
1Z1J.00	Chronic kidney disease stage 4 without proteinuria	Stage 4
1Z1J.11	CKD stage 4 without proteinuria	Stage 4
1Z1K.00	Chronic kidney disease stage 5 with proteinuria	Stage 5
1Z1K.11	CKD stage 5 with proteinuria	Stage 5
1Z1L.00	Chronic kidney disease stage 5 without proteinuria	Stage 5
1Z1L.11	CKD stage 5 without proteinuria	Stage 5
1Z1M.00	CKD with GFR category G1 & albuminuria category A1	Stage 1
1Z1N.00	CKD with GFR category G1 & albuminuria category A2	Stage 1

1Z1P.00	CKD with GFR category G1 & albuminuria category A3	Stage 1
1Z1Q.00	CKD with GFR category G2 & albuminuria category A1	Stage 2
1Z1R.00	CKD with GFR category G2 & albuminuria category A2	Stage 2
1Z1S.00	CKD with GFR category G2 & albuminuria category A3	Stage 2
1Z1T.00	CKD with GFR category G3a & albuminuria category A1	Stage 3
1Z1V.00	CKD with GFR category G3a & albuminuria category A2	Stage 3
1Z1W.00	CKD with GFR category G3a & albuminuria category A3	Stage 3
1Z1X.00	CKD with GFR category G3b & albuminuria category A1	Stage 3
1Z1Y.00	CKD with GFR category G3b & albuminuria category A2	Stage 3
1Z1Z.00	CKD with GFR category G3b & albuminuria category A3	Stage 3
K051.00	Chronic kidney disease stage 1	Stage 1
K052.00	Chronic kidney disease stage 2	Stage 2
K053.00	Chronic kidney disease stage 3	Stage 3
K054.00	Chronic kidney disease stage 4	Stage 4
K055.00	Chronic kidney disease stage 5	Stage 5

Hyperlipidaemia

Read code	Description
1442.00	H/O: raised blood lipids
13AB.00	Diabetic lipid lowering diet
13B3.00	Low cholesterol diet
1W2..00	Probable familial hypercholesterolaemia
44O4.00	Serum lipids high
44O6.00	Lipids abnormal
44P3.00	Serum cholesterol raised
44P4.00	Serum cholesterol very high
66X..00	Lipid disorder monitoring
66X0.00	Lipid disorder treatment started
66X2.00	Lipid disorder treatment changed
66X3.00	Lipid disorder initial assessment
66X4.00	Lipid disorder follow-up assessment
7L1j000	Low density lipoprotein apheresis
8B28.00	Lipid lowering therapy
8B6A.00	Statin prophylaxis
8BAG.00	Cholesterol reduction programme
8BAG000	Cholesterol reduction programme - invited
8BAG100	Cholesterol reduction program - attended
8BAG200	Cholesterol reduction program - declined
8BG2.00	Lipid lowering therapy indicated
8BL1.00	Patient on maximal tolerated lipid lowering therapy
8CA4700	Patient advised re low cholesterol diet
8CP6.00	Discussion about lipid lowering therapy
8CR3.00	Hyperlipidaemia clinical management plan
8H6E.00	Referral to GP - lipid management

8HT1.00	Referral to lipid clinic
8I3C.00	Statin declined
8I3J.00	Lipid lowering therapy declined
8I76.00	Statin not tolerated
9N0I.00	Seen in lipid clinic
9N0J.00	Seen in cholesterol clinic
9N4K.00	DNA - Did not attend cholesterol clinic
9Oc..00	Lipid disorder monitoring administration
9Oc0.00	Attends lipid disorder monitoring
9Oc1.00	Lipid disorder monitoring declined
9Oc2.00	Lipid disorder monitoring first letter
9Oc3.00	Lipid disorder monitoring second letter
9Oc4.00	Lipid disorder monitoring third letter
9Oc5.00	Lipid disorder monitoring verbal invitation
9Oc6.00	Lipid disorder monitoring telephone invitation
C32..00	Disorders of lipoid metabolism
C32..11	Disorder of cholesterol metabolism
C320.00	Pure hypercholesterolaemia
C320.11	Familial hypercholesterolaemia
C320.12	Fredrickson type IIa lipidaemia
C320.13	Low density lipoproteinaemia
C320000	Familial hypercholesterolaemia
C320100	Hyperbetalipoproteinaemia
C320200	Hyperlipidaemia, group A
C320300	Low-density-lipoprotein-type (LDL) hyperlipoproteinaemia
C320400	Fredrickson's hyperlipoproteinaemia, type IIa
C320500	Familial defective apolipoprotein B-100
C320600	Polygenic hypercholesterolaemia
C320y00	Other specified pure hypercholesterolaemia
C320z00	Pure hypercholesterolaemia NOS
C321.00	Pure hyperglyceridaemia
C321.11	Fredrickson type IV lipidaemia
C321.12	Very low density lipoprotinaemia
C321000	Hypertriglyceridaemia
C322.00	Mixed hyperlipidaemia
C322.11	Fredrickson type IIb lipidaemia
C322.12	Fredrickson type III lipidaemia
C322000	Familial combined hyperlipidaemia
C323.12	Fredrickson type I lipaemia
C323.13	Fredrickson type V lipaemia
C324.00	Hyperlipidaemia NOS
C325.00	Lipoprotein deficiencies
C325100	Hypo-alpha-lipoproteinaemia
C325200	Hypo-beta-lipoproteinaemia
C325300	A-beta-lipoproteinaemia

C325z00	Lipoprotein deficiency NOS
C327.00	Lipidoses
C327z00	Lipidoses NOS
C328.00	Dyslipidaemia
C329.00	Hypercholesterolaemia
C32y.00	Other disorders of lipoid metabolism
C32y200	Lipoid dermatoarthritis
C32yz00	Other disorder of lipoid metabolism NOS
C32z.00	Disorder of lipoid metabolism NOS
Cyu8D00	[X]Other hyperlipidaemia
Cyu8E00	[X]Other disorders of lipoprotein metabolism
U60C600	[X]Antihyperlipidaem/antiarterioscl drg caus adv ef ther use
U60C900	[X]Lipid-lowering drug adverse reaction
ZC2CI00	Dietary advice for lipid disorder
ZC2CJ00	Dietary advice for hyperlipidaemia
ZV65317	[V]Dietary surveillance in hypercholesterolaemia

Appendix 5.4: Drug product codes used to define risk factors and covariates

Diabetes

Product code	Description	Category (code)
23	metformin tablets 500mg	Metformin (2)
32	gliclazide tablets 80mg	Sulphonylureas (5)
93	metformin tablets 850mg	Metformin (2)
321	INSULIN HUMAN ACTRAPID (NEUTRAL) 40 I/U INJ	Insulins (1)
322	HUMALOG injection 100 iu/ml [LILLY]	Insulins (1)
469	rosiglitazone tablets 4mg	Thiazolidinediones (6)
479	acarbose tablets 50mg	Acarbose (7)
547	glipizide tablets 2.5mg	Sulphonylureas (5)
548	pioglitazone tablets 15mg	Thiazolidinediones (6)
735	metformin oral suspension 100mg/ml	Metformin (2)
1253	chlorpropamide tablets 100mg	Sulphonylureas (5)
1254	glibenclamide tablets 5mg	Sulphonylureas (5)
1587	MONOTARD injection 100 units/ml [NOVO]	Insulins (1)
1588	ACTRAPID injection 100 iu/ml [NOVO]	Insulins (1)
1592	ACTRAPID PENFILL 100 iu/ml [NOVO]	Insulins (1)
1593	INSULATARD PENFILL 100 iu/ml [NOVO]	Insulins (1)
1594	ACTRAPID NOVOLET 100 iu/ml [NOVO]	Insulins (1)
1595	INSULATARD NOVOLET 100 iu/ml [NOVO]	Insulins (1)
1643	INSULIN NOVO MONOTARD MC 100 I/U INJ	Insulins (1)
1645	INSULIN NOVO ACTRAPID MC 100 I/U INJ	Insulins (1)
1649	HUMAN ACTRAPHANE injection 100 iu/ml [NOVO]	Insulins (1)
1805	MIXTARD 30/70 injection 100 units/ml [NOVO]	Insulins (1)
1806	PENMIX 30/70 PENFILL injection 100 iu/ml [NOVO]	Insulins (1)
1839	INSULIN HUMULIN I (ISOPHANE) 100 I/U INJ	Insulins (1)
1840	HUMULIN S injection 100 units/ml [LILLY]	Insulins (1)
1842	PORK VELOSULIN injection 100 units/ml [NOVO]	Insulins (1)
1843	PORK INSULATARD VIAL injection suspension 100 units/ml [NOVO]	Insulins (1)
1844	ULTRATARD injection 100 units/ml [NOVO]	Insulins (1)
1847	chlorpropamide tablets 250mg	Sulphonylureas (5)
1886	INSULATARD ge injection 100 iu/ml [NOVO]	Insulins (1)
1964	DIAMICRON tablets 80mg [SERVIER]	Sulphonylureas (5)
1965	tolbutamide tablets 500mg	Sulphonylureas (5)
2219	glibenclamide tablets 2.5mg	Sulphonylureas (5)
2220	PENMIX 20/80 pen [NOVO]	Insulins (1)
2221	MIXTARD 30 NOVOLET 100 iu/ml [NOVO]	Insulins (1)
2373	INSULIN HUMAN VELOSULIN 100 I/U INJ	Insulins (1)
2454	MIXTARD 30 PENFILL 100 iu/ml [NOVO]	Insulins (1)
2455	MIXTARD 20 NOVOLET 100 iu/ml [NOVO]	Insulins (1)
2456	MIXTARD 10 NOVOLET 100 iu/ml [NOVO]	Insulins (1)

2459	PORK MIXTARD 30 VIAL injection suspension 100 units/ml [NOVO]	Insulins (1)
2808	INSULIN LENTARD INJ	Insulins (1)
2812	MIXTARD 40 NOVOLET 100 iu/ml [NOVO]	Insulins (1)
2928	METFORMIN HCl 850 MG TAB	Metformin (2)
2929	MIXTARD 30 ge injection 100 iu/ml [NOVO]	Insulins (1)
3252	METFORMIN HCl 500 MG TAB	Metformin (2)
3396	PENMIX 10/90 PENFILL PENFILL [NOVO]	Insulins (1)
3439	PENMIX 10/90 pen [NOVO]	Insulins (1)
3550	MIXTARD 40 PENFILL 100 iu/ml [NOVO]	Insulins (1)
3551	MIXTARD 20 PENFILL 100 iu/ml [NOVO]	Insulins (1)
4093	HUMULIN M2 injection 100 units/ml [LILLY]	Insulins (1)
4129	insulin soluble porcine injection 100 units/ml	Insulins (1)
4163	RAPITARD MC injection 100 units/ml [NOVO]	Insulins (1)
4198	HUMULIN M3 injection 100 units/ml [LILLY]	Insulins (1)
4199	HUMULIN M1 injection 100 units/ml [LILLY]	Insulins (1)
4247	insulin isophane porcine injection 100 units/ml	Insulins (1)
4248	INSULIN NOVO ULTRATARD MC 100 I/U INJ	Insulins (1)
4706	VELOSULIN VIAL injection solution 100 units/ml [NOVO]	Insulins (1)
4715	HUMALOG MIX 25 injection 25:75; 100 units/ml [LILLY]	Insulins (1)
4760	HUMULIN I injection 100 units/ml [LILLY]	Insulins (1)
4784	LENTARD MC injection 100 units/ml [NOVO]	Insulins (1)
4790	MIXTARD 50 PENFILL 100 iu/ml [NOVO]	Insulins (1)
4862	DIABETAMIDE tablets 2.5mg [ASHBOURNE]	Sulphonylureas (5)
5021	NOVORAPID PENFILL injection solution 100 units/ml [NOVO]	Insulins (1)
5174	acarbose tablets 100mg	Acarbose (7)
5214	insulin lispro human prb injection 100 iu/ml	Insulins (1)
5227	rosiglitazone tablets 8mg	Thiazolidinediones (6)
5250	insulin biphasic lispro human prb injection 25:75; 100 units/ml	Insulins (1)
5255	MIXTARD 10 PENFILL 100 iu/ml [NOVO]	Insulins (1)
5276	glimepiride tablets 1mg	Sulphonylureas (5)
5316	glimepiride tablets 4mg	Sulphonylureas (5)
5353	glimepiride tablets 2mg	Sulphonylureas (5)
5501	INSUMAN BASAL injection 100 iu/ml [AVENTIS]	Insulins (1)
5621	GLUCOBAY tablets 50mg [BAYER]	Acarbose (7)
5627	gliclazide modified release tablet 30mg	Sulphonylureas (5)
5636	glipizide tablets 5mg	Sulphonylureas (5)
5678	nateglinide tablets 120mg	Meglitinides (10)
5845	MIXTARD 30 INNOLET injection suspension 30:70; 100 units/ml [NOVO]	Insulins (1)
5891	INSULATARD FLEXPEN injection 100 iu/ml [NOVO]	Insulins (1)
5892	NOVORAPID FLEXPEN injection solution 100 units/ml [NOVO]	Insulins (1)
5933	MIXTARD 50 NOVOLET 100 iu/ml [NOVO]	Insulins (1)
5953	insulin glargine injection 100 iu/ml	Insulins (1)
5989	nateglinide tablets 180mg	Meglitinides (10)

6057	LANTUS injection 100 iu/ml [AVENTIS]	Insulins (1)
6061	NOVOMIX 30 injection 30:70; 100 units/ml [NOVO]	Insulins (1)
6209	NOVORAPID VIAL injection solution 100 units/ml [NOVO]	Insulins (1)
6337	glimepiride tablets 3mg	Sulphonylureas (5)
6447	insulin aspart human pyr injection 100 iu/ml	Insulins (1)
6855	AVANDAMET tablets 2mg + 500mg [GLAXSK PHA]	Metformin + thiazolidinedione (4)
6958	LEVEMIR FLEXPEN injection solution 100 iu/ml [NOVO]	Insulins (1)
6965	LEVEMIR PENFILL injection solution 100 units/ml [NOVO]	Insulins (1)
7048	metformin modified release tablet 500mg	Metformin (2)
7166	GLUCOPHAGE tablets 500mg [MERCK SER]	Metformin (2)
7228	NOVOMIX 30 FLEXPEN injection suspension 100 units/ml [NOVO]	Insulins (1)
7231	MIXTARD 30 PENFILL injection suspension 100 units/ml [NOVO]	Insulins (1)
7237	LANTUS OPTISET injection solution 100 units/ml [AVENTIS]	Insulins (1)
7266	LANTUS CARTRIDGE injection solution 100 units/ml [AVENTIS]	Insulins (1)
7267	NOVOMIX 30 PENFILL injection suspension 100 units/ml [NOVO]	Insulins (1)
7284	AMARYL tablets 2mg [AVENTIS]	Sulphonylureas (5)
7300	MIXTARD 30 VIAL injection suspension 100 units/ml [NOVO]	Insulins (1)
7318	HUMALOG CARTRIDGE injection solution 100 units/ml [LILLY]	Insulins (1)
7319	MIXTARD 20 PENFILL injection suspension 100 units/ml [NOVO]	Insulins (1)
7325	AVANDAMET tablets 4mg + 1000mg [GLAXSK PHA]	Metformin + thiazolidinedione (4)
7332	AMARYL tablets 1mg [AVENTIS]	Sulphonylureas (5)
7349	ACTRAPID VIAL injection solution 100 units/ml [NOVO]	Insulins (1)
7350	insulin isophane porcine vial injection suspension 100 units/ml	Insulins (1)
7375	rosiglitazone with metformin tablets 4mg + 1000mg	Metformin + thiazolidinedione (4)
7393	insulin glargine cartridge injection solution 100 units/ml	Insulins (1)
7400	insulin glargine disposable pen injection solution 100 units/ml	Insulins (1)
7402	LANTUS VIAL injection solution 100 units/ml [AVENTIS]	Insulins (1)
7409	AMARYL tablets 3mg [AVENTIS]	Sulphonylureas (5)
7537	HUMULIN ZN injection 100 units/ml [LILLY]	Insulins (1)
7610	GLUCOPHAGE tablets 850mg [MERCK SER]	Metformin (2)
7744	DAONIL tablets 5mg [AVENTIS]	Sulphonylureas (5)
7757	INSULIN NEULENTE (ZINC SUSP)(PURIFIED) 100 I/U INJ	Insulins (1)
7763	INSULIN NEUPHANE (ISOPHANE)(PURIFIED) 100 I/U INJ	Insulins (1)
7764	INSULIN NEUSULIN (NEUTRAL)(PURIFIED) 100 I/U INJ	Insulins (1)
7765	INSULIN NEUTRAL (HUMAN) 100 I/U INJ	Insulins (1)
7771	HUMAN PROTAPHANE PENFILL 100 units/ml [NOVO]	Insulins (1)
7772	HUMAN PROTAPHANE injection 100 units/ml [NOVO]	Insulins (1)
7783	INSULIN ISOPHANE (HUMAN) 100 I/U INJ	Insulins (1)
7793	HUMAJECT M3 pen 100 iu/ml [LILLY]	Insulins (1)
7815	METFORMIN 800 MG TAB	Metformin (2)
7861	INSULIN HUMULIN S (NEUTRAL) CARTRIDGE 100 I/U	Insulins (1)
7912	SEMI-DAONIL tablets 2.5mg [AVENTIS]	Sulphonylureas (5)
7959	INSULIN MIXTARD 30/70 40 I/U INJ	Insulins (1)

8034	DIABINESE tablets 100mg [PFIZER]	Sulphonylureas (5)
8118	HUMAJECT I pen 100 iu/ml [LILLY]	Insulins (1)
8168	DIABINESE tablets 250mg [PFIZER]	Sulphonylureas (5)
8203	PENMIX 50/50 PENFILL injection 100 iu/ml [NOVO]	Insulins (1)
8322	insulin zinc suspension mixed human pyr injection 100 units/ml	Insulins (1)
8354	INSULIN ISOPHANE 70%/NEUTRAL 30% 100 I/U INJ	Insulins (1)
8376	INSULIN ISOPHANE 100 I/U	Insulins (1)
8390	gliquidone tablets 30mg	Sulphonylureas (5)
8483	MONOJECT INSULIN NEEDLES	Insulins (1)
8646	INSULIN ZINC CRYSTALLINE susp 100 I/U INJ	Insulins (1)
8838	INSULIN SEMITARD 40 I/U INJ	Insulins (1)
8839	INSULIN SEMITARD 100 I/U INJ	Insulins (1)
8841	HUMULIN M5 injection 100 units/ml [LILLY]	Insulins (1)
8895	INITARD 50/50 injection 100 units/ml [NOVO]	Insulins (1)
8976	EUGLUCON tablets 2.5mg [AVENTIS]	Sulphonylureas (5)
9079	INSULIN SOLUBLE 100 I/U INJ	Insulins (1)
9105	GLUCOBAY tablets 100mg [BAYER]	Acarbose (7)
9108	TOLBUTAMIDE 250 MG TAB	Sulphonylureas (5)
9341	insulin biphasic isophane human prb injection 30:70; 100 units/ml	Insulins (1)
9376	insulin zinc suspension crystalline human pyr - long acting injection 100 units/ml	Insulins (1)
9503	HYPURIN BOVINE PROTAMINE ZINC VIAL injection suspension 100 units/ml [CP PHARM]	Insulins (1)
9521	PORK ACTRAPID VIAL injection solution 100 units/ml [NOVO]	Insulins (1)
9565	HUMAJECT S DISPOSABLE PEN injection solution 100 units/ml [LILLY]	Insulins (1)
9618	HYPURIN PORCINE 30/70 MIX injection 100 iu/ml [CP PHARM]	Insulins (1)
9662	AVANDIA tablets 4mg [GLAXSK PHA]	Thiazolidinediones (6)
9699	pioglitazone tablets 30mg	Thiazolidinediones (6)
9707	repaglinide tablets 1mg	Meglitinides (10)
9737	INSULATARD INNOLET injection 100 iu/ml [NOVO]	Insulins (1)
9748	repaglinide tablets 2mg	Meglitinides (10)
9865	repaglinide tablets 500 micrograms	Meglitinides (10)
10001	HUMALOG MIX 50 DISPOSABLE PEN injection suspension 100 units/ml [LILLY]	Insulins (1)
10051	pioglitazone tablets 45mg	Thiazolidinediones (6)
10067	insulin biphasic aspart human pyr injection 30:70; 100 units/ml	Insulins (1)
10175	insulin isophane human pyr injection 100 iu/ml	Insulins (1)
10184	insulin detemir injection solution 100 iu/ml	Insulins (1)
10207	insulin isophane human cartridge injection suspension 100 units/ml	Insulins (1)
10208	INSULATARD INNOLET injection suspension 100 units/ml [NOVO]	Insulins (1)
10225	LANTUS OPTICLIK injection solution 100 units/ml [AVENTIS]	Insulins (1)
10229	HUMULIN I DISPOSABLE PEN injection suspension 100 units/ml [LILLY]	Insulins (1)
10243	HUMALOG MIX 25 CARTRIDGE injection suspension 100 units/ml [LILLY]	Insulins (1)

10244	MIXTARD 40 PENFILL injection suspension 100 units/ml [NOVO]	Insulins (1)
10245	MIXTARD 10 PENFILL injection suspension 100 units/ml [NOVO]	Insulins (1)
10259	insulin glargine vial injection solution 100 units/ml	Insulins (1)
10264	HUMALOG DISPOSABLE PEN injection solution 100 units/ml [LILLY]	Insulins (1)
10277	HUMULIN M3 CARTRIDGE injection suspension 100 units/ml [LILLY]	Insulins (1)
10427	tolazamide tablets 250mg	Sulphonylureas (5)
10484	PENMIX 20/80 PENFILL PENFILL [NOVO]	Insulins (1)
10545	INSULIN HUMULIN M4 CARTRIDGE 100 I/U	Insulins (1)
10546	INSULIN HUMULIN M4 100 I/U INJ	Insulins (1)
10547	HUMULIN LENTE injection 100 units/ml [LILLY]	Insulins (1)
10566	INSULIN HUMULIN M CARTRIDGE 100 I/U	Insulins (1)
10572	insulin soluble bovine injection 100 units/ml	Insulins (1)
10691	INSULIN ISOPHANE (NPH) 100 I/U INJ	Insulins (1)
10887	PENMIX 40/60 PENFILL injection 100 iu/ml [NOVO]	Insulins (1)
10910	HUMAJECT M2 pen 100 iu/ml [LILLY]	Insulins (1)
10915	HUMAJECT M1 pen 100 iu/ml [LILLY]	Insulins (1)
11055	insulin biphasic isophane human pyr injection 20:80; 100 units/ml	Insulins (1)
11056	insulin biphasic isophane human pyr injection 30:70; 100 units/ml	Insulins (1)
11080	insulin isophane human prb injection 100 iu/ml	Insulins (1)
11107	HUMULIN M4 injection 100 units/ml [LILLY]	Insulins (1)
11284	AMARYL tablets 4mg [AVENTIS]	Sulphonylureas (5)
11316	NOVONORM tablets 500 micrograms [NOVO]	Meglitinides (10)
11321	NOVONORM tablets 1mg [NOVO]	Meglitinides (10)
11337	NOVORAPID NOVOLET injection 100 iu/ml [NOVO]	Insulins (1)
11366	NOVONORM tablets 2mg [NOVO]	Meglitinides (10)
11483	nateglinide tablets 60mg	Meglitinides (10)
11601	rosiglitazone with metformin tablets 2mg + 500mg	Metformin + thiazolidinedione (4)
11604	rosiglitazone with metformin tablets 1mg + 500mg	Metformin + thiazolidinedione (4)
11609	metformin with rosiglitazone tablets 500mg + 1mg	Metformin + thiazolidinedione (4)
11610	metformin with rosiglitazone tablets 500mg + 2mg	Metformin + thiazolidinedione (4)
11695	DIAMICRON MR tablets 30mg [SERVIER]	Sulphonylureas (5)
11717	rosiglitazone with metformin tablets 2mg + 1000mg	Metformin + thiazolidinedione (4)
11737	metformin with rosiglitazone tablets 1000mg + 4mg	Metformin + thiazolidinedione (4)
11760	metformin with rosiglitazone tablets 1000mg + 2mg	Metformin + thiazolidinedione (4)
11946	tolbutamide injection 50mg/ml	Sulphonylureas (5)
11990	metformin oral solution 500mg/5ml	Metformin (2)
12035	insulin zinc lente bovine vial injection suspension 100 units/ml	Insulins (1)
12060	INSULIN QUICKSOL (SOLUBLE NEUTRAL) 100 I/U INJ	Insulins (1)

12244	INSULIN ZINC BOVINE susp 100 I/U INJ	Insulins (1)
12245	GLUTRIL tablets 25mg [ROCHE]	Sulphonylureas (5)
12259	glibornuride tablets 25mg	Sulphonylureas (5)
12297	HYPURIN BOVINE NEUTRAL injection 100 units/ml [CP PHARM]	Insulins (1)
12299	SEMITARD MC injection 100 units/ml [NOVO]	Insulins (1)
12300	SYRINGE INSULIN (BS1619/1) 2ML	Insulins (1)
12455	RASTINON tablets 500mg [HOECHSTMAR]	Sulphonylureas (5)
12513	GLIBENESE tablets 5mg [PFIZER]	Sulphonylureas (5)
12638	insulin soluble human pyr injection 100 units/ml	Insulins (1)
12654	insulin soluble human prb injection 100 units/ml	Insulins (1)
12818	MIXTARD 50 injection 50:50; 100 units/ml [NOVO]	Insulins (1)
13277	MIXTARD 50 PENFILL injection suspension 100 units/ml [NOVO]	Insulins (1)
13331	EUGLUCON tablets 5mg [AVENTIS]	Sulphonylureas (5)
13416	insulin biphasic injection 100 units/ml	Insulins (1)
13516	HYPURIN BOVINE ISOPHANE injection 100 units/ml [CP PHARM]	Insulins (1)
13550	INSULIN BP 100 I/U	Insulins (1)
13622	HYPURIN PORCINE NEUTRAL injection 100 units/ml [CP PHARM]	Insulins (1)
13628	ROMOZIN tablets 400mg [GLAXO]	Thiazolidinediones (6)
13729	insulin isophane human emp injection 100 units/ml	Insulins (1)
13819	HYPURIN PORCINE ISOPHANE injection 100 units/ml [CP PHARM]	Insulins (1)
13837	insulin biphasic isophane human prb injection 10:90; 100 units/ml	Insulins (1)
14164	AVANDAMET tablets 2mg + 1000mg [GLAXSK PHA]	Metformin + thiazolidinedione (4)
14270	HUMALOG MIX 25 DISPOSABLE PEN injection suspension 100 units/ml [LILLY]	Insulins (1)
14290	INSULATARD PENFILL injection suspension 100 units/ml [NOVO]	Insulins (1)
14299	insulin glulisine cartridge injection solution 100 units/ml	Insulins (1)
14301	insulin detemir cartridge injection solution 100 units/ml	Insulins (1)
14313	insulin lispro cartridge injection solution 100 units/ml	Insulins (1)
14330	insulin detemir disposable pen injection solution 100 units/ml	Insulins (1)
14339	HYPURIN BOVINE NEUTRAL VIAL injection solution 100 units/ml [CP PHARM]	Insulins (1)
14340	HYPURIN BOVINE ISOPHANE VIAL injection suspension 100 units/ml [CP PHARM]	Insulins (1)
14345	APIDRA CARTRIDGE injection solution 100 units/ml [SANOFI/AVE]	Insulins (1)
14357	HUMULIN I CARTRIDGE injection suspension 100 units/ml [LILLY]	Insulins (1)
14362	insulin lispro disposable pen injection solution 100 units/ml	Insulins (1)
14504	INSULIN HYPURIN PROTAMINE ZINC 100 I/U INJ	Insulins (1)
14505	insulin protamine zinc bovine vial injection suspension 100 units/ml	Insulins (1)
14506	INSULIN BOVINE PROTAMINE ZINC 100 I/U INJ	Insulins (1)
14619	insulin biphasic isophane porcine injection 30:70; 100 units/ml	Insulins (1)
14644	insulin biphasic isophane human prb injection 20:80; 100 units/ml	Insulins (1)
14649	insulin biphasic isophane human pyr injection 10:90; 100 units/ml	Insulins (1)
14918	HUMULIN I VIAL injection suspension 100 units/ml [LILLY]	Insulins (1)

14925	insulin isophane human vial injection suspension 100 units/ml	Insulins (1)
14928	INSULATARD VIAL injection suspension 100 units/ml [NOVO]	Insulins (1)
14930	HYPURIN PORCINE NEUTRAL CARTRIDGE injection solution 100 units/ml [CP PHARM]	Insulins (1)
14933	HYPURIN PORCINE ISOPHANE CARTRIDGE injection suspension 100 units/ml [CP PHARM]	Insulins (1)
14938	insulin soluble bovine cartridge injection solution 100 units/ml	Insulins (1)
14944	HUMULIN S CARTRIDGE injection solution 100 units/ml [LILLY]	Insulins (1)
15040	INSULIN MONOPHANE (ISOPHANE) 100 I/U INJ	Insulins (1)
15199	INSUMAN COMB 25 injection 100 iu/ml [AVENTIS]	Insulins (1)
15232	AVANDIA tablets 8mg [GLAXSK PHA]	Thiazolidinediones (6)
15374	gliclazide oral suspension 40mg/5ml	Sulphonylureas (5)
15484	insulin isophane bovine injection 100 units/ml	Insulins (1)
15624	INSULIN ISOPHANE (HIGHLY PURIFIED) 100 I/U INJ	Insulins (1)
15710	insulin soluble human emp injection 100 units/ml	Insulins (1)
15955	STARLIX tablets 120mg [NOVARTIS]	Meglitinides (10)
15961	insulin isophane human crb injection 100 iu/ml	Insulins (1)
16044	GLUCOPHAGE SR tablets 500mg [MERCK SER]	Metformin (2)
16129	insulin soluble human cartridge injection solution 100 units/ml	Insulins (1)
16142	insulin aspart cartridge injection solution 100 units/ml	Insulins (1)
16152	insulin biphasic isophane human cartridge injection suspension 30:70; 100 units/ml	Insulins (1)
16160	HUMULIN M3 DISPOSABLE PEN injection suspension 100 units/ml [LILLY]	Insulins (1)
16209	INSULIN HYPURIN SOLUBLE 100 I/U INJ	Insulins (1)
16211	TOLBUTAMIDE 100 MG TAB	Sulphonylureas (5)
16213	METFORMIN 250 MG TAB	Metformin (2)
16602	CALABREN tablets 2.5mg [BERK]	Sulphonylureas (5)
16682	TEMPULIN injection 100 units/ml [KNOLL]	Insulins (1)
16700	insulin zinc mixed bovine vial injection suspension 100 units/ml	Insulins (1)
17336	NOVOPEN injection device 100 units/ml [NOVO]	Insulins (1)
17343	GLICLAZIDE tablets 80mg [HILLCROSS]	Sulphonylureas (5)
17580	AVANDAMET tablets 1mg + 500mg [GLAXSK PHA]	Metformin + thiazolidinedione (4)
17698	MINODIAB tablets 5mg [PHARMACIA]	Sulphonylureas (5)
17706	MINODIAB tablets 2.5mg [PHARMACIA]	Sulphonylureas (5)
17712	HYPURIN BOVINE LENTE VIAL injection suspension 100 units/ml [CP PHARM]	Insulins (1)
17731	PENMIX 50/50 injection 100 iu/ml [NOVO]	Insulins (1)
17809	HUMAJECT M4 pen 100 iu/ml [LILLY]	Insulins (1)
18220	pioglitazone with metformin tablets 15mg + 850mg	Metformin + thiazolidinedione (4)
18224	HUMALOG VIAL injection solution 100 units/ml [LILLY]	Insulins (1)
18301	INSULIN SOLUBLE INJ I/U^2	Insulins (1)
18461	insulin zinc suspension mixed human prb injection 100 units/ml	Insulins (1)
18590	insulin isophane bovine vial injection suspension 100 units/ml	Insulins (1)
18592	insulin soluble bovine vial injection solution 100 units/ml	Insulins (1)

18593	HUMALOG MIX 50 CARTRIDGE injection suspension 100 units/ml [LILLY]	Insulins (1)
18645	INSULIN NEUTRAL (PURIFIED) 100 I/U INJ	Insulins (1)
18931	insulin zinc suspension crystalline human prb - intermediate acting injection 100 units/ml	Insulins (1)
19029	SYRINGE PRE-SET INSULIN FOR BLIND 2ML	Insulins (1)
19336	tolazamide tablets 100mg	Sulphonylureas (5)
19472	ACTOS tablets 45mg [TAKEDA]	Thiazolidinediones (6)
19491	APIDRA VIAL injection solution 100 units/ml [SANOFI/AVE]	Insulins (1)
19513	HUMULIN M3 VIAL injection suspension 100 units/ml [LILLY]	Insulins (1)
19658	GLURENORM tablets 30mg [SANOFI S]	Sulphonylureas (5)
19707	INSULIN HUMULIN S (NEUTRAL SOLUBLE)	Insulins (1)
19829	INSULIN NOVO MONOTARD MC	Insulins (1)
19877	insulin aspart disposable pen injection solution 100 units/ml	Insulins (1)
19878	insulin biphasic isophane human disposable pen injection suspension 30:70; 100 units/ml	Insulins (1)
20195	INSULIN BOVINE PROTAMINE ZINC 40 I/U INJ	Insulins (1)
20196	INSULIN SOLUBLE 40 I/U INJ	Insulins (1)
20287	ACTOS tablets 15mg [TAKEDA]	Thiazolidinediones (6)
20422	INSUMAN COMB 15 injection 100 iu/ml [AVENTIS]	Insulins (1)
20671	INSULIN HUM/ACTRAPHANE	Insulins (1)
20672	INSULIN HUM/ACTRAPID	Insulins (1)
20810	METFORMIN	Metformin (2)
20889	ACTOS tablets 30mg [TAKEDA]	Thiazolidinediones (6)
20995	HYPURIN PORCINE 30/70 MIX CARTRIDGE injection suspension 100 units/ml [CP PHARM]	Insulins (1)
21110	insulin biphasic isophane human prb injection 50:50; 100 units/ml	Insulins (1)
21232	insulin biphasic isophane human vial injection suspension 30:70; 100 units/ml	Insulins (1)
21235	HUMULIN S VIAL injection solution 100 units/ml [LILLY]	Insulins (1)
21347	PENMIX 40/60 injection 100 iu/ml [NOVO]	Insulins (1)
21374	insulin biphasic isophane human prb injection 40:60; 100 units/ml	Insulins (1)
21395	insulin biphasic isophane human pyr injection 40:60; 100 units/ml	Insulins (1)
21422	insulin biphasic isophane human cartridge injection suspension 40:60; 100 units/ml	Insulins (1)
21424	glibenclamide oral suspension 5mg/5ml	Sulphonylureas (5)
21459	SYRINGE INSULIN U100 S/U+8MM NEEDLE	Insulins (1)
21489	TOLANASE tablets 250mg [PHARMACIA]	Sulphonylureas (5)
21554	INSUMAN COMB 50 injection 100 iu/ml [AVENTIS]	Insulins (1)
21564	GLICLAZIDE tablets 80mg [WOCKHARDT]	Sulphonylureas (5)
21583	APIDRA OPTISET injection solution 100 units/ml [SANOFI/AVE]	Insulins (1)
21590	insulin glulisine disposable pen injection solution 100 units/ml	Insulins (1)
21832	DIABETAMIDE tablets 5mg [ASHBOURNE]	Sulphonylureas (5)
21892	DIAGLYK tablets 80mg [ASHBOURNE]	Sulphonylureas (5)
21945	INSULIN PORK INSULATARD	Insulins (1)

22058	PUR-IN MIX 15/85 injection [CP PHARM]	Insulins (1)
22094	INSULIN HUMULIN M2 VIAL	Insulins (1)
22145	TOLANASE tablets 100mg [PHARMACIA]	Sulphonylureas (5)
22155	HUMAJECT M5 pen 100 iu/ml [LILLY]	Insulins (1)
22161	INSULIN HUMULIN M1 VIAL	Insulins (1)
22496	INSULIN ZINC LENTE PURIFIED SUSPENSION	Insulins (1)
22636	TOLBUTAMIDE 1 GM TAB	Sulphonylureas (5)
22697	insulin biphasic isophane human pyr injection 50:50; 100 units/ml	Insulins (1)
22806	INSULIN PORK ACTRAPID	Insulins (1)
22823	INSULIN ISOPHANE (PURIFIED) 100 I/U INJ	Insulins (1)
22858	acetohexamide tablets 500mg	Sulphonylureas (5)
22945	INSUMAN RAPID injection 100 iu/ml [AVENTIS]	Insulins (1)
22983	INSUMAN RAPID CARTRIDGE injection solution 100 units/ml [AVENTIS]	Insulins (1)
23003	INSULIN ISOPHANE (NPH) 40 I/U	Insulins (1)
23099	insulin biphasic aspart disposable pen injection suspension 30:70; 100 units/ml	Insulins (1)
23231	HYPURIN BOVINE NEUTRAL CARTRIDGE injection solution 100 units/ml [CP PHARM]	Insulins (1)
23945	STARLIX tablets 60mg [NOVARTIS]	Meglitinides (10)
23992	INSUMAN BASAL OPTISET injection suspension 100 units/ml [AVENTIS]	Insulins (1)
23993	INSUMAN RAPID OPTISET injection solution 100 units/ml [AVENTIS]	Insulins (1)
24002	INSUMAN COMB 25 VIAL injection suspension 100 units/ml [AVENTIS]	Insulins (1)
24485	INSULIN ZINC ANIMAL SUSPENSION	Insulins (1)
24593	neutral insulin bovine injection 100 iu/ml	Insulins (1)
24722	INSULIN ISOPHANE 50%/NEUTRAL 50% 100 I/U INJ	Insulins (1)
24795	insulin biphasic aspart cartridge injection suspension 30:70; 100 units/ml	Insulins (1)
24800	HYPURIN PORCINE 30/70 MIX VIAL injection suspension 100 units/ml [CP PHARM]	Insulins (1)
24845	INSULIN PUR-IN ISOPHANE 100 I/U INJ	Insulins (1)
24846	PUR-IN NEUTRAL injection 100 units/ml [CP PHARM]	Insulins (1)
24848	glymidine sodium tablets 500mg	Sulphonylureas (5)
24866	INSULIN INSULATARD (LEO RETARD) 40 I/U INJ	Insulins (1)
24993	INSUMAN COMB 25 CARTRIDGE injection suspension 100 units/ml [AVENTIS]	Insulins (1)
25006	INSULIN HUMAN ACTRAPID (NEUTRAL)	Insulins (1)
25133	INSUMAN COMB 25 OPTISET injection suspension 100 units/ml [AVENTIS]	Insulins (1)
25479	insulin soluble porcine cartridge injection solution 100 units/ml	Insulins (1)
25636	LIBANIL tablets 2.5mg [APS]	Sulphonylureas (5)
25678	GLUCAMET tablets 500mg [OPUS]	Metformin (2)
25735	insulin biphasic isophane human cartridge injection suspension 20:80; 100 units/ml	Insulins (1)
25736	insulin biphasic isophane human cartridge injection suspension 10:90; 100 units/ml	Insulins (1)

25812	insulin isophane human disposable pen injection suspension 100 units/ml	Insulins (1)
26060	insulin lispro vial injection solution 100 units/ml	Insulins (1)
26098	HYPURIN PORCINE NEUTRAL VIAL injection solution 100 units/ml [CP PHARM]	Insulins (1)
26118	DIMELOR tablets 500mg [LILLY]	Sulphonylureas (5)
26218	CALABREN tablets 5mg [BERK]	Sulphonylureas (5)
26258	GLUCAMET tablets 850mg [OPUS]	Metformin (2)
26403	PUR-IN MIX 25/75 injection [CP PHARM]	Insulins (1)
26498	insulin zinc suspension mixed bovine and porcine injection 100 units/ml	Insulins (1)
26621	insulin soluble human crb injection 100 iu/ml	Insulins (1)
26784	INSULIN ZINC SEMILENTE SUSP BP 100 I/U INJ	Insulins (1)
26795	SYRINGE INSULIN DISPOSABLE	Insulins (1)
27125	STARLIX tablets 180mg [NOVARTIS]	Meglitinides (10)
27151	SYRINGE INSULIN U100 S/U+8MM NEEDLE	Insulins (1)
27177	insulin biphasic lispro human prb injection 50:50; 100 units/ml	Insulins (1)
27280	insulin biphasic isophane porcine vial injection suspension 30:70; 100 units/ml	Insulins (1)
27396	insulin soluble porcine vial injection solution 100 units/ml	Insulins (1)
27402	insulin soluble human vial injection solution 100 units/ml	Insulins (1)
27461	INSUMAN BASAL CARTRIDGE injection suspension 100 units/ml [AVENTIS]	Insulins (1)
27501	ORABET tablets 500mg [LAGAP]	Metformin (2)
27614	PENMIX 30/70 injection 100 iu/ml [NOVO]	Insulins (1)
27911	INSULIN HUMAN ACTRAPID PENFILL	Insulins (1)
27969	GLYMESE tablets 250mg [DDSA]	Sulphonylureas (5)
28096	insulin biphasic isophane human cartridge injection suspension 50:50; 100 units/ml	Insulins (1)
28101	insulin glulisine vial injection solution 100 units/ml	Insulins (1)
28183	HYPURIN PORCINE ISOPHANE VIAL injection suspension 100 units/ml [CP PHARM]	Insulins (1)
28185	insulin biphasic lispro cartridge injection suspension 25:75; 100 units/ml	Insulins (1)
28442	insulin glulisine injection solution 100 units/ml	Insulins (1)
28588	HYPURIN BOVINE ISOPHANE CARTRIDGE injection suspension 100 units/ml [CP PHARM]	Insulins (1)
28708	MALIX tablets 2.5mg [LAGAP]	Sulphonylureas (5)
28723	INSULIN ZINC BOVINE SUSPENSION	Insulins (1)
28978	INSULIN PUR-IN MIX 15/85 100 I/U INJ	Insulins (1)
29326	GLIPIZIDE tablets 5mg [GEN (UK)]	Sulphonylureas (5)
29567	insulin aspart vial injection solution 100 units/ml	Insulins (1)
29837	insulin biphasic isophane human prb injection 25:75; 100 units/ml	Insulins (1)
29939	GLICLAZIDE tablets 80mg [GEN (UK)]	Sulphonylureas (5)
29953	APIDRA OPTICLIK injection solution 100 units/ml [SANOFI/AVE]	Insulins (1)
30209	ACTRAPID MC injection 100 units/ml [ARUN]	Insulins (1)
30236	isophane insulin injection 100 iu/ml	Insulins (1)

30316	metformin with pioglitazone tablets 850mg + 15mg	Metformin + thiazolidinedione (4)
30460	MALIX tablets 5mg [LAGAP]	Sulphonylureas (5)
30686	insulin isophane porcine cartridge injection suspension 100 units/ml	Insulins (1)
30819	INSUMAN COMB 15 OPTISET injection suspension 100 units/ml [AVENTIS]	Insulins (1)
30861	INSULIN ZINC HUMAN SUSPENSION	Insulins (1)
31077	COMPETACT film coated tablets [TAKEDA]	Metformin + thiazolidinedione (4)
31146	METSOL oral solution 500mg/5ml [ORBIS]	Metformin (2)
31205	INSUMAN COMB 50 OPTISET injection suspension 100 units/ml [AVENTIS]	Insulins (1)
31212	GLICLAZIDE tablets 80mg [ACTAVIS]	Sulphonylureas (5)
31258	insulin biphasic lispro disposable pen injection suspension 25:75; 100 units/ml	Insulins (1)
31267	INSULIN PUR-IN MIX 50/50 100 I/U INJ	Insulins (1)
31465	EXUBERA powder for inhalation 1mg [PFIZER]	Insulins (1)
31467	EXUBERA powder for inhalation 3mg [PFIZER]	Insulins (1)
31474	LIBANIL tablets 5mg [APS]	Sulphonylureas (5)
32053	INSULIN HUMALOG MIX 25	Insulins (1)
33087	METFORMIN tablets 500mg [ACTAVIS]	Metformin (2)
33167	insulin biphasic isophane human crb injection 25:75; 100 units/ml	Insulins (1)
33232	insulin biphasic isophane human crb injection 50:50; 100 units/ml	Insulins (1)
33562	DUCLAZIDE tablets 80mg [DUMEX]	Sulphonylureas (5)
33673	TOLBUTAMIDE tablets 500mg [ACTAVIS]	Sulphonylureas (5)
33674	METFORMIN tablets 850mg [HILLCROSS]	Metformin (2)
33966	INSULATARD injection 100 units/ml [NOVO]	Insulins (1)
34004	METFORMIN tablets 500mg [IVAX]	Metformin (2)
34020	METFORMIN tablets 850mg [IVAX]	Metformin (2)
34031	MONOTARD MC injection 100 units/ml [NOVO]	Insulins (1)
34097	HUMAN INITARD 50/50 injection 100 units/ml [NOVO]	Insulins (1)
34135	METFORMIN tablets 500mg [M&A PHARM]	Metformin (2)
34323	METFORMIN tablets 500mg [HILLCROSS]	Metformin (2)
34399	GLICLAZIDE tablets 80mg [IVAX]	Sulphonylureas (5)
34504	METFORMIN tablets 500mg [WOCKHARDT]	Metformin (2)
34507	GLIBENCLAMIDE tablets 2.5mg [CP PHARM]	Sulphonylureas (5)
34563	GLIBENCLAMIDE tablets 5mg [CP PHARM]	Sulphonylureas (5)
34598	METFORMIN tablets 500mg [GEN (UK)]	Metformin (2)
34676	GLIBENCLAMIDE tablets 2.5mg [HILLCROSS]	Sulphonylureas (5)
34697	METFORMIN tablets 850mg [WOCKHARDT]	Metformin (2)
34706	GLIBENCLAMIDE tablets 2.5mg [IVAX]	Sulphonylureas (5)
34742	METFORMIN tablets 850mg [TEVA]	Metformin (2)
34802	GLIPIZIDE tablets 5mg [IVAX]	Sulphonylureas (5)
34836	METFORMIN tablets 850mg [ACTAVIS]	Metformin (2)
34917	METFORMIN tablets 500mg [TEVA]	Metformin (2)

34932	GLICLAZIDE tablets 80mg [GENUS]	Sulphonylureas (5)
34957	TOLBUTAMIDE tablets 500mg [HILLCROSS]	Sulphonylureas (5)
35022	sitagliptin tablets 100mg	DPP4 inhibitors (8)
35144	BYETTA injection 5 micrograms [LILLY]	GLP1 agonists (9)
35149	exenatide injection 10micrograms	GLP1 agonists (9)
35150	BYETTA injection 10micrograms [LILLY]	GLP1 agonists (9)
35251	exenatide injection 5 micrograms	GLP1 agonists (9)
35253	INSUMAN COMB 50 CARTRIDGE injection suspension 100 units/ml [AVENTIS]	Insulins (1)
35260	LEVEMIR INNOLET injection solution 100 units/ml [NOVO]	Insulins (1)
35462	JANUVIA tablets 100mg [M S D]	DPP4 inhibitors (8)
35468	INSUMAN BASAL VIAL injection suspension 100 units/ml [AVENTIS]	Insulins (1)
35561	PRANDIN tablets 2mg [DAIIC-SANK]	Meglitinides (10)
35701	insulin biphasic lispro disposable pen injection suspension 50:50; 100 units/ml	Insulins (1)
36031	insulin biphasic isophane porcine cartridge injection suspension 30:70; 100 units/ml	Insulins (1)
36066	insulin isophane bovine cartridge injection suspension 100 units/ml	Insulins (1)
36146	insulin biphasic lispro cartridge injection suspension 50:50; 100 units/ml	Insulins (1)
36194	insulin biphasic isophane human cartridge injection suspension 25:75; 100 units/ml	Insulins (1)
36355	insulin human powder for inhalation 1mg	Insulins (1)
36356	insulin human powder for inhalation 3mg	Insulins (1)
36430	insulin soluble human disposable pen injection solution 100 units/ml	Insulins (1)
36513	VELOSULIN CARTRIDGE injection 100 units/ml [NOVO]	Insulins (1)
36774	PRANDIN tablets 1mg [DAIIC-SANK]	Meglitinides (10)
36853	LANTUS SOLOSTAR injection solution 100 units/ml [SANOFI/AVE]	Insulins (1)
36856	GLICLAZIDE tablets 80mg [SANDOZ]	Sulphonylureas (5)
36920	APIDRA SOLOSTAR injection solution 100 units/ml [SANOFI/AVE]	Insulins (1)
36948	PRANDIN tablets 500 micrograms [DAIIC-SANK]	Meglitinides (10)
37617	rosiglitazone tablets 2mg	Thiazolidinediones (6)
37874	vildagliptin with metformin tablets 50mg + 850mg	Metformin + DPP4 inhibitor (3)
37875	vildagliptin tablets 50mg	DPP4 inhibitors (8)
37902	vildagliptin with metformin tablets 50mg + 1000mg	Metformin + DPP4 inhibitor (3)
38355	metformin modified release tablet 750mg	Metformin (2)
38400	GLUCOPHAGE SR tablets 750mg [MERCK SER]	Metformin (2)
38422	ISOPHANE injection 100 iu/ml [CELLTECH]	Insulins (1)
38551	EUCREAS tablets 50mg + 1000mg [NOVARTIS]	Metformin + DPP4 inhibitor (3)
38986	HUMALOG KWIKPEN injection solution 100 units/ml [LILLY]	Insulins (1)
39006	HUMALOG MIX 25 KWIKPEN injection suspension 100 units/ml [LILLY]	Insulins (1)
39086	HUMALOG MIX 50 KWIKPEN injection suspension 100 units/ml [LILLY]	Insulins (1)

39149	GALVUS tablets 50mg [NOVARTIS]	DPP4 inhibitors (8)
39203	EUCREAS tablets 50mg + 850mg [NOVARTIS]	Metformin + DPP4 inhibitor (3)
39560	BOLAMYN SR tablets 500mg [TEVA]	Metformin (2)
39598	metformin modified release tablet 1000mg	Metformin (2)
39729	GLUCOPHAGE SR tablets 1000mg [MERCK SER]	Metformin (2)
39988	metformin oral powder 500mg	Metformin (2)
40007	GLUCOPHAGE sachets 1000mg [MERCK SER]	Metformin (2)
40110	GLUCOPHAGE sachets 500mg [MERCK SER]	Metformin (2)
40233	metformin oral powder 1000mg	Metformin (2)
40365	GLIMEPIRIDE tablets 1mg [ACTAVIS]	Sulphonylureas (5)
40425	NAZDOL MR tablets 30mg [TEVA]	Sulphonylureas (5)
40642	VICTOZA injection 18mg/3ml [NOVO]	GLP1 agonists (9)
40693	liraglutide injection 18mg/3ml	GLP1 agonists (9)
41120	insulin biphasic isophane human disposable pen injection suspension 50:50; 100 units/ml	Insulins (1)
41204	saxagliptin tablets 5mg	DPP4 inhibitors (8)
41431	ONGLYZA tablets 5mg [BMS]	DPP4 inhibitors (8)
41558	GLIBENCLAMIDE tablets 5mg [TEVA]	Sulphonylureas (5)
41559	GLIBENCLAMIDE tablets 5mg [HILLCROSS]	Sulphonylureas (5)
41593	GLIBENCLAMIDE tablets 2.5mg [TEVA]	Sulphonylureas (5)

Hyperlipidaemia

Product code	Product name	Drug substance
25	Simvastatin 20mg tablets	Simvastatin
28	Atorvastatin 10mg tablets	Atorvastatin calcium trihydrate
42	Simvastatin 10mg tablets	Simvastatin
51	Simvastatin 40mg tablets	Simvastatin
75	Atorvastatin 20mg tablets	Atorvastatin calcium trihydrate
184	Bezafibrate 200mg tablets	Bezafibrate
379	Fluvastatin 20mg capsules	Fluvastatin sodium
420	Cerivastatin 100microgram tablets	Cerivastatin sodium
490	Pravastatin 10mg tablets	Pravastatin sodium
602	Bezafibrate 400mg modified-release tablets	Bezafibrate
644	Colestyramine 4g oral powder sachets	Colestyramine anhydrous
653	Ezetimibe 10mg tablets	Ezetimibe
713	Rosuvastatin 10mg tablets	Rosuvastatin calcium
730	Pravastatin 20mg tablets	Pravastatin sodium
745	Atorvastatin 40mg tablets	Atorvastatin calcium trihydrate
802	Simvador 40mg tablets (Discovery Pharmaceuticals)	Simvastatin
818	Simvastatin 20mg/5ml oral solution sugar free	Simvastatin
1212	Colestipol 5g granules sachets sugar free	Colestipol hydrochloride
1214	Bezalip 400mg Tablet (Roche Products Ltd)	Bezafibrate
1215	Fenofibrate 100mg Capsule	Fenofibrate

1217	Lipantil micro 200 200mg Capsule (Fournier Pharmaceuticals Ltd)	Fenofibrate micronised
1219	Pravastatin 40mg tablets	Pravastatin sodium
1221	Lipostat 10mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Pravastatin sodium
1223	Lipostat 40mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Pravastatin sodium
1322	Clofibrate 500mg capsules	Clofibrate
1324	Bezalip 200mg Tablet (Roche Products Ltd)	Bezafibrate
1477	Atromid -s 500mg Capsule (AstraZeneca UK Ltd)	Clofibrate
1716	Questran 4g oral powder sachets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Colestyramine anhydrous
1764	Questran Light 4g oral powder sachets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Colestyramine anhydrous
2137	Fluvastatin 40mg capsules	Fluvastatin sodium
2215	Lopid 300mg capsules (Pfizer Ltd)	Gemfibrozil
2435	Lipantil 100mg Capsule (Fournier Pharmaceuticals Ltd)	Fenofibrate
2662	MaxEPA 1g capsules (Seven Seas Ltd)	Eicosapentaenoic acid/Docosahexaenoic acid
2718	Zocor 10mg tablets (Merck Sharp & Dohme Ltd)	Simvastatin
2955	Lipitor 40mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
3089	Ciprofibrate 100mg tablets	Ciprofibrate
3159	Fenofibrate 200mg capsules	Fenofibrate
3204	MaxEPA liquid (Seven Seas Ltd)	Eicosapentaenoic acid/Docosahexaenoic acid
3318	Gemfibrozil 300mg capsules	Gemfibrozil
3411	Lipitor 10mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
3690	Lipostat 20mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Pravastatin sodium
4062	Lopid 600mg tablets (Pfizer Ltd)	Gemfibrozil
4067	Olbetam 250mg capsules (Pfizer Ltd)	Acipimox
4920	Fenofibrate micronised 200mg capsules	Fenofibrate micronised
4928	Lipantil Micro 200 capsules (Mylan Ltd)	Fenofibrate micronised
4961	Lipobay 300microgram Tablet (Bayer Plc)	Cerivastatin sodium
5009	Cerivastatin 200microgram tablets	Cerivastatin sodium
5148	Simvastatin 80mg tablets	Simvastatin
5216	Bezalip mono 400mg Modified-release tablet (Roche Products Ltd)	Bezafibrate
5251	Cerivastatin 300microgram tablets	Cerivastatin sodium
5278	Cerivastatin 400microgram tablets	Cerivastatin sodium
5390	Fenofibrate micronised 267mg capsules	Fenofibrate micronised
5564	Colestid Orange sachets (Pharmacia Ltd)	Colestipol Hydrochloride
5775	Atorvastatin 80mg tablets	Atorvastatin calcium trihydrate
5985	Lescol XL 80mg tablets (Novartis Pharmaceuticals UK Ltd)	Fluvastatin sodium
6120	Ezetrol 10mg tablets (Merck Sharp & Dohme Ltd)	Ezetimibe
6155	Colestyramine with aspartame 4g sugar free powder	Colestyramine Anhydrous

6168	Zocor 40mg tablets (Merck Sharp & Dohme Ltd)	Simvastatin
6213	Rosuvastatin 20mg tablets	Rosuvastatin calcium
6365	Colestid 5g granules sachets plain (Pfizer Ltd)	Colestipol hydrochloride
6572	Omacor capsules (Mylan Ltd)	Eicosapentaenoic acid/Docosahexaenoic acid
7196	Zocor 20mg tablets (Merck Sharp & Dohme Ltd)	Simvastatin
7347	Crestor 10mg tablets (AstraZeneca UK Ltd)	Rosuvastatin calcium
7374	Lipitor 20mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
7540	Lipantil Micro 267 capsules (Mylan Ltd)	Fenofibrate micronised
7544	Niaspan 750mg modified-release tablets (Abbott Laboratories Ltd)	Nicotinic acid
7551	Niaspan 1g modified-release tablets (Abbott Laboratories Ltd)	Nicotinic acid
7552	Simvastatin 20mg / Ezetimibe 10mg tablets	Simvastatin/Ezetimibe
7554	Rosuvastatin 5mg tablets	Rosuvastatin calcium
8082	Gemfibrozil 600mg tablets	Gemfibrozil
8104	Acipimox 250mg capsules	Acipimox
8366	Probucol 250mg tablet	Probucol
8380	Lescol 20mg capsules (Novartis Pharmaceuticals UK Ltd)	Fluvastatin sodium
8706	Modalim 100mg tablets (Sanofi)	Ciprofibrate
8834	Lurselle 250mg Tablet (Hoechst Marion Roussel)	Probucol
9153	Lescol 40mg capsules (Novartis Pharmaceuticals UK Ltd)	Fluvastatin sodium
9315	Lipobay 100microgram Tablet (Bayer Plc)	Cerivastatin sodium
9316	Lipobay 200microgram Tablet (Bayer Plc)	Cerivastatin sodium
9491	Fenofibrate micronised 67mg capsules	Fenofibrate micronised
9639	Fenofibrate micronised 160mg tablets	Fenofibrate micronised
9716	Supralip 160mg tablets (Mylan Ltd)	Fenofibrate micronised
9897	Rosuvastatin 40mg tablets	Rosuvastatin calcium
9920	Simvador 20mg tablets (Discovery Pharmaceuticals)	Simvastatin
9930	Crestor 40mg tablets (AstraZeneca UK Ltd)	Rosuvastatin calcium
10094	Niaspan titration pack (Abbott Laboratories Ltd)	Nicotinic acid
10172	Simvastatin 40mg / Ezetimibe 10mg tablets	Simvastatin/Ezetimibe
10183	Simvastatin 40mg with ezetimibe 10mg tablet	Simvastatin/Ezetimibe
10206	Simvastatin 80mg with ezetimibe 10mg tablet	Simvastatin/Ezetimibe
11627	Fluvastatin 80mg modified-release tablets	Fluvastatin sodium
11785	Colestyramine 4g oral powder sachets sugar free	Colestyramine anhydrous
11815	Simvastatin 20mg with ezetimibe 10mg tablet	Simvastatin/Ezetimibe
11976	Niaspan 500mg modified-release tablets (Abbott Laboratories Ltd)	Nicotinic acid
12211	Nicotinic acid 50mg tablets	Nicotinic acid
13041	Simvador 10mg tablets (Discovery Pharmaceuticals)	Simvastatin
14219	Simvastatin 80mg / Ezetimibe 10mg tablets	Simvastatin/Ezetimibe
14379	Lipantil Micro 67 capsules (Mylan Ltd)	Fenofibrate micronised
14963	Nicotinic acid 500mg modified-release tablets	Nicotinic acid

15252	Crestor 20mg tablets (AstraZeneca UK Ltd)	Rosuvastatin calcium
16186	Inegy 10mg/80mg tablets (Merck Sharp & Dohme Ltd)	Simvastatin/Ezetimibe
17059	Inegy 10mg/40mg tablets (Merck Sharp & Dohme Ltd)	Simvastatin/Ezetimibe
17614	Zimbacol XL 400mg tablets (Archimedes Pharma UK Ltd)	Bezafibrate
17683	Lipitor 80mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
17688	Crestor 5mg tablets (AstraZeneca UK Ltd)	Rosuvastatin calcium
17813	Nicotinic acid 100mg Tablet	Nicotinic Acid
17824	Nicotinic acid 25mg Tablet	Nicotinic Acid
18081	Colestid Orange 5g granules sachets (Pfizer Ltd)	Colestipol hydrochloride
18098	Nicotinic acid 375mg + 500mg + 750mg Modified-release tablet	Nicotinic Acid
18126	Nicotinic acid 1g modified-release tablets	Nicotinic acid
18442	Lipobay 400microgram Tablet (Bayer Plc)	Cerivastatin sodium
19938	Colestipol with aspartame granules	Colestipol Hydrochloride
21020	Inegy 10mg/20mg tablets (Merck Sharp & Dohme Ltd)	Simvastatin/Ezetimibe
22579	Zocor 80mg tablets (Merck Sharp & Dohme Ltd)	Simvastatin
23153	Liparol 400 XL tablets (Ashbourne Pharmaceuticals Ltd)	Bezafibrate
23956	Maxepa Liquid (Seven Seas Ltd)	Eicosapentaenoic Acid/Docosahexaenoic Acid/Alpha Tocopheryl Acetate
24084	Colestyramine 4g oral powder sachets sugar free (PLIVA Pharma Ltd)	Colestyramine anhydrous
24583	Nicotinic acid 750mg modified-release tablets	Nicotinic acid
29213	Bezagen XL 400mg tablets (Mylan Ltd)	Bezafibrate
29328	Bezafibrate 200mg tablets (A A H Pharmaceuticals Ltd)	Bezafibrate
31221	Bezafibrate 200mg tablets (Mylan Ltd)	Bezafibrate
31658	Cerivastatin 800microgram tablets	Cerivastatin sodium
31783	Fenogal 200mg capsules (Genus Pharmaceuticals Ltd)	Fenofibrate
31930	Zocor heart-pro 10mg Tablet (McNeil Products Ltd)	Simvastatin
32110	Colestyramine 4g Sachets (Dominion Pharma)	Colestyramine anhydrous
32909	Simvastatin 80mg tablets (A A H Pharmaceuticals Ltd)	Simvastatin
32921	Pravastatin 10mg Tablet (Dr Reddy's Laboratories (UK) Ltd)	Pravastatin sodium
33082	Simvastatin 20mg tablets (A A H Pharmaceuticals Ltd)	Simvastatin
33603	Fibrazate XL 400mg tablets (Sandoz Ltd)	Bezafibrate
33944	Bezafibrate 200mg tablets (Teva UK Ltd)	Bezafibrate
34181	Bezafibrate 400mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)	Bezafibrate
34201	Colestyramine 4g oral powder sachets sugar free (Actavis UK Ltd)	Colestyramine anhydrous
34277	Gemfibrozil 600mg tablets (Teva UK Ltd)	Gemfibrozil
34312	Simvastatin 20mg tablets (Mylan Ltd)	Simvastatin

34316	Simvastatin 20mg tablets (Teva UK Ltd)	Simvastatin
34353	Simvastatin 40mg tablets (Mylan Ltd)	Simvastatin
34366	Simvastatin 20mg tablets (IVAX Pharmaceuticals UK Ltd)	Simvastatin
34376	Simvastatin 40mg tablets (Teva UK Ltd)	Simvastatin
34381	Simvastatin 40mg tablets (IVAX Pharmaceuticals UK Ltd)	Simvastatin
34476	Simvastatin 20mg Tablet (Ratiopharm UK Ltd)	Simvastatin
34481	Simvastatin 10mg tablets (IVAX Pharmaceuticals UK Ltd)	Simvastatin
34502	Simvastatin 40mg tablets (A A H Pharmaceuticals Ltd)	Simvastatin
34535	Simvastatin 10mg tablets (Mylan Ltd)	Simvastatin
34545	Simvastatin 40mg Tablet (Ratiopharm UK Ltd)	Simvastatin
34560	Simvastatin 10mg Tablet (Ratiopharm UK Ltd)	Simvastatin
34746	Simvastatin 20mg Tablet (Niche Generics Ltd)	Simvastatin
34814	Simvastatin 20mg tablets (Wockhardt UK Ltd)	Simvastatin
34820	Pravastatin 40mg tablets (A A H Pharmaceuticals Ltd)	Pravastatin sodium
34879	Simvastatin 40mg Tablet (Niche Generics Ltd)	Simvastatin
34891	Simvastatin 20mg tablets (Kent Pharmaceuticals Ltd)	Simvastatin
34907	Simvastatin 40mg tablets (Wockhardt UK Ltd)	Simvastatin
34955	Simvastatin 10mg tablets (A A H Pharmaceuticals Ltd)	Simvastatin
34969	Simvastatin 40mg tablets (Actavis UK Ltd)	Simvastatin
36377	Pravastatin 20mg tablets (Teva UK Ltd)	Pravastatin sodium
37266	Colesevelam 625mg tablets	Colesevelam hydrochloride
37434	Simvastatin 40mg tablets (Sandoz Ltd)	Simvastatin
37953	Cholestagel 625mg tablets (Sanofi)	Colesevelam hydrochloride
39060	Simvastatin 20mg tablets (Dexcel-Pharma Ltd)	Simvastatin
39420	Bezalip Mono 400mg modified-release tablets (Teva UK Ltd)	Bezafibrate
39576	Bezalip 200mg tablets (Teva UK Ltd)	Bezafibrate
39652	Simvastatin 40mg/5ml oral solution sugar free	Simvastatin
39675	Simvastatin 20mg/5ml Oral suspension (Martindale Pharmaceuticals Ltd)	Simvastatin
39870	Simvador 80mg tablets (Discovery Pharmaceuticals)	Simvastatin
40340	Simvastatin 10mg tablets (Teva UK Ltd)	Simvastatin
40382	Pravastatin 20mg tablets (A A H Pharmaceuticals Ltd)	Pravastatin sodium
40601	Simvastatin 20mg tablets (Ranbaxy (UK) Ltd)	Simvastatin
40729	Tredaptive 1000mg/20mg modified-release tablets (Merck Sharp & Dohme Ltd)	Laropiprant/Nicotinic acid
40885	Nicotinic acid 1g / Laropiprant 20mg modified-release tablets	Nicotinic Acid/laropiprant
41396	Fenofibrate micronised 200mg capsules (A A H Pharmaceuticals Ltd)	Fenofibrate micronised
41657	Simvastatin 80mg tablets (Teva UK Ltd)	Simvastatin

42801	Bezafibrate xl 400mg Modified-release tablet (Generics (UK) Ltd)	Bezafibrate
43218	Pravastatin 10mg tablets (Teva UK Ltd)	Pravastatin sodium
44528	Simvastatin 20mg/5ml oral suspension sugar free (Rosemont Pharmaceuticals Ltd)	Simvastatin
44650	Simvastatin 40mg tablets (Dexcel-Pharma Ltd)	Simvastatin
44878	Ranzolont 10mg tablets (Ranbaxy (UK) Ltd)	Simvastatin
45219	Simvastatin 40mg tablets (Kent Pharmaceuticals Ltd)	Simvastatin
45235	Simvastatin 20mg tablets (Sandoz Ltd)	Simvastatin
45245	Simvastatin 20mg tablets (Actavis UK Ltd)	Simvastatin
45346	Simvastatin 40mg tablets (Arrow Generics Ltd)	Simvastatin
46878	Simvastatin 40mg tablets (Almus Pharmaceuticals Ltd)	Simvastatin
46956	Simvastatin 80mg tablets (Arrow Generics Ltd)	Simvastatin
47065	Atorvastatin 20mg chewable tablets sugar free	Atorvastatin Calcium
47090	Atorvastatin 10mg chewable tablets sugar free	Atorvastatin Calcium
47630	Lipitor 20mg chewable tablets (Pfizer Ltd)	Atorvastatin Calcium
47721	Lipitor 10mg chewable tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
47774	Simvastatin 10mg tablets (Arrow Generics Ltd)	Simvastatin
47935	Fenofibrate 200mg Capsule (Teva UK Ltd)	Fenofibrate micronised
47948	Simvastatin 10mg tablets (Tillomed Laboratories Ltd)	Simvastatin
47988	Pravastatin 40mg tablets (Mylan Ltd)	Pravastatin sodium
48018	Simvastatin 20mg tablets (Arrow Generics Ltd)	Simvastatin
48051	Simvastatin 10mg tablets (Kent Pharmaceuticals Ltd)	Simvastatin
48058	Simvastatin 10mg tablets (Ranbaxy (UK) Ltd)	Simvastatin
48078	Simvastatin 10mg tablets (Actavis UK Ltd)	Simvastatin
48097	Pravastatin 40mg tablets (Teva UK Ltd)	Pravastatin sodium
48221	Simvastatin 20mg/5ml oral suspension sugar free	Simvastatin
48346	Atorvastatin 60mg tablets	Atorvastatin calcium trihydrate
48431	Simvastatin 40mg/5ml oral suspension sugar free	Simvastatin
48518	Atorvastatin 10mg/5ml oral solution	Atorvastatin calcium trihydrate
48867	Simvastatin 40mg tablets (Alliance Healthcare (Distribution) Ltd)	Simvastatin
48973	Atorvastatin 30mg tablets	Atorvastatin calcium trihydrate
49061	Simvastatin 40mg tablets (Bristol Laboratories Ltd)	Simvastatin
49062	Simvastatin 20mg tablets (Alliance Healthcare (Distribution) Ltd)	Simvastatin
49558	Atorvastatin 20mg tablets (A A H Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
49587	Simvastatin 80mg tablets (Almus Pharmaceuticals Ltd)	Simvastatin
49609	Bezafibrate 400mg Modified-release tablet (Sandoz Ltd)	Bezafibrate
49751	Atorvastatin 40mg tablets (Alliance Healthcare (Distribution) Ltd)	Atorvastatin calcium trihydrate
50071	Fenofibrate 160mg Tablet (Teva UK Ltd)	Fenofibrate micronised

50236	Atorvastatin 10mg tablets (Zentiva)	Atorvastatin calcium trihydrate
50272	Atorvastatin 40mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
50483	Simvastatin 40mg tablets (Relonchem Ltd)	Simvastatin
50564	Simvastatin 20mg tablets (Relonchem Ltd)	Simvastatin
50670	Simvastatin 40mg tablets (Aurobindo Pharma Ltd)	Simvastatin
50703	Simvastatin 40mg tablets (Accord Healthcare Ltd)	Simvastatin
50754	Simvastatin 20mg tablets (Medreich Plc)	Simvastatin
50788	Atorvastatin 20mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
50790	Atorvastatin 20mg tablets (Dexcel-Pharma Ltd)	Atorvastatin calcium trihydrate
50882	Simvastatin 40mg tablets (Somex Pharma)	Simvastatin
50925	Pravastatin 10mg tablets (Sigma Pharmaceuticals Plc)	Pravastatin sodium
50963	Atorvastatin 40mg tablets (Teva UK Ltd)	Atorvastatin calcium trihydrate
51085	Simvastatin 10mg tablets (Medreich Plc)	Simvastatin
51134	Atorvastatin 10mg tablets (A A H Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
51166	Simvastatin 40mg tablets (Medreich Plc)	Simvastatin
51200	Atorvastatin 40mg tablets (Arrow Generics Ltd)	Atorvastatin calcium trihydrate
51233	Simvastatin 10mg tablets (Alliance Healthcare (Distribution) Ltd)	Simvastatin
51359	Atorvastatin 20mg tablets (Arrow Generics Ltd)	Atorvastatin calcium trihydrate
51483	Simvastatin 20mg tablets (Aurobindo Pharma Ltd)	Simvastatin
51622	Atorvastatin 20mg tablets (Consilient Health Ltd)	Atorvastatin calcium trihydrate
51676	Pravastatin 40mg tablets (Medreich Plc)	Pravastatin sodium
51715	Simvastatin 10mg tablets (Sigma Pharmaceuticals Plc)	Simvastatin
51876	Atorvastatin 40mg tablets (Consilient Health Ltd)	Atorvastatin calcium trihydrate
51890	Pravastatin 20mg tablets (Medreich Plc)	Pravastatin sodium
52097	Atorvastatin 40mg tablets (Wockhardt UK Ltd)	Atorvastatin calcium trihydrate
52098	Simvastatin 40mg tablets (Ranbaxy (UK) Ltd)	Simvastatin
52168	Atorvastatin 20mg tablets (Aspire Pharma Ltd)	Atorvastatin calcium trihydrate
52211	Atorvastatin 20mg tablets (Actavis UK Ltd)	Atorvastatin calcium trihydrate
52257	Simvastatin 20mg tablets (Accord Healthcare Ltd)	Simvastatin
52397	Atorvastatin 40mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Atorvastatin calcium trihydrate
52398	Atorvastatin 40mg tablets (A A H Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
52459	Atorvastatin 80mg tablets (Actavis UK Ltd)	Atorvastatin calcium trihydrate
52460	Atorvastatin 40mg tablets (Aspire Pharma Ltd)	Atorvastatin calcium trihydrate
52625	Simvastatin 10mg tablets (Wockhardt UK Ltd)	Simvastatin
52676	Simvastatin 10mg/5ml oral suspension	Simvastatin
52755	Pravastatin 20mg tablets (Alliance Healthcare (Distribution) Ltd)	Pravastatin sodium
52812	Simvastatin 20mg tablets (Sigma Pharmaceuticals Plc)	Simvastatin
52814	Bezafibrate 400mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)	Bezafibrate
52821	Atorvastatin 80mg tablets (Dr Reddy's	Atorvastatin calcium trihydrate

	Laboratories (UK) Ltd)	
52953	Simvastatin 20mg tablets (Bristol Laboratories Ltd)	Simvastatin
52962	Simvastatin 80mg tablets (Medreich Plc)	Simvastatin
53087	Simvastatin 20mg tablets (Somex Pharma)	Simvastatin
53250	Modalim 100mg tablets (Lexon (UK) Ltd)	Ciprofibrate
53340	Zocor 40mg tablets (Lexon (UK) Ltd)	Simvastatin
53415	Simvastatin 10mg tablets (Aurobindo Pharma Ltd)	Simvastatin
53460	Crestor 10mg tablets (DE Pharmaceuticals)	Rosuvastatin calcium
53594	Lipitor 80mg tablets (Mawdsley-Brooks & Company Ltd)	Atorvastatin calcium trihydrate
53676	Simvastatin 20mg tablets (Tillomed Laboratories Ltd)	Simvastatin
53770	Fluvastatin 40mg capsules (A A H Pharmaceuticals Ltd)	Fluvastatin sodium
53772	Atorvastatin 80mg tablets (Alliance Healthcare (Distribution) Ltd)	Atorvastatin calcium trihydrate
53813	Lipobay 100microgram tablets (Bayer Plc)	Cerivastatin sodium
53822	Simvastatin 10mg tablets (Bristol Laboratories Ltd)	Simvastatin
53887	Atorvastatin 40mg tablets (Actavis UK Ltd)	Atorvastatin calcium trihydrate
53890	Atorvastatin 80mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
53908	Simvastatin 10mg tablets (Dexcel-Pharma Ltd)	Simvastatin
53966	Simvastatin 40mg tablets (Phoenix Healthcare Distribution Ltd)	Simvastatin
54240	Simvastatin 40mg tablets (Sigma Pharmaceuticals Plc)	Simvastatin
54266	Simvastatin 20mg/5ml oral suspension	Simvastatin
54435	Pravastatin 40mg tablets (Almus Pharmaceuticals Ltd)	Pravastatin sodium
54493	Simvastatin 10mg tablets (Relonchem Ltd)	Simvastatin
54535	Atorvastatin 10mg tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
54606	Simvastatin 20mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Simvastatin
54607	Pravastatin 20mg tablets (Almus Pharmaceuticals Ltd)	Pravastatin sodium
54655	Simvastatin 10mg tablets (Accord Healthcare Ltd)	Simvastatin
54819	Simvastatin 40mg/5ml oral suspension sugar free (Rosemont Pharmaceuticals Ltd)	Simvastatin
54947	Simvastatin 20mg tablets (Almus Pharmaceuticals Ltd)	Simvastatin
54976	Simvastatin 10mg tablets (Somex Pharma)	Simvastatin
54985	Simvastatin 40mg/5ml oral suspension	Simvastatin
54992	Atorvastatin 10mg/5ml oral suspension	Atorvastatin calcium trihydrate
55032	Atorvastatin 10mg tablets (Dexcel-Pharma Ltd)	Atorvastatin calcium trihydrate
55034	Atorvastatin 40mg/5ml oral suspension	Atorvastatin calcium trihydrate
55207	Lipobay 200microgram tablets (Bayer Plc)	Cerivastatin sodium
55444	Atorvastatin 40mg tablets (Zentiva)	Atorvastatin calcium trihydrate
55452	Simvastatin 20mg tablets (Phoenix Healthcare Distribution Ltd)	Simvastatin

55727	Atorvastatin 10mg tablets (Actavis UK Ltd)	Atorvastatin calcium trihydrate
55912	Pravastatin 40mg tablets (Alliance Healthcare (Distribution) Ltd)	Pravastatin sodium
56016	Lipitor 20mg chewable tablets (Pfizer Ltd)	Atorvastatin calcium trihydrate
56065	Simvastatin 20mg/5ml oral suspension sugar free (Waymade Healthcare Plc)	Simvastatin
56097	Atorvastatin 10mg chewable tablets sugar free	Atorvastatin calcium trihydrate
56146	Pravastatin 10mg tablets (Waymade Healthcare Plc)	Pravastatin sodium
56165	Atorvastatin 20mg chewable tablets sugar free	Atorvastatin calcium trihydrate
56182	Atorvastatin 80mg tablets (Zentiva)	Atorvastatin calcium trihydrate
56248	Atorvastatin 20mg tablets (Sigma Pharmaceuticals Plc)	Atorvastatin calcium trihydrate
56481	Zocor 10mg tablets (Sigma Pharmaceuticals Plc)	Simvastatin
56494	Zocor 20mg tablets (Sigma Pharmaceuticals Plc)	Simvastatin
56564	Atorvastatin 20mg tablets (Almus Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
56607	Pravastatin 20mg tablets (Waymade Healthcare Plc)	Pravastatin sodium
56735	Pravastatin 20mg tablets (Mylan Ltd)	Pravastatin sodium
56841	Atorvastatin 40mg tablets (Dexcel-Pharma Ltd)	Atorvastatin calcium trihydrate
56893	Pravastatin 40mg tablets (Accord Healthcare Ltd)	Pravastatin sodium
56916	Pravastatin 40mg tablets (PLIVA Pharma Ltd)	Pravastatin sodium
57108	Pravastatin 40mg tablets (Waymade Healthcare Plc)	Pravastatin sodium
57117	Atorvastatin 80mg tablets (Waymade Healthcare Plc)	Atorvastatin calcium trihydrate
57137	Pravastatin 10mg tablets (Almus Pharmaceuticals Ltd)	Pravastatin sodium
57219	Fenofibrate micronised 200mg capsules (Sandoz Ltd)	Fenofibrate micronised
57296	Pravastatin 20mg tablets (Phoenix Healthcare Distribution Ltd)	Pravastatin sodium
57329	Simvastatin 25mg/5ml oral suspension	Simvastatin
57348	Atorvastatin 10mg tablets (Consilient Health Ltd)	Atorvastatin calcium trihydrate
57397	Pravastatin 10mg tablets (Accord Healthcare Ltd)	Pravastatin sodium
57489	Ciprofibrate 100mg tablets (Zentiva)	Ciprofibrate
57568	Zocor 10mg tablets (Lexon (UK) Ltd)	Simvastatin
57763	Rosuvastatin 10mg tablets (Waymade Healthcare Plc)	Rosuvastatin calcium
57834	Atorvastatin 40mg tablets (DE Pharmaceuticals)	Atorvastatin calcium trihydrate
57836	Atorvastatin 80mg tablets (Teva UK Ltd)	Atorvastatin calcium trihydrate
57999	Crestor 40mg tablets (Lexon (UK) Ltd)	Rosuvastatin calcium
58041	Atorvastatin 20mg tablets (Teva UK Ltd)	Atorvastatin calcium trihydrate
58110	Atorvastatin 20mg tablets (Zentiva)	Atorvastatin calcium trihydrate
58315	Simvastatin 20mg tablets (Waymade Healthcare Plc)	Simvastatin
58394	Atorvastatin 20mg tablets (Alliance Healthcare (Distribution) Ltd)	Atorvastatin calcium trihydrate
58418	Atorvastatin 80mg tablets (A A H Pharmaceuticals	Atorvastatin calcium trihydrate

	Ltd)	
58480	Lipobay 300microgram tablets (Bayer Plc)	Cerivastatin sodium
58617	Rosuvastatin 20mg/5ml oral suspension	Rosuvastatin calcium
58635	Bezalip Mono 400mg modified-release tablets (DE Pharmaceuticals)	Bezafibrate
58742	Atorvastatin 80mg tablets (Arrow Generics Ltd)	Atorvastatin calcium trihydrate
58755	Simvastatin 10mg tablets (Phoenix Healthcare Distribution Ltd)	Simvastatin
58834	Atorvastatin 10mg tablets (DE Pharmaceuticals)	Atorvastatin calcium trihydrate
58868	Atorvastatin 10mg tablets (Sigma Pharmaceuticals Plc)	Atorvastatin calcium trihydrate
59002	Bezafibrate 400mg modified-release tablets (DE Pharmaceuticals)	Bezafibrate
59272	Atorvastatin 20mg tablets (Waymade Healthcare Plc)	Atorvastatin calcium trihydrate
59278	Fluvastatin 20mg capsules (Zentiva)	Fluvastatin sodium
59331	Lipitor 10mg tablets (DE Pharmaceuticals)	Atorvastatin calcium trihydrate
59357	Atorvastatin 10mg tablets (Ranbaxy (UK) Ltd)	Atorvastatin calcium trihydrate
59446	Atorvastatin 40mg tablets (Almus Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
59447	Crestor 20mg tablets (Waymade Healthcare Plc)	Rosuvastatin calcium
59452	Rosuvastatin 5mg tablets (Waymade Healthcare Plc)	Rosuvastatin calcium
59508	Pravastatin 20mg tablets (Accord Healthcare Ltd)	Pravastatin sodium
59776	Atorvastatin 80mg tablets (Aspire Pharma Ltd)	Atorvastatin calcium trihydrate
59859	Atorvastatin 10mg tablets (Teva UK Ltd)	Atorvastatin calcium trihydrate
60101	Colestyramine 4g oral powder sachets sugar free (Teva UK Ltd)	Colestyramine anhydrous
60160	Rosuvastatin 5mg tablets (Mawdsley-Brooks & Company Ltd)	Rosuvastatin calcium
60251	Pravastatin 10mg tablets (Sandoz Ltd)	Pravastatin sodium
60385	Bezalip Mono 400mg modified-release tablets (Lexon (UK) Ltd)	Bezafibrate
60464	Atorvastatin 20mg/5ml oral suspension	Atorvastatin calcium trihydrate
60511	Atorvastatin 40mg tablets (Ranbaxy (UK) Ltd)	Atorvastatin calcium trihydrate
60607	Atorvastatin 80mg tablets (DE Pharmaceuticals)	Atorvastatin calcium trihydrate
60788	Fenofibrate micronised 267mg capsules (Zentiva)	Fenofibrate micronised
60989	Atorvastatin 80mg tablets (Phoenix Healthcare Distribution Ltd)	Atorvastatin calcium trihydrate
61087	Questran Light 4g oral powder sachets (Mawdsley-Brooks & Company Ltd)	Colestyramine anhydrous
61134	Pravastatin 20mg tablets (Sigma Pharmaceuticals Plc)	Pravastatin sodium
61149	Atorvastatin 10mg tablets (Waymade Healthcare Plc)	Atorvastatin calcium trihydrate
61155	Simvastatin 40mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Simvastatin
61321	Simvastatin 10mg tablets (Sandoz Ltd)	Simvastatin
61360	Simvastatin 10mg tablets (Almus Pharmaceuticals Ltd)	Simvastatin
61665	Simvastatin 10mg tablets (Waymade Healthcare	Simvastatin

	Plc)	
62137	Simvastatin 40mg tablets (Waymade Healthcare Plc)	Simvastatin
62148	Fluvastatin 20mg capsules (Actavis UK Ltd)	Fluvastatin sodium
62219	Atorvastatin 20mg tablets (DE Pharmaceuticals)	Atorvastatin calcium trihydrate
62429	Atorvastatin 20mg tablets (DE Pharmaceuticals)	Atorvastatin calcium trihydrate
62476	Atorvastatin 80mg tablets (Almus Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
62979	Pravastatin 40mg tablets (Kent Pharmaceuticals Ltd)	Pravastatin sodium
63074	Pravastatin 20mg tablets (PLIVA Pharma Ltd)	Pravastatin sodium
63140	Atorvastatin 10mg tablets (Alliance Healthcare (Distribution) Ltd)	Atorvastatin calcium trihydrate
63249	Atorvastatin 80mg tablets (Consilient Health Ltd)	Atorvastatin calcium trihydrate
63469	Atorvastatin 30mg tablets (Consilient Health Ltd)	Atorvastatin calcium trihydrate
63737	Fenofibrate micronised 267mg capsules (Sigma Pharmaceuticals Plc)	Fenofibrate micronised
63787	Pravastatin 10mg tablets (Tillomed Laboratories Ltd)	Pravastatin sodium
64067	Atorvastatin 20mg/5ml oral solution	Atorvastatin calcium trihydrate
64104	Simvastatin 20mg tablets (Crescent Pharma Ltd)	Simvastatin
64180	Simvastatin 10mg tablets (Crescent Pharma Ltd)	Simvastatin
64307	Simvastatin 40mg tablets (Crescent Pharma Ltd)	Simvastatin
64503	Bezalip Mono 400mg modified-release tablets (Waymade Healthcare Plc)	Bezafibrate
64702	Atorvastatin 30mg tablets (A A H Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
64810	Atorvastatin 40mg tablets (Phoenix Healthcare Distribution Ltd)	Atorvastatin calcium trihydrate
64825	Atorvastatin 10mg tablets (Phoenix Healthcare Distribution Ltd)	Atorvastatin calcium trihydrate
64868	Atorvastatin 40mg tablets (Sigma Pharmaceuticals Plc)	Atorvastatin calcium trihydrate
64933	Fenofibrate micronised 267mg capsules (Ranbaxy (UK) Ltd)	Fenofibrate micronised
64968	Simvastatin 10mg tablets (DE Pharmaceuticals)	Simvastatin
64984	Fenofibrate micronised 160mg tablets (Phoenix Healthcare Distribution Ltd)	Fenofibrate micronised
65181	Simvastatin 40mg tablets (DE Pharmaceuticals)	Simvastatin
65193	Atorvastatin 20mg tablets (Ranbaxy (UK) Ltd)	Atorvastatin calcium trihydrate
65572	Fenofibrate micronised 160mg tablets (Genus Pharmaceuticals Ltd)	Fenofibrate micronised
65679	Simvastatin 20mg tablets (DE Pharmaceuticals)	Simvastatin
65901	Simvastatin 40mg tablets (Zentiva)	Simvastatin
65925	Simvastatin 20mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Simvastatin
66087	Modalim 100mg tablets (Mawdsley-Brooks & Company Ltd)	Ciprofibrate
66425	Bezafibrate 400mg modified-release tablets (A A H Pharmaceuticals Ltd)	Bezafibrate
66564	Bezafibrate 400mg modified-release tablets (Phoenix Healthcare Distribution Ltd)	Bezafibrate

66963	Atorvastatin 80mg tablets (Sigma Pharmaceuticals Plc)	Atorvastatin calcium trihydrate
67098	Simvastatin 10mg tablets (Brown & Burk UK Ltd)	Simvastatin
67157	Fenofibrate micronised 200mg capsules (Phoenix Healthcare Distribution Ltd)	Fenofibrate micronised
67328	Lescol XL 80mg tablets (Mawdsley-Brooks & Company Ltd)	Fluvastatin sodium
67329	Lipantil Micro 267 capsules (DE Pharmaceuticals)	Fenofibrate micronised
67402	Atorvastatin 40mg tablets (Kent Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
67573	Atorvastatin 10mg tablets (DE Pharmaceuticals)	Atorvastatin calcium trihydrate
67660	Atorvastatin 80mg tablets (Ranbaxy (UK) Ltd)	Atorvastatin calcium trihydrate
67745	Simvastatin 10mg tablets (Zentiva)	Simvastatin
67773	Simvastatin 20mg tablets (Zentiva)	Simvastatin
67829	Pravastatin 20mg tablets (Sandoz Ltd)	Pravastatin sodium
67846	Atorvastatin 10mg tablets (Almus Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
68023	Atorvastatin 10mg tablets (Aspire Pharma Ltd)	Atorvastatin calcium trihydrate
68048	Atorvastatin 20mg tablets (Phoenix Healthcare Distribution Ltd)	Atorvastatin calcium trihydrate
68156	Pravastatin 10mg tablets (A A H Pharmaceuticals Ltd)	Pravastatin sodium
68386	Colestyramine 4g oral powder sachets (J M McGill Ltd)	Colestyramine anhydrous
68467	Atorvastatin 20mg tablets (Kent Pharmaceuticals Ltd)	Atorvastatin calcium trihydrate
68563	Simvastatin 40mg tablets (Brown & Burk UK Ltd)	Simvastatin
68686	Simvastatin 20mg tablets (Genesis Pharmaceuticals Ltd)	Simvastatin
68785	Atorvastatin 10mg tablets (Mylan Ltd)	Atorvastatin calcium trihydrate
68827	Atorvastatin 20mg tablets (Mylan Ltd)	Atorvastatin calcium trihydrate
69093	Atorvastatin 80mg tablets (Wockhardt UK Ltd)	Atorvastatin calcium trihydrate
69413	Simvastatin 20mg tablets (Brown & Burk UK Ltd)	Simvastatin
69427	Atorvastatin 40mg tablets (Mylan Ltd)	Atorvastatin calcium trihydrate
69528	Cholib 145mg/20mg tablets (Mylan Ltd)	Simvastatin/Fenofibrate

Antiplatelets

Product code	Product name	Drug substance
3	Aspirin 75mg dispersible tablets	Aspirin
16	Aspirin 75mg tablets	Aspirin
34	Aspirin 75mg gastro-resistant tablets	Aspirin
111	ASPIRIN 40 MG CAP	Aspirin
216	ASPIRIN 70 MG TAB	Aspirin
254	Aspirin 300mg tablets	Aspirin
361	DISPRIN TAB	Aspirin
377	Aspirin 300mg dispersible tablets	Aspirin
383	ASPIRIN 60 MG TAB	Aspirin
393	Disprin 300mg dispersible tablets (Reckitt Benckiser Healthcare (UK)	Aspirin

	Ltd)	
395	Aspirin mixture	Aspirin
434	Aspirin 300mg gastro-resistant tablets	Aspirin
645	Aspirin 300mg suppositories	Aspirin
657	Aspirin 500mg granules sachets sugar free	Aspirin
1049	Nu-seals aspirin 600mg Tablet (Eli Lilly and Company Ltd)	Aspirin
1137	Nu-seals aspirin ec 300mg Gastro-resistant tablet (Eli Lilly and Company Ltd)	Aspirin
1486	ASPIRIN 75 MG SUP	Aspirin
1902	Aspirn 600mg gastro-resistant tablets	Aspirin
2105	Solprin 300mg Tablet (Reckitt Benckiser Healthcare (UK) Ltd)	Aspirin
2607	Paynocil Tablet (Beecham Research Laboratories)	Aspirin
2628	Nu-seals aspirin ec 75mg Gastro-resistant tablet (Eli Lilly and Company Ltd)	Aspirin
2754	ASPIRIN SOLUBLE 150 MG TAB	Aspirin
2924	ASPIRIN 150 MG TAB	Aspirin
4271	ASPIRIN SOLUBLE 200 MG TAB	Aspirin
4523	ASPIRIN 50 MG CAP	Aspirin
6006	Nu-Seals 75 gastro-resistant tablets (Alliance Pharmaceuticals Ltd)	Aspirin
6007	Nu-Seals 300 gastro-resistant tablets (Alliance Pharmaceuticals Ltd)	Aspirin
6696	Micropirin 75mg gastro-resistant tablets (Dexcel-Pharma Ltd)	Aspirin
7417	ASPIRIN 40 MG TAB	Aspirin
7462	ASPIRIN 325 MG CAP	Aspirin
7486	ASPIRIN 37.5 MG TAB	Aspirin
7516	Aspirin 300mg effervescent tablets sugar free	Aspirin
7665	ASPIRIN SR 300 MG TAB	Aspirin
7915	ASPIRIN SR 100 MG TAB	Aspirin
7944	ASPIRIN SOLUBLE 40 MG CAP	Aspirin
8185	Disprin CV 300mg modified-release tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Aspirin
8186	Aspirin 300mg modified-release tablets	Aspirin
8645	Aspirin 300mg effervescent tablets	Aspirin
8734	ASPIRIN disp 37.5 MG TAB	Aspirin
8843	ASPIRIN 325 MG TAB	Aspirin
8920	ASPIRIN SOLUBLE 500 MG TAB	Aspirin
9027	ASPIRIN disp 150 MG TAB	Aspirin
9144	Caprin 75mg gastro-resistant tablets (Wockhardt UK Ltd)	Aspirin
9301	Aspirin 100mg modified-release tablets	Aspirin
9939	Aspirin 500mg effervescent tablets sugar free	Aspirin
10305	Aspirin 162.5mg capsules	Aspirin
10310	Aspirin powder	Aspirin
11941	ASPIRIN SACHETS 30 MG	Aspirin
11977	Aspro clear maximum strength tablets	Aspirin
12102	ASPIRIN SOLUBLE 100 MG TAB	Aspirin
15044	ASPIRIN disp 500 MG TAB	Aspirin
15364	Aspirin 150mg suppositories	Aspirin

15397	ASPIRIN SOLUBLE 50 MG TAB	Aspirin
15447	ASPIRIN SOLUBLE 600 MG TAB	Aspirin
15517	ASPIRIN 100 MG SUP	Aspirin
17704	Platet 100mg Effervescent tablet (Roche Products Ltd)	Aspirin
17920	Disprin cv 100mg Modified-release tablet (Reckitt Benckiser Healthcare (UK) Ltd)	Aspirin
18217	Aspirin 300mg orodispersible tablets sugar free	Aspirin
18329	Enprin 75mg gastro-resistant tablets (Galpharm International Ltd)	Aspirin
19189	Micropirin 75mg Gastro-resistant tablet (Ratiopharm UK Ltd)	Aspirin
19577	NU-SEALS ASPIRIN	Aspirin
19674	ASPIRIN DISPERSIBLE	Aspirin
19797	NU-SEALS ASPIRIN	Aspirin
19813	ASPIRIN SOLUBLE	Aspirin
20206	ASPIRIN 50 MG SUP	Aspirin
20840	Acetylsalicylic acid mix	Aspirin
21921	Postmi ec 300mg Gastro-resistant tablet (Ashbourne Pharmaceuticals Ltd)	Aspirin
22107	ASPIRIN disp 200 MG TAB	Aspirin
22138	Aspirin 324mg modified-release tablets	Aspirin
22232	Disprin Direct 300mg orodispersible tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Aspirin
22618	Solprin 75mg Tablet (Reckitt Benckiser Healthcare (UK) Ltd)	Aspirin
22824	ASPIRIN disp 600 MG TAB	Aspirin
22863	ASPIRIN S/R 500 MG TAB	Aspirin
23488	Claradin 300mg Tablet (Nicholas Laboratories Ltd)	Aspirin
23491	ASPIRIN 500 MG SUP	Aspirin
23495	ASPIRIN	Aspirin
23593	PostMI 75 dispersible tablets (Ashbourne Pharmaceuticals Ltd)	Aspirin
23878	Nu-seals cardio ec 75mg Gastro-resistant tablet (Genus Pharmaceuticals Ltd)	Aspirin
23932	Aspro Clear 300mg effervescent tablets (Bayer Plc)	Aspirin
24025	Caprin 300mg gastro-resistant tablets (Pinewood Healthcare)	Aspirin
24857	ASPIRIN 250 MG SUP	Aspirin
24960	Aspirin 300mg tablets (Vantage)	Aspirin
25335	PostMI 75 EC tablets (Ashbourne Pharmaceuticals Ltd)	Aspirin
25718	Angettes 75 tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Aspirin
26099	ASPIRIN 175 MG SUP	Aspirin
26424	ASPIRIN 200 MG SUP	Aspirin
26792	ASPIRIN 125 MG SUP	Aspirin
27467	ASPIRIN SOLUBLE 400 MG TAB	Aspirin
28707	ASPIRIN M/F 324 MG TAB	Aspirin
28810	Aspirin 300mg with Glycine 133mg soluble tablets	Aspirin
29759	Aspro Tablet (Roche Consumer Health)	Aspirin
29848	Aspirin 300mg with Glycine 150mg chewable tablets	Aspirin
30695	ASPIRIN 120 MG SUP	Aspirin
30920	Aspirin 300mg Dispersible tablet (M & A Pharmachem Ltd)	Aspirin

31210	Aspirin 300mg Tablet (Co-operative)	Aspirin
31211	Aspirin 75mg Dispersible tablet (A A H Pharmaceuticals Ltd)	Aspirin
31858	Caspac xl 162.5mg Capsule (Pharmacia Ltd)	Aspirin
31870	Aspirin 320mg tablets	Aspirin
31938	Aspirin 75mg gastro-resistant tablets (Sandoz Ltd)	Aspirin
31953	Aspirin 75mg dispersible tablets (IVAX Pharmaceuticals UK Ltd)	Aspirin
31954	Aspirin 75mg dispersible tablets (Teva UK Ltd)	Aspirin
31956	Aspirin 75mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Aspirin
32036	Aspirin 75mg dispersible tablets (Actavis UK Ltd)	Aspirin
32210	Aspirin 300mg dispersible tablets (Actavis UK Ltd)	Aspirin
32992	Aspirin 75mg gastro-resistant tablets (Mylan Ltd)	Aspirin
33293	Aspirin 75mg gastro-resistant tablets (Sterwin Medicines)	Aspirin
33320	Aspirin 75mg Dispersible tablet (Sovereign Medical Ltd)	Aspirin
33656	Aspirin 75mg dispersible tablets (A A H Pharmaceuticals Ltd)	Aspirin
33662	Aspirin 300mg Dispersible tablet (A A H Pharmaceuticals Ltd)	Aspirin
33668	Aspirin 300mg Dispersible tablet (Rusco Ltd)	Aspirin
33676	Aspirin 75mg dispersible tablets (Kent Pharmaceuticals Ltd)	Aspirin
34309	Aspirin 300mg dispersible tablets (A A H Pharmaceuticals Ltd)	Aspirin
34385	Aspirin 75mg Soluble tablet (Co-operative)	Aspirin
34386	Aspirin 300mg tablets (Actavis UK Ltd)	Aspirin
34434	Aspirin 75mg dispersible tablets (Thornton & Ross Ltd)	Aspirin
34485	Aspirin 75mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	Aspirin
34611	Aspirin 75mg gastro-resistant tablets (C P Pharmaceuticals Ltd)	Aspirin
34666	Aspirin ec 300mg Gastro-resistant tablet (A A H Pharmaceuticals Ltd)	Aspirin
34762	Aspirin 300mg Gastro-resistant tablet (Galen Ltd)	Aspirin
34796	Aspirin 75mg Gastro-resistant tablet (Galen Ltd)	Aspirin
34797	Aspirin 75mg gastro-resistant tablets (Actavis UK Ltd)	Aspirin
34942	Aspirin 75mg Dispersible tablet (Nucare Plc)	Aspirin
36521	Aspirin 500mg modified-release tablets	Aspirin
36543	Aspirin 100mg effervescent tablets	Aspirin
37541	Aspirin 227mg medicated chewing-gum	Aspirin
39738	Aspirin 162.5mg modified-release capsules	Aspirin
40144	Aspirin 300mg Dispersible tablet (Thornton & Ross Ltd)	Aspirin
40381	Aspirin 75mg Soluble tablet (C P Pharmaceuticals Ltd)	Aspirin
41512	Aspirin 75mg gastro-resistant tablets (Teva UK Ltd)	Aspirin
41569	Aspirin 300mg tablets (A A H Pharmaceuticals Ltd)	Aspirin
41594	Aspirin 300mg Dispersible tablet (Teva UK Ltd)	Aspirin
41766	Maximum Strength Aspro Clear 500mg effervescent tablets (Bayer Plc)	Aspirin
42061	ASPIRIN 65 MG SUP	Aspirin
43060	Aspirin 300mg Soluble tablet (Celltech Pharma Europe Ltd)	Aspirin
43434	Aspirin 300mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Aspirin
43679	Flamasacard 162.5mg Modified-release capsule (Abbey Pharmaceuticals Ltd)	Aspirin
43709	Aspirin 75mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Aspirin

43806	Aspirin 300mg gastro-resistant tablets (Sandoz Ltd)	Aspirin
44639	Aspirin 300mg Dispersible tablet (Nucare Plc)	Aspirin
45643	Aspirin 75mg Soluble tablet (Celltech Pharma Europe Ltd)	Aspirin
45840	Aspirin 300mg Dispersible tablet (Numark Management Ltd)	Aspirin
45851	Aspirin 300mg Soluble tablet (Ranbaxy (UK) Ltd)	Aspirin
47937	Aspirin 75mg dispersible tablets (Wockhardt UK Ltd)	Aspirin
47992	Aspirin 75mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Aspirin
48000	Aspirin 300mg tablets (Sigma Pharmaceuticals Plc)	Aspirin
48021	Aspirin 75mg Tablet (Hillcross Pharmaceuticals Ltd)	Aspirin
48165	Aspirin 300mg tablets (Aspar Pharmaceuticals Ltd)	Aspirin
48974	Aspirin 75mg tablets (Phoenix Healthcare Distribution Ltd)	Aspirin
49060	Aspirin 75mg dispersible tablets (Alliance Healthcare (Distribution) Ltd)	Aspirin
49220	Aspirin 300mg tablets (Kent Pharmaceuticals Ltd)	Aspirin
49685	Aspirin 75mg dispersible tablets (Sigma Pharmaceuticals Plc)	Aspirin
49799	Aspirin 150mg suppositories (A A H Pharmaceuticals Ltd)	Aspirin
50555	Aspirin 300mg dispersible tablets (DE Pharmaceuticals)	Aspirin
50926	Aspirin 75mg dispersible tablets (The Boots Company Plc)	Aspirin
50949	Aspirin 75mg tablets (A A H Pharmaceuticals Ltd)	Aspirin
51474	Aspirin 150mg suppositories (Martindale Pharmaceuticals Ltd)	Aspirin
51561	Aspirin 75mg gastro-resistant tablets (Zanza Laboratories Ltd)	Aspirin
52044	Aspirin 300mg caplets (The Boots Company Plc)	Aspirin
52280	Aspirin 300mg Tablet (Wockhardt UK Ltd)	Aspirin
52618	Aspirin 75mg dispersible tablets (Bristol Laboratories Ltd)	Aspirin
52905	Aspirin 300mg tablets (Lloyds Pharmacy Ltd)	Aspirin
53178	Aspirin 75mg gastro-resistant tablets (Wockhardt UK Ltd)	Aspirin
53622	Aspirin 300mg Tablet (M & A Pharmachem Ltd)	Aspirin
53711	Aspirin 300mg Tablet (Nucare Plc)	Aspirin
53791	Aspirin 150mg suppositories (Alliance Healthcare (Distribution) Ltd)	Aspirin
53804	Aspirin 300mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)	Aspirin
53816	Aspirin 300mg dispersible tablets (Alliance Healthcare (Distribution) Ltd)	Aspirin
54284	Aspirin 75mg dispersible tablets (Almus Pharmaceuticals Ltd)	Aspirin
54430	Aspirin 75mg tablets (Alliance Healthcare (Distribution) Ltd)	Aspirin
54526	Aspirin 300mg tablets (Alliance Healthcare (Distribution) Ltd)	Aspirin
54565	Aspirin 75mg dispersible tablets (Lloyds Pharmacy Ltd)	Aspirin
54734	Aspirin 300mg tablets (Wockhardt UK Ltd)	Aspirin
54997	Aspirin 75mg dispersible tablets (Dowelhurst Ltd)	Aspirin
55230	Aspirin 300mg dispersible tablets (Kent Pharmaceuticals Ltd)	Aspirin
55579	Aspirin 300mg tablets (Almus Pharmaceuticals Ltd)	Aspirin
56007	Aspirin 300mg dispersible tablets (Sigma Pharmaceuticals Plc)	Aspirin
56736	Aspirin 300mg tablets (Waymade Healthcare Plc)	Aspirin
56883	Aspirin 75mg tablets (Waymade Healthcare Plc)	Aspirin
56995	Aspirin 75mg dispersible tablets (Phoenix Healthcare Distribution Ltd)	Aspirin

56996	Aspirin 75mg dispersible tablets (Waymade Healthcare Plc)	Aspirin
57057	Aspirin 75mg dispersible tablets (Wockhardt UK Ltd)	Aspirin
58331	Aspirin 300mg gastro-resistant tablets (Mylan Ltd)	Aspirin
59021	Aspirin 75mg gastro-resistant tablets (Bristol Laboratories Ltd)	Aspirin
59244	Aspirin 100mg capsules	Aspirin
59253	Aspirin 75mg gastro-resistant tablets (Waymade Healthcare Plc)	Aspirin
59728	Aspirin 75mg tablets (Alissa Healthcare Research Ltd)	Aspirin
59791	Aspirin 75mg dispersible tablets (Aspar Pharmaceuticals Ltd)	Aspirin
60127	Aspirin 75mg tablets (DE Pharmaceuticals)	Aspirin
60278	Aspirin 300mg tablets (DE Pharmaceuticals)	Aspirin
60693	Aspirin 15mg/5ml oral solution	Aspirin
60694	Aspirin 25mg/5ml oral solution	Aspirin
60777	Aspirin 75mg gastro-resistant tablets (DE Pharmaceuticals)	Aspirin
62334	Aspirin 300mg caplets (Wockhardt UK Ltd)	Aspirin
62430	Aspirin 300mg suppositories (A A H Pharmaceuticals Ltd)	Aspirin
63603	Laboprin Tablet (Laboratories For Applied Biology Ltd)	Aspirin
64071	Aspirin powder (J M Loveridge Ltd)	Aspirin
66171	Aspirin 150mg Suppository (Distriphar (UK))	Aspirin
66345	Aspirin 75mg dispersible tablets (DE Pharmaceuticals)	Aspirin
66546	Aspirin 75mg dispersible tablets (Numark Ltd)	Aspirin
66563	Aspirin 75mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	Aspirin
66861	Aspirin 75mg effervescent tablets	Aspirin
67160	Aspirin 300mg dispersible tablets (Lloyds Pharmacy Ltd)	Aspirin
67362	Aspirin 300mg suppositories (Alliance Healthcare (Distribution) Ltd)	Aspirin
67521	Aspirin 15mg/5ml oral suspension	Aspirin
67754	Aspirin 300mg dispersible tablets (Almus Pharmaceuticals Ltd)	Aspirin
67858	Aspirin 25mg capsules	Aspirin
68051	Aspirin 150mg suppositories (Colorama Pharmaceuticals Ltd)	Aspirin
68752	Aspirin 75mg tablets (Sigma Pharmaceuticals Plc)	Aspirin
489	Clopidogrel 75mg tablets	Clopidogrel
836	Plavix 75mg tablets (Sanofi)	Clopidogrel
17817	CLOPIDOGREL FC	Clopidogrel
38349	Clopidogrel 300mg tablets	Clopidogrel
38998	Plavix 300mg tablets (Sanofi)	Clopidogrel
40913	Grepid 75mg tablets (Kent Pharmaceuticals Ltd)	Clopidogrel
42750	Clopidogrel 75mg tablets (Actavis UK Ltd)	Clopidogrel
45905	Clopidogrel 1mg/ml oral suspension	Clopidogrel
46891	Clopidogrel 75mg/5ml oral suspension	Clopidogrel
52761	Clopidogrel 75mg tablets (Dr Reddy's Laboratories (UK) Ltd)	Clopidogrel
53751	Clopidogrel 75mg tablets (Phoenix Healthcare Distribution Ltd)	Clopidogrel
54700	Clopidogrel 75mg tablets (A A H Pharmaceuticals Ltd)	Clopidogrel
55161	Clopidogrel 75mg tablets (Wockhardt UK Ltd)	Clopidogrel
56807	Clopidogrel 75mg tablets (Teva UK Ltd)	Clopidogrel
57036	Clopidogrel 75mg tablets (Mylan Ltd)	Clopidogrel

58347	Clopidogrel 75mg tablets (DE Pharmaceuticals)	Clopidogrel
58448	Clopidogrel 75mg tablets (Aspire Pharma Ltd)	Clopidogrel
59904	Clopidogrel 75mg/5ml oral solution	Clopidogrel
62855	Clopidogrel 75mg tablets (Alliance Healthcare (Distribution) Ltd)	Clopidogrel
62978	Clopidogrel 75mg tablets (Sandoz Ltd)	Clopidogrel
63450	Clopidogrel 75mg tablets (Almus Pharmaceuticals Ltd)	Clopidogrel
65909	Clopidogrel 75mg tablets (Milpharm Ltd)	Clopidogrel
67037	Clopidogrel 75mg tablets (Zentiva)	Clopidogrel
39932	Prasugrel 10mg tablets	Prasugrel hydrochloride
40114	Prasugrel 5mg tablets	Prasugrel hydrochloride
40591	Efient 5mg tablets (Eli Lilly and Company Ltd)	Prasugrel hydrochloride
41229	Efient 10mg tablets (Eli Lilly and Company Ltd)	Prasugrel hydrochloride
45576	Ticagrelor 90mg tablets	Ticagrelor
47895	Brilique 90mg tablets (AstraZeneca UK Ltd)	Ticagrelor
66973	Ticagrelor 60mg tablets	Ticagrelor

Anticoagulants

Product code	Product name	Drug substance
45	Warfarin 1mg tablets	Warfarin sodium
61	Warfarin 3mg tablets	Warfarin sodium
833	Warfarin 3mg/5ml oral solution	Warfarin sodium
1781	Warfarin 5mg tablets	Warfarin sodium
6262	Warfarin 500microgram tablets	Warfarin sodium
8466	Marevan 1mg tablets (AMCo)	Warfarin sodium
8467	Marevan 3mg tablets (AMCo)	Warfarin sodium
10560	WARFARIN 10 MG TAB	Warfarin sodium
13348	Marevan 5mg tablets (AMCo)	Warfarin sodium
17965	Marevan 500microgram tablets (AMCo)	Warfarin sodium
20754	WARFARIN	Warfarin sodium
23078	Warfarin 1mg Tablet (WB Pharmaceuticals Ltd)	Warfarin sodium
30202	Warfarin wbp 1mg Tablet (Boehringer Ingelheim Ltd)	Warfarin sodium
30203	Warfarin wbp 3mg Tablet (Boehringer Ingelheim Ltd)	Warfarin sodium
31511	Warfarin 3mg Tablet (WB Pharmaceuticals Ltd)	Warfarin sodium
31937	Warfarin 5mg tablets (Teva UK Ltd)	Warfarin sodium
33711	Warfarin 5mg Tablet (WB Pharmaceuticals Ltd)	Warfarin sodium
34019	Warfarin 1mg tablets (IVAX Pharmaceuticals UK Ltd)	Warfarin sodium
34086	Warfarin 3mg Tablet (Celltech Pharma Europe Ltd)	Warfarin sodium
34087	Warfarin 1mg Tablet (Celltech Pharma Europe Ltd)	Warfarin sodium
34088	Warfarin 5mg Tablet (Celltech Pharma Europe Ltd)	Warfarin sodium
34095	Warfarin wbp 5mg Tablet (Boehringer Ingelheim Ltd)	Warfarin sodium

34299	Warfarin 1mg tablets (Teva UK Ltd)	Warfarin sodium
34416	Warfarin 1mg tablets (Kent Pharmaceuticals Ltd)	Warfarin sodium
34417	Warfarin 3mg tablets (Teva UK Ltd)	Warfarin sodium
34418	Warfarin 5mg tablets (Mylan Ltd)	Warfarin sodium
34517	Warfarin 1mg tablets (Mylan Ltd)	Warfarin sodium
34526	Warfarin 3mg tablets (Mylan Ltd)	Warfarin sodium
34576	Warfarin 1mg Tablet (Lagap)	Warfarin sodium
34691	Warfarin 5mg Tablet (Regent Laboratories Ltd)	Warfarin sodium
34758	Warfarin 3mg tablets (IVAX Pharmaceuticals UK Ltd)	Warfarin sodium
34864	Warfarin 5mg tablets (IVAX Pharmaceuticals UK Ltd)	Warfarin sodium
34918	Warfarin 5mg tablets (Actavis UK Ltd)	Warfarin sodium
36099	Warfarin 1mg/5ml oral suspension	Warfarin sodium
38041	Warfarin sodium 5mg/ml oral suspension	Warfarin Sodium
38044	Warfarin 5mg/5ml oral solution	Warfarin sodium
39866	Warfarin 1mg tablets (Almus Pharmaceuticals Ltd)	Warfarin sodium
40143	Warfarin 500microgram tablets (A A H Pharmaceuticals Ltd)	Warfarin sodium
43407	Warfarin 3mg tablets (A A H Pharmaceuticals Ltd)	Warfarin sodium
43408	Warfarin 1mg tablets (A A H Pharmaceuticals Ltd)	Warfarin sodium
43409	Warfarin 5mg tablets (A A H Pharmaceuticals Ltd)	Warfarin sodium
43655	Warfarin sodium oral solution	Warfarin Sodium
44866	Warfarin sodium 1mg/ml oral supension SF	Warfarin Sodium
47944	Warfarin 1mg tablets (Actavis UK Ltd)	Warfarin sodium
48070	Warfarin sodium tablets	Warfarin Sodium
48869	Warfarin 1mg/ml oral suspension sugar free	Warfarin Sodium
48869	Warfarin 1mg/ml oral suspension sugar free	Warfarin Sodium
50000	Warfarin 1mg/ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Warfarin Sodium
51484	Warfarin 1mg tablets (Bristol Laboratories Ltd)	Warfarin Sodium
51496	Warfarin 1mg tablets (Phoenix Healthcare Distribution Ltd)	Warfarin Sodium
51509	Warfarin 1mg tablets (APC Pharmaceuticals & Chemicals (Europe) Ltd)	Warfarin Sodium
53745	Warfarin 3mg tablets (Bristol Laboratories Ltd)	Warfarin Sodium
53752	Warfarin 1mg tablets (Alliance Healthcare (Distribution) Ltd)	Warfarin Sodium
54892	Warfarin 1mg/ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Warfarin Sodium
54946	Warfarin 3mg tablets (Actavis UK Ltd)	Warfarin Sodium
55316	Warfarin 3mg/5ml oral suspension	Warfarin Sodium
56314	Warfarin 3mg tablets (Kent Pharmaceuticals Ltd)	Warfarin Sodium
57032	Warfarin 1mg/ml oral suspension sugar free (Rosemont Pharmaceuticals Ltd)	Warfarin Sodium
58519	Warfarin 1mg tablets (DE Pharmaceuticals)	Warfarin sodium
58787	Warfarin 5mg tablets (Alliance Healthcare (Distribution) Ltd)	Warfarin sodium
58962	Warfarin 3mg tablets (DE Pharmaceuticals)	Warfarin sodium
59400	Warfarin 500microgram tablets (Sigma Pharmaceuticals Plc)	Warfarin sodium
59578	Warfarin 3mg tablets (Phoenix Healthcare Distribution Ltd)	Warfarin sodium
60589	Warfarin 500microgram tablets (Actavis UK Ltd)	Warfarin sodium

60949	Warfarin 5mg/5ml oral suspension	Warfarin sodium
62309	Warfarin 500microgram tablets (Kent Pharmaceuticals Ltd)	Warfarin sodium
62310	Warfarin 500microgram tablets (AMCo)	Warfarin sodium
63071	Warfarin 4mg tablets	Warfarin sodium
65285	Warfarin 1mg tablets (Crescent Pharma Ltd)	Warfarin sodium
65496	Warfarin 500microgram tablets (Phoenix Healthcare Distribution Ltd)	Warfarin sodium
65746	Warfarin 500microgram tablets (DE Pharmaceuticals)	Warfarin sodium
66286	Warfarin 2.5mg/5ml oral solution	Warfarin sodium
66570	Warfarin 1mg tablets (Waymade Healthcare Plc)	Warfarin sodium
68591	Warfarin 500microgram tablets (Alliance Healthcare (Distribution) Ltd)	Warfarin sodium
68667	Warfarin 5mg capsules	Warfarin sodium
68795	Warfarin 1mg capsules	Warfarin sodium
69128	Warfarin 500micrograms/5ml oral solution	Warfarin sodium
47566	Apixaban 2.5mg tablets	Apixaban
53740	Eliquis 2.5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Apixaban
54066	Apixaban 5mg tablets	Apixaban
58594	Eliquis 5mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Apixaban
39119	Rivaroxaban 10mg tablets	Rivaroxaban
39639	Xarelto 10mg tablets (Bayer Plc)	Rivaroxaban
47207	Rivaroxaban 20mg tablets	Rivaroxaban
47353	Rivaroxaban 15mg tablets	Rivaroxaban
47925	Xarelto 20mg tablets (Bayer Plc)	Rivaroxaban
48134	Xarelto 15mg tablets (Bayer Plc)	Rivaroxaban
48966	Rivaroxaban 15mg tablets	Rivaroxaban
54451	Rivaroxaban 20mg tablets	Rivaroxaban
62150	Rivaroxaban 2.5mg tablets	Rivaroxaban
64500	Xarelto 2.5mg tablets (Bayer Plc)	Rivaroxaban
39444	Dabigatran etexilate 110mg capsules	Dabigatran Etexilate Mesilate
39503	Dabigatran etexilate 75mg capsules	Dabigatran etexilate mesilate
39755	Pradaxa 110mg capsules (Boehringer Ingelheim Ltd)	Dabigatran Etexilate Mesilate
42474	Pradaxa 75mg capsules (Boehringer Ingelheim Ltd)	Dabigatran etexilate mesilate
46632	Dabigatran etexilate 150mg capsules	Dabigatran Etexilate Mesilate
46678	Pradaxa 150mg capsules (Boehringer Ingelheim Ltd)	Dabigatran etexilate mesilate

Selective serotonin re-uptake inhibitors (SSRIs)

Product code	Product name	Drug substance
22	Fluoxetine 20mg capsules	Fluoxetine hydrochloride
50	Paroxetine 20mg tablets	Paroxetine hydrochloride
67	Citalopram 20mg tablets	Citalopram hydrobromide

252	Prozac 20mg/5ml liquid (Eli Lilly and Company Ltd)	Fluoxetine hydrochloride
418	Prozac 20mg capsules (Eli Lilly and Company Ltd)	Fluoxetine hydrochloride
476	Citalopram 10mg tablets	Citalopram hydrobromide
488	Sertraline 50mg tablets	Sertraline hydrochloride
513	Citalopram 40mg/ml oral drops sugar free	Citalopram hydrochloride
527	Paroxetine 10mg/5ml oral suspension sugar free	Paroxetine hydrochloride
603	Escitalopram 10mg tablets	Escitalopram oxalate
648	Cipralex 10mg tablets (Lundbeck Ltd)	Escitalopram oxalate
727	Sertraline 100mg tablets	Sertraline hydrochloride
785	Cipralex 5mg tablets (Lundbeck Ltd)	Escitalopram oxalate
815	Cipramil 40mg/ml drops (Lundbeck Ltd)	Citalopram hydrochloride
841	Seroxat 20mg tablets (GlaxoSmithKline UK Ltd)	Paroxetine hydrochloride
1397	Paroxetine 30mg tablets	Paroxetine hydrochloride
1575	Seroxat 30mg tablets (GlaxoSmithKline UK Ltd)	Paroxetine hydrochloride
1612	Lustral 50mg tablets (Pfizer Ltd)	Sertraline hydrochloride
1712	Cipramil 20mg tablets (Lundbeck Ltd)	Citalopram hydrobromide
2290	Fluvoxamine 100mg tablets	Fluvoxamine maleate
2408	Cipramil 40mg tablets (Lundbeck Ltd)	Citalopram hydrobromide
2548	Fluoxetine 20mg/5ml oral solution	Fluoxetine hydrochloride
2880	Fluvoxamine 50mg tablets	Fluvoxamine maleate
2897	Faverin 50mg tablets (BGP Products Ltd)	Fluvoxamine maleate
3601	Seroxat 20mg/10ml liquid (GlaxoSmithKline UK Ltd)	Paroxetine hydrochloride
3861	Cipramil 10mg tablets (Lundbeck Ltd)	Citalopram hydrobromide
4075	Fluoxetine 60mg capsules	Fluoxetine hydrochloride
4352	Lustral 100mg tablets (Pfizer Ltd)	Sertraline hydrochloride
4770	Citalopram 40mg tablets	Citalopram hydrobromide
4907	Prozac 60mg capsules (Eli Lilly and Company Ltd)	Fluoxetine hydrochloride
6218	Escitalopram 20mg tablets	Escitalopram oxalate
6360	Cipralex 20mg tablets (Lundbeck Ltd)	Escitalopram oxalate
6405	Escitalopram 5mg tablets	Escitalopram oxalate
7328	Sertraline 50mg/5ml oral suspension	Sertraline hydrochloride
12123	Faverin 100mg tablets (BGP Products Ltd)	Fluvoxamine maleate
14740	Oxactin 20mg capsules (Discovery Pharmaceuticals)	Fluoxetine hydrochloride
19183	Fluoxetine 20mg capsules (A A H Pharmaceuticals Ltd)	Fluoxetine hydrochloride
19470	Fluoxetine 20mg capsules (Ranbaxy (UK) Ltd)	Fluoxetine hydrochloride
20152	Escitalopram 10mg/ml oral drops sugar free	Escitalopram oxalate
26016	Citalopram 20mg tablets (Sandoz Ltd)	Citalopram hydrobromide
26056	Cipralex 10mg/ml oral drops (Lundbeck Ltd)	Escitalopram oxalate
29756	Paxoran 20mg Tablet (Ranbaxy (UK) Ltd)	Citalopram hydrobromide
29786	Ranflutin 20mg capsules (Ranbaxy (UK) Ltd)	Fluoxetine hydrochloride
30258	Fluoxetine 20mg/5ml oral solution (Teva UK Ltd)	Fluoxetine hydrochloride
32401	Sertraline 50mg tablets (A A H Pharmaceuticals Ltd)	Sertraline hydrochloride
32546	Paxoran 10mg Tablet (Ranbaxy (UK) Ltd)	Citalopram hydrobromide
32848	Citalopram 10mg tablets (Actavis UK Ltd)	Citalopram hydrobromide
32899	Paroxetine 20mg tablets (Actavis UK Ltd)	Paroxetine hydrochloride

33071	Felicium 20mg capsules (Opus Pharmaceuticals Ltd)	Fluoxetine hydrochloride
33410	Fluoxetine 20mg capsules (Zentiva)	Fluoxetine hydrochloride
33720	Citalopram 10mg tablets (IVAX Pharmaceuticals UK Ltd)	Citalopram hydrobromide
33779	Prozit 20mg/5ml oral solution (Pinewood Healthcare)	Fluoxetine hydrochloride
33978	Paroxetine 20mg tablets (Mylan Ltd)	Paroxetine hydrochloride
34202	Fluoxetine 20mg capsules (Genus Pharmaceuticals Ltd)	Fluoxetine hydrochloride
34216	Fluoxetine 20mg/5ml oral solution (A A H Pharmaceuticals Ltd)	Fluoxetine hydrochloride
34288	Fluoxetine 20mg capsules (Mylan Ltd)	Fluoxetine hydrochloride
34294	Fluoxetine 20mg capsules (IVAX Pharmaceuticals UK Ltd)	Fluoxetine hydrochloride
34351	Paroxetine 20mg tablets (IVAX Pharmaceuticals UK Ltd)	Paroxetine hydrochloride
34356	Citalopram 20mg tablets (A A H Pharmaceuticals Ltd)	Citalopram hydrobromide
34413	Citalopram 10mg tablets (Zentiva)	Citalopram hydrobromide
34415	Citalopram 20mg tablets (Mylan Ltd)	Citalopram hydrobromide
34419	Paroxetine 20mg tablets (A A H Pharmaceuticals Ltd)	Paroxetine hydrochloride
34436	Citalopram 10mg tablets (Mylan Ltd)	Citalopram hydrobromide
34456	Fluoxetine 20mg capsules (Teva UK Ltd)	Fluoxetine hydrochloride
34466	Citalopram 40mg tablets (Sandoz Ltd)	Citalopram hydrobromide
34498	Citalopram 10mg Tablet (Neo Laboratories Ltd)	Citalopram hydrobromide
34499	Citalopram 10mg tablets (Sandoz Ltd)	Citalopram hydrobromide
34586	Citalopram 10mg tablets (A A H Pharmaceuticals Ltd)	Citalopram hydrobromide
34587	Paroxetine 30mg tablets (A A H Pharmaceuticals Ltd)	Paroxetine hydrochloride
34603	Citalopram 40mg tablets (Mylan Ltd)	Citalopram hydrobromide
34722	Citalopram 20mg Tablet (Neo Laboratories Ltd)	Citalopram hydrobromide
34822	Citalopram 20mg tablets (Zentiva)	Citalopram hydrobromide
34849	Fluoxetine 20mg capsules (Tillomed Laboratories Ltd)	Fluoxetine hydrochloride
34856	Fluoxetine 60mg capsules (Mylan Ltd)	Fluoxetine hydrochloride
34871	Citalopram 20mg tablets (Actavis UK Ltd)	Citalopram hydrobromide
34966	Citalopram 20mg tablets (Teva UK Ltd)	Citalopram hydrobromide
34970	Citalopram 20mg tablets (Niche Generics Ltd)	Citalopram hydrobromide
35021	Paroxetine 10mg tablets	Paroxetine hydrochloride
35112	Seroxat 10mg tablets (GlaxoSmithKline UK Ltd)	Paroxetine hydrochloride
36746	Citalopram 40mg tablets (A A H Pharmaceuticals Ltd)	Citalopram hydrobromide
36893	Fluoxetine 20mg/5ml oral solution sugar free	Fluoxetine hydrochloride
37256	Prozep 20mg/5ml oral solution (Chemidex Pharma Ltd)	Fluoxetine hydrochloride
38890	Fluoxetine 20mg Capsule (Milpharm Ltd)	Fluoxetine hydrochloride
40165	Paroxetine 30mg tablets (Actavis UK Ltd)	Paroxetine hydrochloride
40726	Escitalopram 20mg/ml oral drops sugar free	Escitalopram Oxalate
40892	Paroxetine 20mg tablets (Genus Pharmaceuticals Ltd)	Paroxetine hydrochloride
41062	Cipralex 20mg/ml oral drops (Lundbeck Ltd)	Escitalopram Oxalate
41528	Citalopram 10mg tablets (Teva UK Ltd)	Citalopram hydrobromide
42107	Fluoxetine 20mg capsules (Niche Generics Ltd)	Fluoxetine hydrochloride
42387	Sertraline 50mg tablets (Actavis UK Ltd)	Sertraline hydrochloride
42499	Fluoxetine 10mg tablets	Fluoxetine hydrochloride
42660	Citalopram 10mg tablets (Almus Pharmaceuticals Ltd)	Citalopram hydrobromide

42803	Fluoxetine 20mg/5ml oral solution (IVAX Pharmaceuticals UK Ltd)	Fluoxetine hydrochloride
43518	Fluvoxamine 100mg tablets (IVAX Pharmaceuticals UK Ltd)	Fluvoxamine maleate
43519	Citalopram 40mg Tablet (Neo Laboratories Ltd)	Citalopram hydrobromide
44861	Fluvoxamine 100mg tablets (Actavis UK Ltd)	Fluvoxamine maleate
44944	Sertraline 100mg tablets (Teva UK Ltd)	Sertraline hydrochloride
45223	Citalopram 40mg tablets (Niche Generics Ltd)	Citalopram hydrobromide
45224	Fluoxetine 20mg capsules (Sandoz Ltd)	Fluoxetine hydrochloride
45247	Fluoxetine 20mg capsules (Fannin UK Ltd)	Fluoxetine hydrochloride
45286	Citalopram 10mg tablets (Niche Generics Ltd)	Citalopram hydrobromide
45304	Citalopram 40mg tablets (Teva UK Ltd)	Citalopram hydrobromide
45316	Fluoxetine 20mg capsules (Wockhardt UK Ltd)	Fluoxetine hydrochloride
45329	Fluoxetine 20mg capsules (Actavis UK Ltd)	Fluoxetine hydrochloride
45915	Sertraline 50mg tablets (Almus Pharmaceuticals Ltd)	Sertraline hydrochloride
46926	Citalopram 40mg tablets (Zentiva)	Citalopram hydrobromide
46977	Citalopram 40mg tablets (Actavis UK Ltd)	Citalopram hydrobromide
48026	Citalopram 20mg tablets (Almus Pharmaceuticals Ltd)	Citalopram hydrobromide
48045	Fluvoxamine 100mg tablets (A A H Pharmaceuticals Ltd)	Fluvoxamine maleate
48220	Prozac 20mg capsules (Lexon (UK) Ltd)	Fluoxetine hydrochloride
49165	Citalopram 10mg tablets (Alliance Healthcare (Distribution) Ltd)	Citalopram hydrobromide
49519	Sertraline 100mg/5ml oral suspension	Sertraline hydrochloride
52100	Citalopram 10mg tablets (Arrow Generics Ltd)	Citalopram hydrobromide
52354	Citalopram 20mg tablets (DE Pharmaceuticals)	Citalopram hydrobromide
52408	Citalopram 10mg tablets (Kent Pharmaceuticals Ltd)	Citalopram hydrobromide
52607	Citalopram 20mg tablets (Bristol Laboratories Ltd)	Citalopram hydrobromide
52824	Citalopram 10mg tablets (PLIVA Pharma Ltd)	Citalopram hydrobromide
53394	Citalopram 20mg tablets (Alliance Healthcare (Distribution) Ltd)	Citalopram hydrobromide
53787	Citalopram 10mg tablets (Bristol Laboratories Ltd)	Citalopram hydrobromide
54081	Sertraline 25mg/5ml oral suspension	Sertraline hydrochloride
54826	Sertraline 150mg/5ml oral suspension	Sertraline hydrochloride
54827	Citalopram 10mg/5ml oral suspension	Citalopram hydrobromide
54933	Sertraline 100mg tablets (PLIVA Pharma Ltd)	Sertraline hydrochloride
55023	Paroxetine 20mg tablets (Medreich Plc)	Paroxetine hydrochloride
55033	Citalopram 40mg tablets (DE Pharmaceuticals)	Citalopram hydrobromide
55146	Sertraline 100mg tablets (A A H Pharmaceuticals Ltd)	Sertraline hydrochloride
55488	Sertraline 50mg tablets (Teva UK Ltd)	Sertraline hydrochloride
55537	Seroxat 30mg tablets (Lexon (UK) Ltd)	Paroxetine hydrochloride
56009	Citalopram 20mg tablets (Arrow Generics Ltd)	Citalopram hydrobromide
56292	Citalopram 40mg/ml oral drops sugar free (Actavis UK Ltd)	Citalopram hydrochloride
56355	Citalopram 10mg tablets (Waymade Healthcare Plc)	Citalopram hydrobromide
57532	Prozac 20mg capsules (Waymade Healthcare Plc)	Fluoxetine hydrochloride
57936	Citalopram 40mg/ml oral drops sugar free (A A H Pharmaceuticals Ltd)	Citalopram hydrochloride

58476	Citalopram 20mg tablets (Aurobindo Pharma Ltd)	Citalopram hydrobromide
58664	Sertraline 50mg tablets (Mylan Ltd)	Sertraline hydrochloride
58723	Sertraline 50mg tablets (Accord Healthcare Ltd)	Sertraline hydrochloride
59193	Citalopram 10mg tablets (Ranbaxy (UK) Ltd)	Citalopram hydrobromide
59288	Paroxetine 10mg tablets (Actavis UK Ltd)	Paroxetine hydrochloride
59358	Fluoxetine 20mg capsules (Milpharm Ltd)	Fluoxetine hydrochloride
59600	Sertraline 100mg tablets (Almus Pharmaceuticals Ltd)	Sertraline hydrochloride
59650	Citalopram 10mg tablets (Aurobindo Pharma Ltd)	Citalopram hydrobromide
60138	Fluoxetine 20mg orodispersible tablets sugar free	Fluoxetine hydrochloride
60534	Fluoxetine 20mg dispersible tablets sugar free	Fluoxetine hydrochloride
60568	Citalopram 20mg tablets (Waymade Healthcare Plc)	Citalopram hydrobromide
60619	Fluoxetine 20mg/5ml oral solution (Kent Pharmaceuticals Ltd)	Fluoxetine hydrochloride
60839	Citalopram 40mg tablets (Almus Pharmaceuticals Ltd)	Citalopram hydrobromide
60888	Citalopram 10mg tablets (Sigma Pharmaceuticals Plc)	Citalopram hydrobromide
60962	Fluoxetine 20mg capsules (Alliance Healthcare (Distribution) Ltd)	Fluoxetine hydrochloride
61335	Prozac 20mg capsules (Mawdsley-Brooks & Company Ltd)	Fluoxetine hydrochloride
61503	Sertraline 100mg tablets (Actavis UK Ltd)	Sertraline hydrochloride
62155	Fluoxetine 20mg capsules (Phoenix Healthcare Distribution Ltd)	Fluoxetine hydrochloride
62335	Olena 20mg dispersible tablets (AMCo)	Fluoxetine hydrochloride
62692	Sertraline 100mg tablets (Bristol Laboratories Ltd)	Sertraline hydrochloride
62693	Sertraline 50mg tablets (Bristol Laboratories Ltd)	Sertraline hydrochloride
62819	Sertraline 12.5mg/5ml oral suspension	Sertraline hydrochloride
62927	Sertraline 50mg tablets (Wockhardt UK Ltd)	Sertraline hydrochloride
62950	Sertraline 100mg tablets (Accord Healthcare Ltd)	Sertraline hydrochloride
63441	Citalopram 10mg tablets (Rivopharm (UK) Ltd)	Citalopram hydrobromide
63481	Sertraline 50mg tablets (Aurobindo Pharma Ltd)	Sertraline hydrochloride
63916	Escitalopram 10mg tablets (Actavis UK Ltd)	Escitalopram oxalate
63953	Cipramil 20mg tablets (DE Pharmaceuticals)	Citalopram hydrobromide
64423	Citalopram 10mg tablets (Accord Healthcare Ltd)	Citalopram hydrobromide
64785	Paroxetine 30mg tablets (Alliance Healthcare (Distribution) Ltd)	Paroxetine hydrochloride
65771	Sertraline 200mg/5ml oral suspension (Special Order)	Sertraline hydrochloride
66292	Seroxat 10mg tablets (Waymade Healthcare Plc)	Paroxetine hydrochloride
66413	Sertraline 100mg tablets (Ranbaxy (UK) Ltd)	Sertraline hydrochloride
66560	Sertraline 100mg tablets (Mylan Ltd)	Sertraline hydrochloride
66744	Fluoxetine 20mg capsules (Morningside Healthcare Ltd)	Fluoxetine hydrochloride
67092	Fluoxetine 20mg capsules (Waymade Healthcare Plc)	Fluoxetine hydrochloride
67097	Citalopram 20mg tablets (Accord Healthcare Ltd)	Citalopram hydrobromide
67259	Paroxetine 10mg/5ml oral solution	Paroxetine hydrochloride
67431	Fluoxetine 10mg capsules	Fluoxetine hydrochloride
67496	Fluoxetine 30mg capsules	Fluoxetine hydrochloride
67562	Fluoxetine 40mg capsules	Fluoxetine hydrochloride
67730	Sertraline 50mg tablets (Ranbaxy (UK) Ltd)	Sertraline hydrochloride

67736	Fluoxetine 20mg capsules (Dr Reddy's Laboratories (UK) Ltd)	Fluoxetine hydrochloride
67758	Prozac 20mg capsules (DE Pharmaceuticals)	Fluoxetine hydrochloride
67769	Fluoxetine 20mg capsules (Strides Shasun (UK) Ltd)	Fluoxetine hydrochloride
67888	Fluoxetine 60mg capsules (Kent Pharmaceuticals Ltd)	Fluoxetine hydrochloride
67928	Sertraline 100mg tablets (Aurobindo Pharma Ltd)	Sertraline hydrochloride
68266	Fluoxetine 20mg/5ml oral solution sugar free (Actavis UK Ltd)	Fluoxetine hydrochloride
68325	Paroxetine 40mg tablets	Paroxetine hydrochloride
68756	Sertraline 100mg tablets (Sandoz Ltd)	Sertraline hydrochloride
69525	Fluoxetine 20mg capsules (Medreich Plc)	Fluoxetine hydrochloride
69542	Prozac 20mg capsules (Necessity Supplies Ltd)	Fluoxetine hydrochloride
69571	Citalopram 40mg tablets (Accord Healthcare Ltd)	Citalopram hydrobromide
69685	Fluoxetine 20mg/5ml oral solution sugar free (Morningside Healthcare Ltd)	Fluoxetine hydrochloride
69725	Sertraline 50mg tablets (Crescent Pharma Ltd)	Sertraline hydrochloride
69726	Sertraline 100mg tablets (Crescent Pharma Ltd)	Sertraline hydrochloride
69898	Sertraline 50mg tablets (Sandoz Ltd)	Sertraline hydrochloride
69941	Fluoxetine 10mg capsules (A A H Pharmaceuticals Ltd)	Fluoxetine hydrochloride

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Product code	Product name	Drug substance
15	Ibuprofen 400mg tablets	Ibuprofen
40	Diclofenac sodium 50mg gastro-resistant tablets	Diclofenac sodium
120	Indocid 25mg capsules (Merck Sharp & Dohme Ltd)	Indometacin
126	Ponstan 250mg capsules (Chemidex Pharma Ltd)	Mefenamic acid
129	Naprosyn 500mg suppositories (Roche Products Ltd)	Naproxen
140	Naproxen 500mg suppositories	Naproxen
141	Piroxicam 10mg capsules	Piroxicam
157	Voltarol 100mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
162	Arthrotec 50 gastro-resistant tablets (Pfizer Ltd)	Diclofenac sodium/Misoprostol
167	Butacote 100mg gastro-resistant tablets (Novartis Pharmaceuticals UK Ltd)	Phenylbutazone
177	Indometacin 25mg capsules	Indometacin
215	IBUPROFEN 200 MG CAP	Ibuprofen
259	Mefenamic acid 250mg capsules	Mefenamic acid
296	Ponstan Forte 500mg tablets (Chemidex Pharma Ltd)	Mefenamic acid
316	PHENYLBUTAZONE 250 MG SUP	
341	Feldene 10mg capsules (Pfizer Ltd)	Piroxicam
344	Acemetacin 60mg capsules	Acemetacin
345	IBUPROFEN S/R 300 MG CAP	Ibuprofen
349	VOLTAROL 75 MG INJ	Diclofenac sodium
360	Brufen 100mg/5ml syrup (Mylan Ltd)	Ibuprofen
387	Surgam 200mg tablets (Sanofi)	Tiaprofenic acid
389	Ketoprofen 50mg capsules	Ketoprofen

392	Ibuprofen 200mg modified-release capsules	Ibuprofen
402	Nurofen 200mg Tablet (Crookes Healthcare Ltd)	Ibuprofen
407	Brufen 600mg effervescent granules sachets (Mylan Ltd)	Ibuprofen
416	Ibuprofen 200mg tablets	Ibuprofen
417	Diclofenac 50mg dispersible tablets sugar free	Diclofenac sodium
447	Diclofenac sodium 75mg modified-release capsules	Diclofenac sodium
474	Celecoxib 100mg capsules	Celecoxib
497	Voltarol 25mg gastro-resistant tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
499	Diclofenac 50mg suppositories	Diclofenac sodium
518	Rofecoxib 12.5mg tablets	Rofecoxib
526	Aceclofenac 100mg tablets	Aceclofenac
538	Vioxx 12.5mg tablets (Merck Sharp & Dohme Ltd)	Rofecoxib
560	Diflunisal 250mg tablets	Diflunisal
570	Dynastat 40mg Powder for solution for injection (Pharmacia Ltd)	Parecoxib Sodium
580	Diclofenac sodium 75mg modified-release tablets	Diclofenac sodium
586	Ibuprofen 200mg Capsule	Ibuprofen
589	Voltarol 50mg dispersible tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
597	Diclofenac potassium 50mg tablets	Diclofenac potassium
612	Dicloflex 25mg gastro-resistant tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
613	Vioxx 12.5mg/5ml oral suspension (Merck Sharp & Dohme Ltd)	Rofecoxib
628	Diclofenac potassium 25mg tablets	Diclofenac potassium
637	Rofecoxib 25mg/5ml oral suspension sugar free	Rofecoxib
640	Rofecoxib 12.5mg/5ml oral suspension sugar free	Rofecoxib
647	Ibuprofen 100mg/5ml oral suspension	Ibuprofen
649	Diclofenac sodium 25mg gastro-resistant tablets	Diclofenac sodium
650	Etoricoxib 60mg tablets	Etoricoxib
661	Naproxen 250mg tablets	Naproxen
666	Vioxx 25mg tablets (Merck Sharp & Dohme Ltd)	Rofecoxib
676	Diclofenac 75mg/3ml solution for injection ampoules	Diclofenac sodium
706	Rofecoxib 25mg tablets	Rofecoxib
723	Valdecoxib 10mg tablets	Valdecoxib
736	Indometacin 50mg capsules	Indometacin
754	Mobic 7.5mg suppositories (Boehringer Ingelheim Ltd)	Meloxicam
784	Ibuprofen 300mg modified-release capsules	Ibuprofen
807	Naproxen 500mg tablets	Naproxen
838	Oruvail 200mg Modified-release capsule (Hawgreen Ltd)	Ketoprofen
849	Ibumed 400mg Tablet (Medipharma Ltd)	Ibuprofen
850	Mobic 7.5mg tablets (Boehringer Ingelheim Ltd)	Meloxicam
917	Diclofenac sodium 50mg tablets	Diclofenac Sodium
919	Indometacin 100mg suppositories	Indometacin
920	Indocid 100mg suppositories (Aspen Pharma Trading Ltd)	Indometacin
928	Diclofenac sodium 25mg tablets	Diclofenac Sodium
1030	Junifen 100mg/5ml Oral suspension (Crookes Healthcare Ltd)	Ibuprofen
1043	Naproxen sodium 275mg tablets	Naproxen sodium

1051	Indometacin 75mg modified-release tablets	Indometacin
1073	Mefenamic acid 500mg tablets	Mefenamic acid
1075	Diclofenac sodium 50mg gastro-resistant tablets	Diclofenac Sodium
1086	Ibuprofen 600mg tablets	Ibuprofen
1096	Diclofenac sodium 25mg gastro-resistant tablets	Diclofenac Sodium
1115	Diclofenac sodium 100mg modified-release capsules	Diclofenac sodium
1116	Diclofenac 100mg suppositories	Diclofenac sodium
1139	Voltarol 25mg Tablet (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
1210	Indometacin 75mg modified-release capsules	Indometacin
1231	Ketoprofen 100mg capsules	Ketoprofen
1233	Diclofenac sodium 75mg modified-release tablets	Diclofenac Sodium
1246	Ponstan 250mg Dispersible tablet (Chemidex Pharma Ltd)	Mefenamic Acid
1392	Ibuprofen 800mg modified-release tablets	Ibuprofen
1446	Voltarol 50mg Tablet (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
1468	Ibuprofen 200mg Soluble tablet	Ibuprofen
1469	Meloxicam 15mg tablets	Meloxicam
1470	Mobic 15mg tablets (Boehringer Ingelheim Ltd)	Meloxicam
1496	Indocid R 75mg capsules (Merck Sharp & Dohme Ltd)	Indometacin
1571	Ketoprofen 100mg modified-release capsules	Ketoprofen
1621	Brufen 200mg tablets (Abbott Laboratories Ltd)	Ibuprofen
1688	Indocid 50mg capsules (Merck Sharp & Dohme Ltd)	Indometacin
1692	Diclofenac sodium 50mg gastro-resistant / Misoprostol 200microgram tablets	Diclofenac sodium/Misoprostol
1708	Codafen Continus tablets (Napp Pharmaceuticals Ltd)	Ibuprofen/Codeine phosphate
1739	Brufen 400mg tablets (Mylan Ltd)	Ibuprofen
1755	Piroxicam 20mg capsules	Piroxicam
1757	Choline Mg trisalicylate 500mg tablets	Magnesium Trisilicate
1766	Voltarol sr 75mg Modified-release tablet (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
1778	Surgam 300mg Tablet (Sanofi)	Tiaprofenic acid
1866	Naprosyn 500mg tablets (Atnahs Pharma UK Ltd)	Naproxen
1983	Mefenamic acid 250mg Dispersible tablet	Mefenamic Acid
1984	Diclofenac sodium 100mg modified-release tablets	Diclofenac Sodium
2129	Brufen retard tabs 800mg Modified-release tablet (Abbott Laboratories Ltd)	Ibuprofen
2197	Naproxen 375mg Tablet	Naproxen
2200	Indometacin 25mg modified-release capsules	Indometacin
2234	Nabumetone 500mg tablets	Nabumetone
2235	Relifex 500mg tablets (Meda Pharmaceuticals Ltd)	Nabumetone
2243	Meloxicam 7.5mg tablets	Meloxicam
2257	Surgam SA 300mg capsules (Sanofi)	Tiaprofenic acid
2258	Emflex 60mg capsules (Merck Serono Ltd)	Acemetacin
2288	Naprosyn 250mg tablets (Atnahs Pharma UK Ltd)	Naproxen
2293	Voltarol 25mg/ml Injection (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
2363	Dolobid 250mg tablets (Merck Sharp & Dohme Ltd)	Diflunisal

2366	Flurbiprofen 100mg tablets	Flurbiprofen
2382	Tiaprofenic acid 300mg modified-release capsules	Tiaprofenic acid
2386	Voltarol Retard 100mg tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
2387	Arthrotec 75 gastro-resistant tablets (Pfizer Ltd)	Diclofenac sodium/Misoprostol
2391	NAPROXEN 250 MG CAP	Naproxen
2463	Piroxicam 10mg dispersible tablets	Piroxicam
2622	Ibuprofen 800mg tablets	Ibuprofen
2671	Indometacin 50mg modified-release tablets	Indometacin
2827	Feldene 10mg dispersible tablets (Pfizer Ltd)	Piroxicam
2863	Tiaprofenic acid 300mg tablets	Tiaprofenic acid
2904	Diclofenac sodium 75mg gastro-resistant modified-release capsules	Diclofenac sodium
2938	Ibuprofen 100mg/5ml Oral suspension	Ibuprofen
3043	Ketoprofen 200mg modified-release capsules	Ketoprofen
3053	Naproxen 500mg gastro-resistant tablets	Naproxen
3168	Indometacin 25mg/5ml oral suspension sugar free	Indometacin
3170	Meloxicam 15mg suppositories	Meloxicam
3182	Froben 50mg tablets (Abbott Laboratories Ltd)	Flurbiprofen
3216	Indometacin 25mg modified-release tablets	Indometacin
3262	Azapropazone 600mg tablets	Azapropazone
3266	Flurbiprofen 50mg tablets	Flurbiprofen
3311	Etodolac 200mg capsules	Etodolac
3326	Oruvail 100mg Modified-release capsule (Hawgreen Ltd)	Ketoprofen
3336	Toradol 10mg tablets (Roche Products Ltd)	Ketorolac trometamol
3409	Feldene 20mg Orodispersible tablet (Pfizer Ltd)	Piroxicam
3416	Diclofenac sodium 100mg modified-release tablets	Diclofenac sodium
3421	Diclomax sr 75mg Modified-release capsule (Provalis Healthcare Ltd)	Diclofenac sodium
3431	Naproxen 250mg gastro-resistant tablets	Naproxen
3432	Naproxen 375mg gastro-resistant tablets	Naproxen
3492	Diflunisal 500mg tablets	Diflunisal
3496	Nycopren 250mg gastro-resistant tablets (Ardern Healthcare Ltd)	Naproxen
3597	Nurofen 200mg Soluble tablet (Crookes Healthcare Ltd)	Ibuprofen
3599	Ibuprofen 600mg effervescent granules sachets	Ibuprofen
3710	Piroxicam 20mg dispersible tablets	Piroxicam
3739	Rheumox 300mg capsules (Mercury Pharma Group Ltd)	Azapropazone
3817	Synflex 275mg tablets (Roche Products Ltd)	Naproxen sodium
3852	Diclomax 100mg Modified-release capsule (Provalis Healthcare Ltd)	Diclofenac sodium
3897	Sulindac 100mg tablets	Sulindac
3899	Dolobid 500mg tablets (Merck Sharp & Dohme Ltd)	Diflunisal
3901	Naprosyn EC 500mg tablets (Atnahs Pharma UK Ltd)	Naproxen
3935	Feldene 20 capsules (Pfizer Ltd)	Piroxicam
3939	Napratec OP tablets (Pfizer Ltd)	Naproxen
3958	Diclofenac 25mg suppositories	Diclofenac sodium
3972	Naprosyn EC 250mg tablets (Atnahs Pharma UK Ltd)	Naproxen
3974	Tenoxicam 20mg tablets	Tenoxicam

4043	Froben sr 200mg Modified-release capsule (Abbott Laboratories Ltd)	Flurbiprofen
4045	Naprosyn EC 375mg tablets (Atnahs Pharma UK Ltd)	Naproxen
4049	Azapropazone 300mg capsules	Azapropazone
4095	Voltarol 12.5mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
4216	Brufen 600mg tablets (Mylan Ltd)	Ibuprofen
4298	Nurofen 200mg Tablet (Crookes Healthcare Ltd)	Ibuprofen
4309	Ibuprofen lysine 200mg tablets	Ibuprofen lysine
4320	Naprosyn 125mg/5ml oral suspension (Roche Products Ltd)	Naproxen
4368	Lodine 200mg Capsule (Shire Pharmaceuticals Ltd)	Etodolac
4469	Fenoprofen 300mg tablets	Fenoprofen calcium
4506	Volsaid Retard 75 tablets (Chiesi Ltd)	Diclofenac sodium
4564	Fenoprofen 200mg Tablet	Fenoprofen Calcium
4565	Fenoprofen 600mg tablets	Fenoprofen calcium
4625	Voltarol 75mg SR tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
4631	Voltarol 50mg gastro-resistant tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
4692	Dicloflex 50mg gastro-resistant tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
4710	Mefenamic acid 250mg Capsule (Actavis UK Ltd)	Mefenamic acid
4713	Voltarol 75mg/3ml solution for injection ampoules (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
4731	Nurofen for children 100mg/5ml Oral suspension (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
4806	Voltarol 100mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
4880	Diclofenac sodium 75mg gastro-resistant / Misoprostol 200microgram tablets	Diclofenac sodium/Misoprostol
4911	Ibuprofen 400mg Granules	Ibuprofen
4965	Piroxicam 20mg orodispersible tablets sugar free	Piroxicam
4984	Naproxen 500mg tablets and Misoprostol 200microgram tablets	Naproxen
5080	Celebrex 200mg capsules (Pfizer Ltd)	Celecoxib
5085	Voltarol Rapid 50mg tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac potassium
5173	Dexketoprofen 25mg tablets	Dexketoprofen trometamol
5175	Celebrex 100mg capsules (Pfizer Ltd)	Celecoxib
5200	Voltarol 50mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
5254	Celecoxib 200mg capsules	Celecoxib
5266	Lodine sr 600mg Modified-release tablet (Shire Pharmaceuticals Ltd)	Etodolac
5268	Naproxen 500mg modified-release tablets	Naproxen sodium
5401	Voltarol Rapid 25mg tablets (Novartis Pharmaceuticals UK Ltd)	Diclofenac potassium
5407	Naproxen 125mg/5ml oral suspension	Naproxen
5455	Etodolac 600mg modified-release tablets	Etodolac
5482	Sulindac 200mg tablets	Sulindac
5648	Ibuprofen 200mg orodispersible tablets sugar free	Ibuprofen
5695	VioxxAcute 50mg tablets (Merck Sharp & Dohme Ltd)	Rofecoxib
5739	Vioxx 25mg/5ml oral suspension (Merck Sharp & Dohme Ltd)	Rofecoxib
5812	Etoricoxib 90mg tablets	Etoricoxib
5841	Rofecoxib 50mg tablets	Rofecoxib

5938	Etoricoxib 120mg tablets	Etoricoxib
6249	Froben 100mg tablets (Abbott Laboratories Ltd)	Flurbiprofen
6460	VioxxAcute 25mg tablets (Merck Sharp & Dohme Ltd)	Rofecoxib
6464	Arcoxia 60mg tablets (Grunenthal Ltd)	Etoricoxib
6498	Arcoxia 90mg tablets (Grunenthal Ltd)	Etoricoxib
6663	Valdecoxib 20mg tablets	Valdecoxib
7058	Calprofen 100mg/5ml Oral suspension (McNeil Products Ltd)	Ibuprofen
7118	Prexige 100mg tablets (Novartis Pharmaceuticals UK Ltd)	Lumiracoxib
7222	Tolfenamic acid 200mg tablets	Tolfenamic acid
7424	Fenbufen 300mg capsules	Fenbufen
7426	Lederfen 300mg Capsule (Wyeth Pharmaceuticals)	Fenbufen
7432	Oruvail IM 100mg/2ml solution for injection ampoules (Sanofi)	Ketoprofen
7434	Clinoril 100mg tablets (Merck Sharp & Dohme Ltd)	Sulindac
7458	DICLOFENAC SODIUM (3ML) 25 MG/ML INJ	Diclofenac sodium
7481	Lederfen 450mg Tablet (Wyeth Pharmaceuticals)	Fenbufen
7483	Butazolidin 100mg Tablet (Novartis Pharmaceuticals UK Ltd)	Phenylbutazone
7490	Froben 100mg suppositories (Abbott Laboratories Ltd)	Flurbiprofen
7522	Lederfen 300mg Tablet (Wyeth Pharmaceuticals)	Fenbufen
7524	Feldene 20mg dispersible tablets (Pfizer Ltd)	Piroxicam
7535	Nurofen 200mg Capsule (Crookes Healthcare Ltd)	Ibuprofen
7667	Diclofenac 12.5mg suppositories	Diclofenac sodium
7688	Rheumox 600mg tablets (Mercury Pharma Group Ltd)	Azapropazone
7774	DICLOFENAC 75 MG INJ	Diclofenac sodium
7840	Oruvail 150mg Modified-release capsule (Hawgreen Ltd)	Ketoprofen
7913	Tiaprofenic acid 200mg tablets	Tiaprofenic acid
8062	Motifene 75mg modified-release capsules (Daiichi Sankyo UK Ltd)	Diclofenac sodium
8145	Fenbufen 300mg tablets	Fenbufen
8385	Ketoprofen 150mg modified-release capsules	Ketoprofen
8401	Motrin 400mg tablets (Pfizer Ltd)	Ibuprofen
8451	Etodolac 200mg Tablet	Etodolac
8544	Fenbufen 450mg tablets	Fenbufen
8600	Piroxicam 20mg suppositories	Piroxicam
8663	Naprosyn S/R 500mg tablets (Roche Products Ltd)	Naproxen sodium
8672	Feldene 20mg suppositories (Pfizer Ltd)	Piroxicam
8789	Dicloflex retard tabs 100 100mg Modified-release tablet (Dexcel-Pharma Ltd)	Diclofenac sodium
8969	Lodine 300mg Capsule (Shire Pharmaceuticals Ltd)	Etodolac
9222	Dicloflex 75mg SR tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
9439	Flurbiprofen 200mg modified-release capsules	Flurbiprofen
9465	Diclotard 100 100mg Modified-release tablet (Galen Ltd)	Diclofenac sodium
9474	Preservex 100mg tablets (Almirall Ltd)	Aceclofenac
9500	Diclotard 75mg modified-release tablets (Galen Ltd)	Diclofenac sodium
9637	Keral 25mg tablets (A. Menarini Farmaceutica Internazionale SRL)	Dexketoprofen trometamol
9688	Diclovol 75mg SR tablets (Mylan Ltd)	Diclofenac sodium

9736	Mefenamic acid 50mg/5ml oral suspension	Mefenamic acid
9822	Arcoxia 120mg tablets (Grunenthal Ltd)	Etoricoxib
9886	Dicloflex 50mg Gastro-resistant tablet (Ratiopharm UK Ltd)	Diclofenac sodium
9899	Bextra 10mg tablets (Pfizer Ltd)	Valdecoxib
9912	Bextra 20mg tablets (Pfizer Ltd)	Valdecoxib
9978	Bextra 40mg tablets (Pfizer Ltd)	Valdecoxib
10033	Etodolac 300mg capsules	Etodolac
10149	Ibuprofen 200mg capsules	Ibuprofen
10169	Brexidol 20mg tablets (Chiesi Ltd)	Piroxicam betadex
10209	Ibufem 200mg tablets (Galpharm International Ltd)	Ibuprofen
10212	Lumiracoxib 100mg tablets	Lumiracoxib
10295	Relifex 500mg/5ml oral suspension (Meda Pharmaceuticals Ltd)	Nabumetone
10325	Dexibuprofen 300mg tablets	Dexibuprofen
10336	Ketoprofen 100mg/2ml solution for injection ampoules	Ketoprofen
10481	Lederfen f 450mg Tablet (Wyeth Pharmaceuticals)	Fenbufen
10558	Flexin-75 Continus tablets (Napp Pharmaceuticals Ltd)	Indometacin
10589	Fenopron 600 tablets (Typharm Ltd)	Fenoprofen calcium
10625	Indocid 5mg/ml oral suspension (Merck Sharp & Dohme Ltd)	Indometacin
10678	Fenopron 300 tablets (Typharm Ltd)	Fenoprofen calcium
10711	Tolectin 400mg Capsule (Cilag Pharmaceuticals Ltd)	Tolmetin Sodium
10785	Fenbid 300mg Spansules (Mercury Pharma Group Ltd)	Ibuprofen
10792	Voltarol 50mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
10917	Flamrase SR 100mg tablets (Teva UK Ltd)	Diclofenac sodium
10939	Toradol 10mg/1ml solution for injection ampoules (Roche Products Ltd)	Ketorolac trometamol
10978	Voltarol 25mg Suppository (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
11168	Volsaid Retard 100 tablets (Chiesi Ltd)	Diclofenac sodium
11215	Voltarol 25mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
11322	Flamrase sr 75mg Modified-release tablet (APS Berk)	Diclofenac sodium
11461	Ibuprofen 300mg modified-release / Codeine 20mg tablets	Ibuprofen/Codeine phosphate
11466	Nabumetone 500mg/5ml oral-suspension	Nabumetone
11495	Piroxicam betadex 20mg tablets	Piroxicam betadex
11550	Nurofen Meltlets 200mg tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
11554	Ibuprofen 200mg / Codeine 12.8mg tablets	Ibuprofen/Codeine phosphate
11907	Dexibuprofen 400mg tablets	Dexibuprofen
11952	Phenylbutazone 100mg gastro-resistant tablets	Phenylbutazone
11970	Meloxicam 7.5mg suppositories	Meloxicam
11980	Cuprofen 400mg Tablet (SSL International Plc)	Ibuprofen
11995	Orudis 100mg Suppository (Hawgreen Ltd)	Ketoprofen
11999	Orudis 100mg Capsule (Hawgreen Ltd)	Ketoprofen
12000	Ketoprofen 100mg suppositories	Ketoprofen
12075	Mobiflex 20mg Tablet (Roche Products Ltd)	Tenoxicam
12122	Orudis 50mg Capsule (Hawgreen Ltd)	Ketoprofen
12188	Trilisate 500mg Tablet (Napp Pharmaceuticals Ltd)	Magnesium Trisilicate

12364	Aloxiprin 600mg tablets	Aloxiprin
12607	KETOROLAC TROMETAMOL 30 MG/ML INJ	Ketorolac trometamol
12709	Ibuprofen and codeine 200mg + 12.5mg Tablet	Codeine Phosphate/Ibuprofen
12766	Flurbiprofen 8.75mg lozenges	Flurbiprofen
13347	Alrheumat 50mg Capsule (Bayer Plc)	Ketoprofen
13380	Clinoril 200mg tablets (Merck Sharp & Dohme Ltd)	Sulindac
13459	Dysman 500 tablets (Ashbourne Pharmaceuticals Ltd)	Mefenamic acid
13606	Flexin-25 Continus tablets (Napp Pharmaceuticals Ltd)	Indometacin
13627	Mobic 15mg suppositories (Boehringer Ingelheim Ltd)	Meloxicam
13639	Flexin-50 Continus tablets (Napp Pharmaceuticals Ltd)	Indometacin
13818	Nabumetone 500mg tablets (Actavis UK Ltd)	Nabumetone
13893	Nurofen Plus tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen/Codeine phosphate
14084	Diclovol 75mg SR tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
14085	Diclovol Retard 100mg tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
14251	Ketorolac 30mg/1ml solution for injection ampoules	Ketorolac trometamol
14333	Ibuprofen 400mg capsules	Ibuprofen
14380	Lederfen 300mg capsules (Mercury Pharma Group Ltd)	Fenbufen
14385	Cuprofen 200mg Tablet (SSL International Plc)	Ibuprofen
14422	Fenbufen 450mg Effervescent tablet	Fenbufen
14476	Indolar SR 75mg capsules (Sandoz Ltd)	Indometacin
14541	Ponstan 50mg/5ml paediatric Liquid (Chemidex Pharma Ltd)	Mefenamic acid
14672	Defanac 75mg SR tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
14678	Defanac sr 100mg Modified-release tablet (Ranbaxy (UK) Ltd)	Diclofenac sodium
14707	Defanac Retard 100mg tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
14776	Surgam 300mg tablets (Sanofi)	Tiaprofenic acid
14994	Clotam Rapid 200mg tablets (Galen Ltd)	Tolfenamic acid
15005	Indomod 25mg modified-release capsules (Pfizer Ltd)	Indometacin
15023	Naproxen 375mg Modified-release tablet	Naproxen
15068	Arthrofen 400 tablets (Ashbourne Pharmaceuticals Ltd)	Ibuprofen
15104	Naproxen 500mg Granules	Naproxen
15159	Tolfenamic acid 200mg Capsule	Tolfenamic Acid
15180	Naproxen and misoprostol 500mgwith200microgram combined Tablet	Naproxen/Misoprostol
15201	Volraman 50mg gastro-resistant tablets (LPC Medical (UK) Ltd)	Diclofenac sodium
15286	Ketocid 200 modified-release capsules (Chiesi Ltd)	Ketoprofen
15363	Nurofen Cold and Flu tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen/Pseudoephedrine hydrochloride
15501	Flurbiprofen 100mg suppositories	Flurbiprofen
15732	Diclovol 50mg gastro-resistant tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
16001	Ibuprofen 200mg tablets (A A H Pharmaceuticals Ltd)	Ibuprofen
16170	Fenbufen 300mg capsules (Genus Pharmaceuticals Ltd)	Fenbufen
16176	Lederfen 450mg tablets (Mercury Pharma Group Ltd)	Fenbufen
16192	Motrin 200mg Tablet (Pharmacia Ltd)	Ibuprofen
16193	Motrin 800mg tablets (Pfizer Ltd)	Ibuprofen
16194	Lodine 200mg Tablet (Shire Pharmaceuticals Ltd)	Etodolac

16205	Palaprin forte 600mg Tablet (Nicholas Laboratories Ltd)	Aloxiprin
16221	Diclozip 25mg gastro-resistant tablets (Ashbourne Pharmaceuticals Ltd)	Diclofenac sodium
16222	Diclozip 50mg gastro-resistant tablets (Ashbourne Pharmaceuticals Ltd)	Diclofenac sodium
16225	Dexomon retard 100mg Modified-release tablet (Hillcross Pharmaceuticals Ltd)	Diclofenac sodium
16272	Lofensaid Retard 100 tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
16286	Lofensaid Retard 75 tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
16473	Relifex 500mg dispersible tablets (Meda Pharmaceuticals Ltd)	Nabumetone
16474	Nabumetone 500mg dispersible tablets sugar free	Nabumetone
16637	Ketorolac 10mg tablets	Ketorolac trometamol
17029	Rhumalgan CR 75 tablets (Sandoz Ltd)	Diclofenac sodium
17030	Rhumalgan SR 75mg capsules (Sandoz Ltd)	Diclofenac sodium
17124	Dicloflex sr 100mg Tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
17126	Fenactol SR 75mg tablets (Discovery Pharmaceuticals)	Diclofenac sodium
17128	Fenactol 50mg gastro-resistant tablets (Discovery Pharmaceuticals)	Diclofenac sodium
17131	Lederfen 300mg tablets (Mercury Pharma Group Ltd)	Fenbufen
17165	Nycopren 500mg gastro-resistant tablets (Ardern Healthcare Ltd)	Naproxen
17201	Motrin 600mg tablets (Pfizer Ltd)	Ibuprofen
17491	Dicloflex sr 75mg Tablet (Ratiopharm UK Ltd)	Diclofenac sodium
17525	Fenactol Retard 100mg tablets (Discovery Pharmaceuticals)	Diclofenac sodium
17532	Dicloflex Retard 100mg tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
17572	Tenoxicam 20mg powder and solvent for solution for injection vials	Tenoxicam
17680	Indomax 75 SR capsules (Ashbourne Pharmaceuticals Ltd)	Indometacin
17733	Condrotec 500mg+200microgram Tablet (Pharmacia Ltd)	Naproxen/Misoprostol
17750	Indomax 25mg Capsule (Ashbourne Pharmaceuticals Ltd)	Indometacin
17754	Progesic 200mg Tablet (Eli Lilly and Company Ltd)	Fenoprofen Calcium
17818	Ketovail 100mg modified-release capsules (Teva UK Ltd)	Ketoprofen
18066	Valdecoxib 40mg tablets	Valdecoxib
18196	Orbifen for children 100mg/5ml Oral suspension (Orbis Consumer Products Ltd)	Ibuprofen
18234	Rheumacin LA 75mg capsules (Hillcross Pharmaceuticals Ltd)	Indometacin
18242	Indocid PDA 1mg powder for solution for injection vials (Lundbeck Pharmaceuticals Ireland Ltd)	Indometacin sodium trihydrate
18364	Ibular 400mg Tablet (Lagap)	Ibuprofen
18371	Digenac xl 100mg Modified-release tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
18448	Voltarol 12.5mg suppositories (Novartis Pharmaceuticals UK Ltd)	Diclofenac sodium
18527	Mandafen 400mg tablets (M & A Pharmachem Ltd)	Ibuprofen
18640	Tolectin 200mg Capsule (Cilag Pharmaceuticals Ltd)	Tolmetin Sodium
18647	Fenoket 200mg modified-release capsules (Opus Pharmaceuticals Ltd)	Ketoprofen
18662	Indomod 75mg modified-release capsules (Pfizer Ltd)	Indometacin
18798	Lofensaid 50mg gastro-resistant tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
18812	Nurofen meltlets lemon 200mg Orodispersible tablet (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
18820	Fenpaed 100mg/5ml Oral suspension (Pinewood Healthcare)	Ibuprofen
18921	Fenactol 25mg gastro-resistant tablets (Discovery Pharmaceuticals)	Diclofenac sodium

19007	Naprosyn 500mg Granules (Roche Products Ltd)	Naproxen
19036	Arthrofen 200 tablets (Ashbourne Pharmaceuticals Ltd)	Ibuprofen
19046	Ibuprofen 400mg tablets (A A H Pharmaceuticals Ltd)	Ibuprofen
19320	Piroflam 20mg Capsule (Opus Pharmaceuticals Ltd)	Piroxicam
19322	Disalcid 500mg Capsule (3M Health Care Ltd)	Salsalate
19382	Slofenac 75mg SR tablets (Sterwin Medicines)	Diclofenac sodium
19575	Proflex 200mg Tablet (Novartis Consumer Health UK Ltd)	Ibuprofen
19975	Parecoxib 40mg powder for injection	Parecoxib Sodium
20016	Tolmetin 400mg Capsule	Tolmetin Sodium
20036	Clotam 200mg Capsule (Thames Laboratories Ltd)	Tolfenamic Acid
20059	Tiaprofenic acid 300mg sachets	Tiaprofenic Acid
20105	Dicloflex 25mg Gastro-resistant tablet (Ratiopharm UK Ltd)	Diclofenac sodium
20230	Salsalate 500mg capsules	Salsalate
20384	Flamatak MR 100mg tablets (Actavis UK Ltd)	Diclofenac sodium
20385	Arthrosin 500 tablets (Ashbourne Pharmaceuticals Ltd)	Naproxen
20386	Ramodar 200mg Tablet (Wyeth Pharmaceuticals)	Etodolac
20395	Flamatak MR 75mg tablets (Actavis UK Ltd)	Diclofenac sodium
20621	Dicloflex 75mg SR tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
20648	Indometacin 1mg powder for solution for injection vials	Indometacin sodium trihydrate
20653	DICLOFENAC SODIUM S/R	Diclofenac sodium
20663	PIROXICAM	Piroxicam
20699	PIROXICAM DISPERSIBLE	Piroxicam
20704	NAPROXEN SODIUM	Naproxen
20742	PIROXICAM DISPERSIBLE	Piroxicam
20805	Dicloflex 75mg SR tablets (Teva UK Ltd)	Diclofenac sodium
20907	Sudafed Sinus Pressure & Pain tablets (McNeil Products Ltd)	Ibuprofen/Pseudoephedrine hydrochloride
20978	Anadin Ultra liquid capsules (Wyeth Consumer Healthcare)	Ibuprofen
21045	Ibumetin 400mg Tablet (Alfred Benzon (UK) Ltd)	Ibuprofen
21050	Ketonal 100mg Capsule (Lagap)	Ketoprofen
21123	Piroxicam 20mg Capsule (Berk Pharmaceuticals Ltd)	Piroxicam
21150	Strefen 8.75mg lozenges (Reckitt Benckiser Healthcare (UK) Ltd)	Flurbiprofen
21387	Diclofenac sodium 50mg gastro-resistant tablets (Mylan Ltd)	Diclofenac sodium
21419	Seractil 300mg tablets (Thornton & Ross Ltd)	Dexibuprofen
21421	Seractil 400mg tablets (Thornton & Ross Ltd)	Dexibuprofen
21444	Volraman 25mg gastro-resistant tablets (LPC Medical (UK) Ltd)	Diclofenac sodium
21610	Rhumalgan CR 100 tablets (Sandoz Ltd)	Diclofenac sodium
21807	Flamrase 25 EC tablets (Teva UK Ltd)	Diclofenac sodium
21811	Lidifen 200mg Tablet (Berk Pharmaceuticals Ltd)	Ibuprofen
21813	Lidifen 400mg Tablet (Berk Pharmaceuticals Ltd)	Ibuprofen
21815	Arthrofen 600 tablets (Ashbourne Pharmaceuticals Ltd)	Ibuprofen
21816	Pranoxen continus 500mg Tablet (Napp Pharmaceuticals Ltd)	Naproxen sodium
21821	Lidifen f 600mg Tablet (Berk Pharmaceuticals Ltd)	Ibuprofen
21824	Flamrase 50 EC tablets (Teva UK Ltd)	Diclofenac sodium

21831	Dysman 250mg Capsule (Ashbourne Pharmaceuticals Ltd)	Mefenamic acid
21840	Arthrosin 250 tablets (Ashbourne Pharmaceuticals Ltd)	Naproxen
21843	Pranoxen continus 375mg Tablet (Napp Pharmaceuticals Ltd)	Naproxen
21846	Pirozip 20 capsules (Ashbourne Pharmaceuticals Ltd)	Piroxicam
21864	Pirozip 10 capsules (Ashbourne Pharmaceuticals Ltd)	Piroxicam
21949	Toradol 30mg/1ml solution for injection ampoules (Atnahs Pharma UK Ltd)	Ketorolac trometamol
21955	Ketozip 200 XL capsules (Ashbourne Pharmaceuticals Ltd)	Ketoprofen
22206	Nurofen Long Lasting 300mg capsules (Crookes Healthcare Ltd)	Ibuprofen
22230	Meflam 250mg Capsule (Trinity Pharmaceuticals Ltd)	Mefenamic acid
22283	Lemsip flu 12 hr Modified-release capsule (Reckitt Benckiser Healthcare (UK) Ltd)	Pseudoephedrine hydrochloride/Ibuprofen
22410	TOLMETIN 200 MG TAB	Tolmetin sodium
23026	Artracin sr 75mg Modified-release capsule (Trinity Pharmaceuticals Ltd)	Indometacin
23121	Arthroxen 500mg Tablet (C P Pharmaceuticals Ltd)	Naproxen
23204	Pardelprin MR 75mg capsules (Actavis UK Ltd)	Indometacin
23323	Prosaid 500mg Tablet (BHR Pharmaceuticals Ltd)	Naproxen
23425	Nurofen Migraine Pain 342mg tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen lysine
23795	Imbrilon 100mg Suppository (Berk Pharmaceuticals Ltd)	Indometacin
24007	Valrox 500mg Tablet (Shire Pharmaceuticals Ltd)	Naproxen
24020	Valrox 250mg Tablet (Shire Pharmaceuticals Ltd)	Naproxen
24111	Ketorolac 10mg/1ml solution for injection ampoules	Ketorolac trometamol
24121	Diclofenac sodium 25mg gastro-resistant tablets (Actavis UK Ltd)	Diclofenac sodium
24122	Diclofenac sodium 50mg gastro-resistant tablets (Actavis UK Ltd)	Diclofenac sodium
24128	Diclofenac sodium 25mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
24137	Indometacin 25mg capsules (Actavis UK Ltd)	Indometacin
24193	Imbrilon 25mg Capsule (Berk Pharmaceuticals Ltd)	Indometacin
24212	Imbrilon 50mg Capsule (Berk Pharmaceuticals Ltd)	Indometacin
24236	Slofenac 100mg Modified-release tablet (Sterwin Medicines)	Diclofenac sodium
24305	Ibufac 400mg Tablet (DDSA Pharmaceuticals Ltd)	Ibuprofen
24308	Slo-Indo 75mg capsules (Mylan Ltd)	Indometacin
24320	Indolar 50mg Capsule (Lagap)	Indometacin
24356	Eccoxolac 300mg capsules (Meda Pharmaceuticals Ltd)	Etodolac
24469	Cuprofen for Children 100mg/5ml oral suspension (SSL International Plc)	Ibuprofen
24531	Mobiflex 20mg Effervescent tablet (Roche Products Ltd)	Tenoxicam
24682	Tenoxicam 20mg effervescent tablets	Tenoxicam
24887	Nurofen Advance 200mg tablets (Crookes Healthcare Ltd)	Ibuprofen lysine
25092	NAPROXEN	Naproxen
25205	Ibuprofen 100mg/5ml oral suspension 5ml sachets sugar free (Thornton & Ross Ltd)	Ibuprofen
25257	Advil 200mg tablets (Wyeth Consumer Healthcare)	Ibuprofen
25283	Valenac ec 50mg Gastro-resistant tablet (Shire Pharmaceuticals Ltd)	Diclofenac sodium

25329	Lofensaid 25mg gastro-resistant tablets (Opus Pharmaceuticals Ltd)	Diclofenac sodium
25330	Solpaflex tablets (GlaxoSmithKline Consumer Healthcare)	Ibuprofen/Codeine phosphate
25341	Arthrosin EC 250 tablets (Ashbourne Pharmaceuticals Ltd)	Naproxen
25342	Arthrosin EC 500 tablets (Ashbourne Pharmaceuticals Ltd)	Naproxen
25358	Defanac 50mg gastro-resistant tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
25361	Diclovol 25mg gastro-resistant tablets (Arun Pharmaceuticals Ltd)	Diclofenac sodium
25362	Defanac 25mg gastro-resistant tablets (Ranbaxy (UK) Ltd)	Diclofenac sodium
25619	Nurofen 400mg Tablet (Crookes Healthcare Ltd)	Ibuprofen
25643	Surgam 300mg Sachets (Sanofi)	Tiaprofenic Acid
25701	Ketovail 200mg modified-release capsules (Teva UK Ltd)	Ketoprofen
25750	Rheuflex 250mg Tablet (Goldshield Pharmaceuticals Ltd)	Naproxen
25790	Rhumalgan 25mg Tablet (Lagap)	Diclofenac sodium
25794	Isisfen 400mg Tablet (Isis Products Ltd)	Ibuprofen
25800	Feverfen 100mg/5ml oral suspension (Wise Pharmaceuticals Ltd)	Ibuprofen
26083	Indolar 100mg Suppository (Lagap)	Indometacin
26095	Ibuprofen lysine 400mg tablets	Ibuprofen lysine
26165	Diclofenac sodium 50mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
26205	Fenbuzip 300mg Capsule (Ashbourne Pharmaceuticals Ltd)	Fenbufen
26214	Fenbuzip 450mg Tablet (Ashbourne Pharmaceuticals Ltd)	Fenbufen
26216	Timpron 500mg Tablet (Berk Pharmaceuticals Ltd)	Naproxen
26231	Timpron 500mg Gastro-resistant tablet (Berk Pharmaceuticals Ltd)	Naproxen
26234	Flamatrol 10mg Capsule (Berk Pharmaceuticals Ltd)	Piroxicam
26242	Timpron 250mg Tablet (Berk Pharmaceuticals Ltd)	Naproxen
26247	Opustan 500mg Tablet (Opus Pharmaceuticals Ltd)	Mefenamic acid
26351	Rheumatac Retard 75 tablets (AMCo)	Diclofenac sodium
26404	Tolmetin 200mg Capsule	Tolmetin Sodium
26522	Meflam 500mg Tablet (Trinity Pharmaceuticals Ltd)	Mefenamic acid
26575	Streflam 8.75mg Lozenge (Crookes Healthcare Ltd)	Flurbiprofen
26631	Rhumalgan XL 100mg capsules (Sandoz Ltd)	Diclofenac sodium
26888	Difenor xl 100mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
26970	Ibuprofen 100mg/5ml oral suspension sugar free (Teva UK Ltd)	Ibuprofen
26994	Fenbuzip 300mg Tablet (Ashbourne Pharmaceuticals Ltd)	Fenbufen
27013	Tiloket 200mg Modified-release capsule (Tillomed Laboratories Ltd)	Ketoprofen
27055	Diclofenac sodium 50mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
27082	Ketpron XL 100mg capsules (Mercury Pharma Group Ltd)	Ketoprofen
27200	Diclovol Retard 100mg tablets (Mylan Ltd)	Diclofenac sodium
27362	Diclofenac 100mg Modified-release tablet (Actavis UK Ltd)	Diclofenac sodium
27366	Naproxen 500mg gastro-resistant tablets (Teva UK Ltd)	Naproxen
27438	Pseudoephedrine 45mg with ibuprofen 300mg modified-release capsule	Pseudoephedrine Hydrochloride/Ibuprofen
27484	Piroxicam 20mg/1ml solution for injection ampoules	Piroxicam
27490	Feldene IM 20mg/1ml solution for injection ampoules (Pfizer Ltd)	Piroxicam

27677	Diclofenac 75mg/3ml Injection (Antigen Pharmaceuticals)	Diclofenac sodium
27723	Phenylbutazone 200mg tablets	Phenylbutazone
27782	Ibuprofen 400mg tablets (Teva UK Ltd)	Ibuprofen
27783	Ibuprofen 400mg tablets sugar coated (Actavis UK Ltd)	Ibuprofen
27968	Apsifen 400mg Tablet (Approved Prescription Services Ltd)	Ibuprofen
28168	Nurofen Recovery 200mg orodispersible tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
28171	Lumiracoxib 400mg tablets	Lumiracoxib
28172	Ibuprofen 300mg / Pseudoephedrine 45mg modified-release capsules	Pseudoephedrine hydrochloride/Ibuprofen
28255	Naproxen 250mg tablets (Wockhardt UK Ltd)	Naproxen
28256	Diclofenac 50mg Tablet (Berk Pharmaceuticals Ltd)	Diclofenac sodium
28313	NAPROXEN	Naproxen
28332	Mobiflex 20mg powder and solvent for solution for injection vials (Roche Products Ltd)	Tenoxicam
28348	Ibuprofen 200mg tablets (Teva UK Ltd)	Ibuprofen
28383	Prexige 400mg tablets (Novartis Pharmaceuticals UK Ltd)	Lumiracoxib
28390	Valenac ec 25mg Gastro-resistant tablet (Shire Pharmaceuticals Ltd)	Diclofenac sodium
28479	Nurofen Back Pain SR 300mg capsules (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
28519	Pseudoephedrine 30mg with ibuprofen 200mg tablet	Pseudoephedrine Hydrochloride/Ibuprofen
28522	Ibuprofen 200mg / Pseudoephedrine hydrochloride 30mg tablets	Ibuprofen/Pseudoephedrine hydrochloride
28553	Diclofenac sodium 50mg gastro-resistant tablets (Teva UK Ltd)	Diclofenac sodium
28695	Piroflam 10mg Capsule (Opus Pharmaceuticals Ltd)	Piroxicam
28764	Closteril 100mg Modified-release tablet (Pharmalife Healthcare Services Ltd)	Diclofenac sodium
28816	Rheuflex 500mg Tablet (Goldshield Pharmaceuticals Ltd)	Naproxen
28822	Ibuprofen with pseudoephedrine hc 400mg + 60mg Liquid	Pseudoephedrine Hydrochloride/Ibuprofen
28888	Galprofen Long Lasting 200mg capsules (Galpharm International Ltd)	Ibuprofen
28900	Indometacin 25mg Capsule (Generics (UK) Ltd)	Indometacin
29010	Phenylbutazone 100mg tablets	Phenylbutazone
29037	Valdic 100 Retard tablets (Fannin UK Ltd)	Diclofenac sodium
29068	Nurofen Extra Strength 400mg capsules (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
29110	Lornoxicam 4mg tablets	Lornoxicam
29181	Dicloflex 75mg SR tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
29316	Care ibuprofen 400mg Tablet (Thornton & Ross Ltd)	Ibuprofen
29330	Diclofenac sodium 50mg gastro-resistant tablets (Sandoz Ltd)	Diclofenac sodium
29332	Ibuprofen 100mg/5ml oral suspension sugar free (Sandoz Ltd)	Ibuprofen
29345	Ibuprofen 100mg/5ml Oral suspension (Hillcross Pharmaceuticals Ltd)	Ibuprofen
29352	Ibuprofen 100mg/5ml oral suspension sugar free (Vantage)	Ibuprofen
29455	Flexotard MR 100mg tablets (Pfizer Ltd)	Diclofenac sodium
29465	Piroxicam 20mg capsules (Actavis UK Ltd)	Piroxicam

29523	DICLOFENAC SODIUM (3ML)	Diclofenac sodium
29524	Ibumetin 600mg Tablet (Alfred Benzon (UK) Ltd)	Ibuprofen
29587	Ebufac 400mg Tablet (DDSA Pharmaceuticals Ltd)	Ibuprofen
29674	Butazolidin 200mg Tablet (Novartis Pharmaceuticals UK Ltd)	Phenylbutazone
29704	Paxofen 200mg Tablet (M A Steinhard Ltd)	Ibuprofen
29749	Ibuprofen 200mg tablets (Ranbaxy (UK) Ltd)	Ibuprofen
29772	Ketotard XL 200mg capsules (Galen Ltd)	Ketoprofen
30090	ROFECOXIB	Rofecoxib
30122	Lornoxicam 8mg tablets	Lornoxicam
30164	Lemsip Cold and Flu Sinus 12 Hr Ibuprofen + Pseudoephedrine modified-release capsules (Reckitt Benckiser Healthcare (UK) Ltd)	Pseudoephedrine hydrochloride/Ibuprofen
30168	Arthroxen 250mg Tablet (C P Pharmaceuticals Ltd)	Naproxen
30243	Ibuprofen 200mg effervescent tablets	Ibuprofen
30282	Diclofenac 75mg Modified-release tablet (Galen Ltd)	Diclofenac sodium
30297	Diclofenac 50mg Gastro-resistant tablet (Pharmacia Ltd)	Diclofenac sodium
30327	Jomethid XL 200mg capsules (Actavis UK Ltd)	Ketoprofen
30382	Ibuprofen 200mg Tablet (C P Pharmaceuticals Ltd)	Ibuprofen
30389	Contraflam 250mg Capsule (Berk Pharmaceuticals Ltd)	Mefenamic acid
30391	Contraflam 500mg Tablet (Berk Pharmaceuticals Ltd)	Mefenamic acid
30724	Galprofen 100mg/5ml oral suspension (Galpharm International Ltd)	Ibuprofen
30790	Dicloflex sr 75mg Tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
30806	Rhumalgan 50mg Tablet (Lagap)	Diclofenac sodium
30811	Proflex 300mg Modified-release capsule (Novartis Consumer Health UK Ltd)	Ibuprofen
30849	Valdic 75 Retard tablets (Fannin UK Ltd)	Diclofenac sodium
30892	Mandafen for Children 100mg/5ml oral suspension sugar free (M & A Pharmachem Ltd)	Ibuprofen
30923	Diclofenac 100mg suppositories (A A H Pharmaceuticals Ltd)	Diclofenac sodium
30942	Diclofenac 50mg Tablet (Regent Laboratories Ltd)	Diclofenac sodium
30982	Naproxen 500mg gastro-resistant tablets (Actavis UK Ltd)	Naproxen
31064	Mobiflex 20mg Granules (Roche Products Ltd)	Tenoxicam
31383	Dexomon 75mg SR tablets (Hillcross Pharmaceuticals Ltd)	Diclofenac sodium
31429	Timpron 250mg Gastro-resistant tablet (Berk Pharmaceuticals Ltd)	Naproxen
31469	Apsifen -f 600mg Tablet (Approved Prescription Services Ltd)	Ibuprofen
31482	Apsifen 200mg Tablet (Approved Prescription Services Ltd)	Ibuprofen
31589	Diclofenac sodium 75mg modified-release tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
31777	Piroxicam 20mg dispersible tablets (Mylan Ltd)	Piroxicam
31787	Econac SR 75mg tablets (AMCo)	Diclofenac sodium
31916	Tiloket CR 100mg capsules (Tillomed Laboratories Ltd)	Ketoprofen
31944	Diclofenac sodium 25mg gastro-resistant tablets (Mylan Ltd)	Diclofenac sodium
31945	Naproxen 500mg Gastro-resistant tablet (Sterwin Medicines)	Naproxen
31950	Diclofenac sodium 50mg gastro-resistant tablets (Sterwin Medicines)	Diclofenac sodium
31959	Indometacin 50mg capsules (A A H Pharmaceuticals Ltd)	Indometacin
31962	Ketpron XL 200mg capsules (Mercury Pharma Group Ltd)	Ketoprofen

32090	Mefenamic acid 500mg tablets (Actavis UK Ltd)	Mefenamic acid
32097	Indometacin 75mg Modified-release capsule (Actavis UK Ltd)	Indometacin
32100	Ibuprofen 600mg tablets (A A H Pharmaceuticals Ltd)	Ibuprofen
32105	Mefenamic acid 500mg tablets (A A H Pharmaceuticals Ltd)	Mefenamic acid
32108	Diclofenac sodium 25mg gastro-resistant tablets (Teva UK Ltd)	Diclofenac sodium
32136	Ibular 200mg Tablet (Lagap)	Ibuprofen
32227	Larafen CR 200mg capsules (Ennogen Pharma Ltd)	Ketoprofen
32234	Mefenamic acid 500mg tablets (IVAX Pharmaceuticals UK Ltd)	Mefenamic acid
32242	Ibuprofen 400mg tablets (Sterwin Medicines)	Ibuprofen
32362	ROFECOXIB	Rofecoxib
32365	Relcofen 400mg tablets (Actavis UK Ltd)	Ibuprofen
32366	Relcofen 200mg Tablet (Actavis UK Ltd)	Ibuprofen
32509	Anadin Ibuprofen 200mg tablets (Pfizer Consumer Healthcare Ltd)	Ibuprofen
32536	Diclofenac 25mg Tablet (Berk Pharmaceuticals Ltd)	Diclofenac sodium
32601	Econac 100mg suppositories (AMCo)	Diclofenac sodium
32641	Indometacin 25mg capsules (A A H Pharmaceuticals Ltd)	Indometacin
32704	Advil cold and sinus 200mg+30mg Tablet (Wyeth Consumer Healthcare)	Ibuprofen/Pseudoephedrine hydrochloride
32854	Diclofenac sodium 75mg modified-release capsules (A A H Pharmaceuticals Ltd)	Diclofenac sodium
32862	Ibuprofen 100mg/5ml oral suspension sugar free (Thornton & Ross Ltd)	Ibuprofen
32875	Ibuprofen 400mg tablets (Sandoz Ltd)	Ibuprofen
32916	Diclofenac 75mg Modified-release capsule (Sandoz Ltd)	Diclofenac sodium
33111	Prosaid 250mg Tablet (BHR Pharmaceuticals Ltd)	Naproxen
33113	Artracin 50mg Capsule (DDSA Pharmaceuticals Ltd)	Indometacin
33180	Ketoprofen cr 200mg Capsule (Bristol-Myers Squibb Pharmaceuticals Ltd)	Ketoprofen
33308	Butazone 100mg Tablet (DDSA Pharmaceuticals Ltd)	Phenylbutazone
33318	Indometacin 50mg Capsule (Generics (UK) Ltd)	Indometacin
33321	Indometacin 50mg capsules (Actavis UK Ltd)	Indometacin
33357	Pacifene 200mg tablets (Sussex Pharmaceutical Ltd)	Ibuprofen
33457	Isclofen 50mg Gastro-resistant tablet (Isis Products Ltd)	Diclofenac sodium
33559	Diclofenac 50mg Tablet (C P Pharmaceuticals Ltd)	Diclofenac sodium
33568	Ketoprofen 200mg Modified-release capsule (Actavis UK Ltd)	Ketoprofen
33589	Ibuprofen 400mg tablets (Thornton & Ross Ltd)	Ibuprofen
33645	Diclofenac 75mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
33669	Diclofenac 50mg Gastro-resistant tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
33704	Ibuprofen 100mg/5ml oral suspension sugar free (A A H Pharmaceuticals Ltd)	Ibuprofen
33785	Galprofen 200mg tablets (Galpharm International Ltd)	Ibuprofen
33801	Opustan 250mg Capsule (Opus Pharmaceuticals Ltd)	Mefenamic acid
33935	Nurofen Maximum Strength Migraine Pain 684mg caplets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen lysine
33994	Diclofenac sodium 25mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
34091	Diclofenac sodium 25mg gastro-resistant tablets (Sandoz Ltd)	Diclofenac sodium

34143	Naprosyn 375 Tablet (Roche Products Ltd)	Naproxen
34190	Indometacin 75mg modified-release capsules (A A H Pharmaceuticals Ltd)	Indometacin
34199	Indometacin 100mg suppositories (Actavis UK Ltd)	Indometacin
34212	Diclofenac 75mg Modified-release tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
34218	Diclofenac 25mg Gastro-resistant tablet (Pharmacia Ltd)	Diclofenac sodium
34271	Diclofenac sodium 100mg modified-release tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium
34289	Naproxen 250mg gastro-resistant tablets (Mylan Ltd)	Naproxen
34290	Naproxen 250mg gastro-resistant tablets (Teva UK Ltd)	Naproxen
34354	Ibuprofen 200mg tablets (Vantage)	Ibuprofen
34359	Ibuprofen 400mg tablets (Vantage)	Ibuprofen
34362	Diclofenac 25mg Gastro-resistant tablet (Genus Pharmaceuticals Ltd)	Diclofenac sodium
34425	Ibuprofen 400mg Tablet (Family Health)	Ibuprofen
34438	Mefenamic acid 250mg capsules (A A H Pharmaceuticals Ltd)	Mefenamic acid
34447	Ibuprofen 200mg tablets (Thornton & Ross Ltd)	Ibuprofen
34487	Diclofenac sodium 50mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
34527	Ibuprofen 200mg tablets (Zentiva)	Ibuprofen
34536	Ibuprofen 400mg tablets (IVAX Pharmaceuticals UK Ltd)	Ibuprofen
34550	Ibuprofen 400mg tablets film coated (Actavis UK Ltd)	Ibuprofen
34595	Mefenamic acid 500mg tablets (Zentiva)	Mefenamic acid
34610	Naproxen 500mg gastro-resistant tablets (Mylan Ltd)	Naproxen
34621	Ibuprofen 200mg Tablet (Nucare Plc)	Ibuprofen
34663	Ibuprofen 100mg/5ml Oral suspension (Neo Laboratories Ltd)	Ibuprofen
34670	Naproxen 250mg Gastro-resistant tablet (Galen Ltd)	Naproxen
34725	Flurbiprofen 50mg Tablet (Bristol-Myers Squibb Pharmaceuticals Ltd)	Flurbiprofen
34729	Ibuprofen 400mg tablets (OBG Pharmaceuticals Ltd)	Ibuprofen
34738	Naproxen 250mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Naproxen
34743	Naproxen 500mg gastro-resistant tablets (A A H Pharmaceuticals Ltd)	Naproxen
34744	Diclofenac 100mg Modified-release capsule (Sandoz Ltd)	Diclofenac sodium
34757	Ibuprofen 400mg Tablet (Unichem)	Ibuprofen
34769	Naproxen 500mg tablets (A A H Pharmaceuticals Ltd)	Naproxen
34793	Mefenamic acid 250mg capsules (Zentiva)	Mefenamic acid
34850	Ibuprofen 600mg tablets (Teva UK Ltd)	Ibuprofen
34889	Ibuprofen 400mg Tablet (Celltech Pharma Europe Ltd)	Ibuprofen
34898	Mefenamic acid 250mg Capsule (Berk Pharmaceuticals Ltd)	Mefenamic acid
34910	Mefenamic acid 500mg Tablet (Berk Pharmaceuticals Ltd)	Mefenamic acid
34911	Ibuprofen 200mg Tablet (Celltech Pharma Europe Ltd)	Ibuprofen
34922	Naproxen 500mg Tablet (Berk Pharmaceuticals Ltd)	Naproxen
34923	Naproxen 250mg Tablet (Berk Pharmaceuticals Ltd)	Naproxen
34924	Mefenamic acid 250mg Capsule (Teva UK Ltd)	Mefenamic acid
34931	Ibuprofen 200mg Tablet (Regent Laboratories Ltd)	Ibuprofen
34961	Ibuprofen 600mg tablets (Sandoz Ltd)	Ibuprofen
34977	Naproxen 500mg Gastro-resistant tablet (Galen Ltd)	Naproxen
34980	Ibuprofen 200mg tablets sugar coated (Actavis UK Ltd)	Ibuprofen

35265	Nurofen for children 3 months to 9 years 100mg/5ml Oral suspension (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
35292	Nurofen 200mg liquid capsules (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
35653	Etopan XL 600mg tablets (Ranbaxy (UK) Ltd)	Etodolac
35711	Dicloflex 25mg gastro-resistant tablets (Teva UK Ltd)	Diclofenac sodium
35890	Nurofen 200mg caplets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
35893	Dicloflex Retard 100mg tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
35935	Meloxicam 7.5mg tablets (Somex Pharma)	Meloxicam
36030	Biatain-Ibu Soft-Hold dressing 15cm x 15cm square (Coloplast Ltd)	Ibuprofen
36260	Mendys 250mg Capsule (Kent Pharmaceuticals Ltd)	Mefenamic acid
36486	Econac XL 100mg tablets (AMCo)	Diclofenac sodium
36577	Indometacin 50mg Capsule (Meridian Healthcare (UK) Ltd)	Indometacin
36597	Hedex Ibuprofen 200mg tablets (Omega Pharma Ltd)	Ibuprofen
36606	Manorfen 400mg tablets (The Manor Drug Company (Nottingham) Ltd)	Ibuprofen
36650	Nurofen 200mg tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
36669	ROFECOXIB	Rofecoxib
36787	Nurofen Express 684mg caplets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen lysine
37002	Nurofen Express 200mg liquid capsules (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
37053	Migrafen 200mg tablets (Chatfield Laboratories)	Ibuprofen
37094	Cuprofen 200mg tablets (SSL International Plc)	Ibuprofen
37235	Ibuprofen 100mg/5ml / Pseudoephedrine 15mg/5ml oral suspension sugar free	Ibuprofen/pseudoephedrine Hydrochloride
37253	Anadin ultra double strength 400mg Capsule (Wyeth Consumer Healthcare)	Ibuprofen
37502	Ibuprofen 10mg/2ml solution for infusion ampoules	Ibuprofen
37553	Ibucalm 400mg tablets (Aspar Pharmaceuticals Ltd)	Ibuprofen
37562	Arcoxia 30mg tablets (Grunenthal Ltd)	Etoricoxib
37587	Etoricoxib 30mg tablets	Etoricoxib
37648	Nurofen Express 400mg liquid capsules (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
37731	Nurofen Express 342mg caplets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen lysine
37750	Piroxicam 20mg capsules (Mylan Ltd)	Piroxicam
37763	Diclofenac 75mg/2ml solution for injection vials	Diclofenac sodium
37816	Cuprofen PLUS tablets (SSL International Plc)	Ibuprofen/Codeine phosphate
38332	Ibucalm 200mg tablets (Aspar Pharmaceuticals Ltd)	Ibuprofen
38493	Anadin Joint Pain 200mg tablets (Pfizer Consumer Healthcare Ltd)	Ibuprofen
38511	Feminax Ultra 250mg gastro-resistant tablets (Bayer Plc)	Naproxen
38770	Lodine SR 600mg tablets (Almirall Ltd)	Etodolac
38817	Diclofenac potassium 12.5mg tablets	Diclofenac potassium
38881	Diclomax SR 75mg capsules (Galen Ltd)	Diclofenac sodium
38944	Froben SR 200mg capsules (Abbott Laboratories Ltd)	Flurbiprofen
38948	Diclomax Retard 100mg capsules (Galen Ltd)	Diclofenac sodium
38992	Flamrase 75mg SR tablets (Teva UK Ltd)	Diclofenac sodium
39019	Brufen Retard 800mg tablets (Mylan Ltd)	Ibuprofen
39085	Naproxen 250mg tablets (A A H Pharmaceuticals Ltd)	Naproxen

39109	Feldene Melt 20mg tablets (Pfizer Ltd)	Piroxicam
39264	Dicloflex Retard 100mg tablets (Dexcel-Pharma Ltd)	Diclofenac sodium
39317	Naproxen 500mg tablets (Wockhardt UK Ltd)	Naproxen
39354	Galpharm ibuprofen for children 100mg/5ml Oral suspension (Galpharm International Ltd)	Ibuprofen
39461	Solpadeine Migraine Ibuprofen & Codeine tablets (Omega Pharma Ltd)	Ibuprofen/Codeine phosphate
39502	Ibuprofen sodium dihydrate 200mg tablets	Ibuprofen sodium dihydrate
39693	Naproxen 200mg/5ml oral suspension	Naproxen
39722	Voltarol Pain-eze 12.5mg tablets (Novartis Consumer Health UK Ltd)	Diclofenac potassium
39758	Nurofen Express 256mg caplets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen sodium dihydrate
39823	Dicloflex 50mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
39873	Cuprofen Maximum Strength 400mg tablets (SSL International Plc)	Ibuprofen
40083	Ibuprofen 200mg caplets (Galpharm International Ltd)	Ibuprofen
40086	Acoflam 50mg gastro-resistant tablets (Mercury Pharma Group Ltd)	Diclofenac sodium
40141	Ketoprofen 100mg capsules (A A H Pharmaceuticals Ltd)	Ketoprofen
40185	Oruvail 200 modified-release capsules (Sanofi)	Ketoprofen
40215	Oruvail 100 modified-release capsules (Sanofi)	Ketoprofen
40253	Ibuprofen 600mg Tablet (Sovereign Medical Ltd)	Ibuprofen
40336	Orudis 50mg capsules (Sanofi)	Ketoprofen
40394	Advil 400mg Tablet (Wyeth Consumer Healthcare)	Ibuprofen
40401	Naproxen 250mg gastro-resistant tablets (IVAX Pharmaceuticals UK Ltd)	Naproxen
40484	Orudis 100mg capsules (Sanofi)	Ketoprofen
40516	Anadin Ultra 200mg capsules (Pfizer Consumer Healthcare Ltd)	Ibuprofen
40664	Oruvail 150 modified-release capsules (Sanofi)	Ketoprofen
40756	Dicloflex 25mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Diclofenac sodium
41364	Ketoprofen 100mg / Omeprazole 20mg modified-release capsules	Ketoprofen/omeprazole
41365	Axorid 200mg/20mg modified-release capsules (Meda Pharmaceuticals Ltd)	Ketoprofen/Omeprazole
41366	Axorid 100mg/20mg modified-release capsules (Meda Pharmaceuticals Ltd)	Ketoprofen/omeprazole
41367	Ketoprofen 200mg / Omeprazole 20mg modified-release capsules	Ketoprofen/Omeprazole
41450	Orudis 100mg suppositories (Sanofi)	Ketoprofen
41513	Ibuprofen 200mg tablets (IVAX Pharmaceuticals UK Ltd)	Ibuprofen
41521	Indometacin 25mg Capsule (Approved Prescription Services Ltd)	Indometacin
41524	Mefenamic acid 500mg tablets (Teva UK Ltd)	Mefenamic acid
41615	Indometacin 50mg Capsule (Approved Prescription Services Ltd)	Indometacin
41621	Piroxicam 20mg capsules (A A H Pharmaceuticals Ltd)	Piroxicam
41622	Piroxicam 10mg capsules (A A H Pharmaceuticals Ltd)	Piroxicam
41623	Piroxicam 20mg capsules (IVAX Pharmaceuticals UK Ltd)	Piroxicam
41624	Piroxicam 10mg capsules (IVAX Pharmaceuticals UK Ltd)	Piroxicam
41677	Mefenamic acid 250mg Capsule (IVAX Pharmaceuticals UK Ltd)	Mefenamic acid
41701	Ibuprofen 600mg tablets (Actavis UK Ltd)	Ibuprofen

41817	Indometacin sr 75mg Modified-release capsule (C P Pharmaceuticals Ltd)	Indometacin
41823	Indometacin sr 75mg Modified-release capsule (Generics (UK) Ltd)	Indometacin
42003	Indometacin sr 75mg Capsule (Lagap)	Indometacin
42108	Ibuprofen 200mg tablets (OBG Pharmaceuticals Ltd)	Ibuprofen
42397	Nurofen Express 256mg tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen sodium dihydrate
42406	Diclofenac 50mg Gastro-resistant tablet (Almus Pharmaceuticals Ltd)	Diclofenac sodium
42455	Dicloflex Retard 100mg tablets (Teva UK Ltd)	Diclofenac sodium
42500	Ketoprofen sr 100mg Capsule (Approved Prescription Services Ltd)	Ketoprofen
42604	Mobiflex 20mg tablets (Meda Pharmaceuticals Ltd)	Tenoxicam
42793	Diclofenac 100mg Modified-release tablet (IVAX Pharmaceuticals UK Ltd)	Diclofenac sodium
42821	Nabumetone 500mg tablets (A A H Pharmaceuticals Ltd)	Nabumetone
42905	Diclofenac 75mg Modified-release tablet (Actavis UK Ltd)	Diclofenac sodium
43032	Inoven 200mg Tablet (Janssen-Cilag Ltd)	Ibuprofen
43045	Diclofenac potassium 50mg tablets (Actavis UK Ltd)	Diclofenac potassium
43456	Anadin LiquiFast 400mg capsules (Pfizer Consumer Healthcare Ltd)	Ibuprofen
43541	Piroxicam 10mg capsules (Actavis UK Ltd)	Piroxicam
43616	Celecoxib 400mg capsules	Celecoxib
43904	Feminax Express 342mg tablets (Bayer Plc)	Ibuprofen lysine
43911	Ibuprofen 600mg Tablet (C P Pharmaceuticals Ltd)	Ibuprofen
44112	Voltarol Joint Pain 12.5mg tablets (Novartis Consumer Health UK Ltd)	Diclofenac potassium
44233	Nurofen for children baby 100mg/5ml Oral suspension (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
44313	Indoflex 25mg Capsule (Unimed Pharmaceuticals Ltd)	Indometacin
44483	Nurofen Express 512mg tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen sodium dihydrate
44703	Piroxicam 10mg Capsule (Berk Pharmaceuticals Ltd)	Piroxicam
45213	Diclofenac 10mg dispersible tablets	Diclofenac sodium
45216	Ibuprofen 400mg Tablet (C P Pharmaceuticals Ltd)	Ibuprofen
45256	Indometacin 25mg Capsule (Meridian Healthcare (UK) Ltd)	Indometacin
45262	Naproxen Oral solution	Naproxen
45320	Ibuprofen 200mg tablets (Sandoz Ltd)	Ibuprofen
45331	Ibuprofen 200mg Tablet (Co-Pharma Ltd)	Ibuprofen
45814	First Resort Double Action Pain Relief 12.5mg tablets (Actavis UK Ltd)	Diclofenac potassium
45842	Ibuprofen 600mg Tablet (Celltech Pharma Europe Ltd)	Ibuprofen
46141	Nurofen Tension Headache 342mg caplets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen lysine
46342	Medifen 3with months 100mg/5ml Oral suspension (SSL International Plc)	Ibuprofen
46440	Naproxen 500mg Tablet (M & A Pharmachem Ltd)	Naproxen
46844	Dicloflex 75mg SR tablets (Actavis UK Ltd)	Diclofenac sodium
46848	Naproxen 500mg Gastro-resistant tablet (Almus Pharmaceuticals Ltd)	Naproxen
46860	Anadin LiquiFast 200mg effervescent tablets (Pfizer Consumer Healthcare Ltd)	Ibuprofen
46919	Ketoprofen sr 200mg Capsule (Approved Prescription Services Ltd)	Ketoprofen
46920	Ketoprofen 200mg Modified-release capsule (Generics (UK) Ltd)	Ketoprofen

46921	Ibuprofen 400mg tablets (Ranbaxy (UK) Ltd)	Ibuprofen
46940	Ketoprofen 100mg capsules (Mylan Ltd)	Ketoprofen
46942	Ibuprofen 600mg tablets (IVAX Pharmaceuticals UK Ltd)	Ibuprofen
46967	Mefenamic acid 250mg Capsule (Sandoz Ltd)	Mefenamic acid
46968	Mefenamic acid 250mg capsules (Mylan Ltd)	Mefenamic acid
47501	Rhumalgan SR 75mg capsules (Almus Pharmaceuticals Ltd)	Diclofenac sodium
47816	Tenoxicam 20mg Tablet (Sovereign Medical Ltd)	Tenoxicam
47820	Voltarol Pain-eze Extra Strength 25mg tablets (Novartis Consumer Health UK Ltd)	Diclofenac potassium
47994	Naproxen 250mg Gastro-resistant tablet (Almus Pharmaceuticals Ltd)	Naproxen
48059	Diclofenac potassium 50mg tablets (A A H Pharmaceuticals Ltd)	Diclofenac potassium
48062	Ibuprofen 200mg Tablet (Wockhardt UK Ltd)	Ibuprofen
48084	Ibuprofen 200mg/5ml oral suspension	Ibuprofen
48138	Ibuprofen 200mg tablets (Aspar Pharmaceuticals Ltd)	Ibuprofen
48161	Naproxen 500mg Tablet (Almus Pharmaceuticals Ltd)	Naproxen
48218	Dicloflex sr 100mg Tablet (Teva UK Ltd)	Diclofenac sodium
48326	Ibuprofen 100mg/5ml oral suspension sugar free	Ibuprofen
48546	Ibuprofen 400mg caplets (Bristol Laboratories Ltd)	Ibuprofen
48562	Ibuprofen 100mg/5ml oral suspension 5ml sachets sugar free	Ibuprofen
48568	Boots Rapid Ibuprofen lysine 342mg tablets (The Boots Company Plc)	Ibuprofen lysine
48644	Ibuprofen 400mg caplets (Lloyds Pharmacy Ltd)	Ibuprofen
48738	Nurofen for Children 100mg/5ml oral suspension orange (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
48810	Dysman 250 capsules (Ashbourne Pharmaceuticals Ltd)	Mefenamic acid
48871	Diclofenac potassium 25mg tablets (Actavis UK Ltd)	Diclofenac potassium
49059	Voltarol 50mg dispersible tablets (Lexon (UK) Ltd)	Diclofenac sodium
49133	Nurofen for Children 100mg/5ml oral suspension strawberry (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
49266	Ibuprofen for Children 100mg/5ml oral suspension (Galpharm International Ltd)	Ibuprofen
49277	Ibuprofen 200mg caplets (Bristol Laboratories Ltd)	Ibuprofen
49432	Calprofen 100mg/5ml oral suspension (McNeil Products Ltd)	Ibuprofen
50058	Voltarol 50mg dispersible tablets (DE Pharmaceuticals)	Diclofenac sodium
50059	Celebrex 100mg capsules (Necessity Supplies Ltd)	Celecoxib
50080	Dynastat 40mg powder and solvent for solution for injection vials (Pfizer Ltd)	Parecoxib sodium
50117	Brufen 100mg/5ml syrup (Lexon (UK) Ltd)	Ibuprofen
50266	Ibuprofen 200mg caplets (The Boots Company Plc)	Ibuprofen
50269	Arthrotec 75 gastro-resistant tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium/Misoprostol
50314	Brufen 600mg effervescent granules sachets (DE Pharmaceuticals)	Ibuprofen
50317	Voltarol 75mg SR tablets (Lexon (UK) Ltd)	Diclofenac sodium
50363	Nurofen for Children Singles 100mg/5ml oral suspension 5ml sachets strawberry (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
50602	Diclofenac potassium 50mg tablets (Alliance Healthcare (Distribution) Ltd)	Diclofenac potassium
50628	Ibuprofen 400mg caplets (The Boots Company Plc)	Ibuprofen
50652	Junior Ibuprofen 100mg/5ml oral suspension (Numark Ltd)	Ibuprofen

50785	Diclofenac sodium 50mg gastro-resistant tablets (Genesis Pharmaceuticals Ltd)	Diclofenac sodium
51099	Voltarol Rapid 50mg tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac potassium
51242	Naproxen 500mg tablets (Pfizer Ltd)	Naproxen
51284	Arcoxia 60mg tablets (Sigma Pharmaceuticals Plc)	Etoricoxib
51293	Diclofenac potassium 50mg tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac potassium
51306	Parecoxib 40mg powder for solution for injection vials	Parecoxib sodium
51339	Indometacin 25mg capsules (Genesis Pharmaceuticals Ltd)	Indometacin
51343	Voltarol Rapid 25mg tablets (DE Pharmaceuticals)	Diclofenac potassium
51360	Naproxen 250mg tablets (Accord Healthcare Ltd)	Naproxen
51614	Ibuprofen 200mg caplets (Lloyds Pharmacy Ltd)	Ibuprofen
51769	Nurofen for Children Singles 100mg/5ml oral suspension 5ml sachets orange (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
51808	Diclofenac 12.5mg/5ml oral solution	Diclofenac sodium
51827	Mefenamic acid 500mg tablets (Sigma Pharmaceuticals Plc)	Mefenamic acid
51828	Ibuprofen 100mg/5ml oral suspension sugar free (Kent Pharmaceuticals Ltd)	Ibuprofen
51829	Naproxen 250mg tablets (Kent Pharmaceuticals Ltd)	Naproxen
51874	Arcoxia 30mg tablets (Lexon (UK) Ltd)	Etoricoxib
51943	Orbifen For Children 100mg/5ml oral suspension (Orbis Consumer Products Ltd)	Ibuprofen
52009	Ibuprofen 200mg capsules (Galpharm International Ltd)	Ibuprofen
52141	Mobilan 25mg Capsule (Galen Ltd)	Indometacin
52154	Ibuprofen 200mg tablets (Galpharm International Ltd)	Ibuprofen
52338	Diclofenac potassium 50mg tablets (Focus Pharmaceuticals Ltd)	Diclofenac potassium
52389	Voltarol 50mg suppositories (Sigma Pharmaceuticals Plc)	Diclofenac sodium
52420	Celebrex 100mg capsules (Mawdsley-Brooks & Company Ltd)	Celecoxib
52617	Ibuprofen 100mg/5ml oral suspension sugar free (Sigma Pharmaceuticals Plc)	Ibuprofen
52714	Etodolac 600mg modified-release tablets (Alliance Healthcare (Distribution) Ltd)	Etodolac
52931	Naproxen 500mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Naproxen
53145	Vioxx 12.5mg tablets (Dowelhurst Ltd)	Rofecoxib
53164	Diclofenac sodium 25mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Diclofenac sodium
53331	Ibuprofen 100mg/5ml oral suspension sugar free (Alliance Healthcare (Distribution) Ltd)	Ibuprofen
53345	Voltarol Rapid 50mg tablets (Lexon (UK) Ltd)	Diclofenac potassium
53384	Voltarol 50mg dispersible tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium
53397	Brufen 100mg/5ml syrup (Mawdsley-Brooks & Company Ltd)	Ibuprofen
53576	Arcoxia 120mg tablets (DE Pharmaceuticals)	Etoricoxib
53604	Ibuprofen 200mg capsules (Numark Ltd)	Ibuprofen
53617	Ibuprofen and codeine 200mg+12.8mg Tablet (Almus Pharmaceuticals Ltd)	Ibuprofen/Codeine phosphate
53626	Naproxen 500mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)	Naproxen
53700	Naproxen 250mg gastro-resistant tablets (Alliance Healthcare (Distribution) Ltd)	Naproxen

53803	Ibuprofen 200mg capsules (Kent Pharmaceuticals Ltd)	Ibuprofen
53980	Naproxen 250mg tablets (Phoenix Healthcare Distribution Ltd)	Naproxen
54021	Voltarol Retard 100mg tablets (Sigma Pharmaceuticals Plc)	Diclofenac sodium
54075	Voltarol 50mg dispersible tablets (Stephar (U.K.) Ltd)	Diclofenac sodium
54137	Ibuprofen 400mg tablets (Aspar Pharmaceuticals Ltd)	Ibuprofen
54304	Naproxen 500mg tablets (Actavis UK Ltd)	Naproxen
54463	Diclofenac 50mg Tablet (Approved Prescription Services Ltd)	Diclofenac sodium
54476	Naproxen 500mg gastro-resistant tablets (Genesis Pharmaceuticals Ltd)	Naproxen
54514	Ibuprofen lysine 400mg oral powder sachets	Ibuprofen lysine
54518	Diclofenac sodium 50mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
54660	Diclofenac sodium 50mg capsules	Diclofenac Sodium
54760	Parecoxib 40mg powder and solvent for solution for injection vials	Parecoxib sodium
54783	Naproxen 250mg tablets (Teva UK Ltd)	Naproxen
54906	Diclofenac 50mg/5ml oral suspension	Diclofenac sodium
55009	Brufen 600mg effervescent granules sachets (Necessity Supplies Ltd)	Ibuprofen
55099	Acoflam 100mg Retard tablets (Mercury Pharma Group Ltd)	Diclofenac sodium
55153	Nurofen Express Soluble 400mg oral powder sachets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen lysine
55233	Ibuprofen 400mg Tablet (Nucare Plc)	Ibuprofen
55313	Ibuprofen 400mg tablets (Boston Healthcare Ltd)	Ibuprofen
55434	Ibuprofen 400mg tablets (Bristol Laboratories Ltd)	Ibuprofen
55454	Naproxen 500mg tablets (Kent Pharmaceuticals Ltd)	Naproxen
55486	Naproxen 500mg tablets (Teva UK Ltd)	Naproxen
55505	Naproxen 250mg gastro-resistant tablets (Kent Pharmaceuticals Ltd)	Naproxen
55582	Celebrex 200mg capsules (Lexon (UK) Ltd)	Celecoxib
55894	Naproxen 500mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	Naproxen
55913	Voltarol 50mg suppositories (Lexon (UK) Ltd)	Diclofenac sodium
56039	Ibuprofen 600mg tablets (Waymade Healthcare Plc)	Ibuprofen
56078	Rhumalgan XL 100mg capsules (Almus Pharmaceuticals Ltd)	Diclofenac sodium
56106	Naproxen 500mg/5ml oral suspension	Naproxen
56213	Ibuprofen 400mg tablets sugar coated (Kent Pharmaceuticals Ltd)	Ibuprofen
56275	Meloxicam 7.5mg tablets (Teva UK Ltd)	Meloxicam
56441	Calprofen 100mg/5ml oral suspension 5ml sachets (McNeil Products Ltd)	Ibuprofen
56554	Naproxen 250mg/5ml oral suspension	Naproxen
56584	Arcoxia 60mg tablets (Lexon (UK) Ltd)	Etoricoxib
56762	Naproxen 100mg/5ml oral suspension	Naproxen
56898	Rhumalgan SR 75mg capsules (Actavis UK Ltd)	Diclofenac sodium
56925	Naproxen 250mg tablets (Actavis UK Ltd)	Naproxen
57006	Diclofenac sodium 25mg gastro-resistant tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
57007	Mefenamic acid 250mg capsules (Essential Generics Ltd)	Mefenamic acid
57045	Voltarol 50mg dispersible tablets (Waymade Healthcare Plc)	Diclofenac sodium
57112	Ibuprofen 400mg tablets (Alliance Healthcare (Distribution) Ltd)	Ibuprofen

57162	Diclofenac 50mg dispersible tablets sugar free (DE Pharmaceuticals)	Diclofenac sodium
57297	Mefenamic acid 500mg tablets (Alliance Healthcare (Distribution) Ltd)	Mefenamic acid
57370	Meloxicam 15mg orodispersible tablets sugar free	Meloxicam
57475	Meloxicam 7.5mg orodispersible tablets sugar free	Meloxicam
57943	Valket 200 Retard capsules (Tillomed Laboratories Ltd)	Ketoprofen
58048	Diclofenac sodium 50mg gastro-resistant tablets (Waymade Healthcare Plc)	Diclofenac sodium
58071	Voltarol Rapid 50mg tablets (Waymade Healthcare Plc)	Diclofenac potassium
58213	Naproxen 500mg tablets (Aurobindo Pharma Ltd)	Naproxen
58221	Naproxen 250mg gastro-resistant tablets (Actavis UK Ltd)	Naproxen
58415	Diclofenac sodium 50mg gastro-resistant / Misoprostol 200microgram tablets (A A H Pharmaceuticals Ltd)	Diclofenac sodium/Misoprostol
58523	Indometacin 50mg capsules (Almus Pharmaceuticals Ltd)	Indometacin
58572	Diclofenac potassium 25mg tablets (A A H Pharmaceuticals Ltd)	Diclofenac potassium
58644	Dynastat 40mg powder for solution for injection vials (Pfizer Ltd)	Parecoxib sodium
58652	Ibuprofen 600mg tablets (Sigma Pharmaceuticals Plc)	Ibuprofen
58708	Naproxen 500mg gastro-resistant tablets (Ranbaxy (UK) Ltd)	Naproxen
58842	Misofen 75mg/200microgram gastro-resistant tablets (Morningside Healthcare Ltd)	Diclofenac sodium/Misoprostol
59067	Ibuprofen 200mg capsules (AM Distributions (Yorkshire) Ltd)	Ibuprofen
59139	Ketorolac 30mg/1ml solution for injection ampoules (A A H Pharmaceuticals Ltd)	Ketorolac trometamol
59203	Brufen 100mg/5ml syrup (Sigma Pharmaceuticals Plc)	Ibuprofen
59246	Naproxen 500mg tablets (Accord Healthcare Ltd)	Naproxen
59289	Diclofenac sodium 100mg modified-release tablets (AM Distributions (Yorkshire) Ltd)	Diclofenac sodium
59502	Nurofen for Children Cold, Pain and Fever Strawberry Flavour 100mg/5ml oral suspension (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
59553	Ibuprofen 200mg tablets (Alliance Healthcare (Distribution) Ltd)	Ibuprofen
59562	Ibuprofen 600mg tablets (Boston Healthcare Ltd)	Ibuprofen
59595	Diclofenac 50mg dispersible tablets sugar free (Sigma Pharmaceuticals Plc)	Diclofenac sodium
59878	Naproxen 250mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Naproxen
59880	Diclofenac sodium 75mg modified-release capsules (Waymade Healthcare Plc)	Diclofenac sodium
60035	Ibuprofen 200mg tablets film coated (Actavis UK Ltd)	Ibuprofen
60115	Naproxen 250mg tablets (Alliance Healthcare (Distribution) Ltd)	Naproxen
60368	Diclofenac 10mg/5ml oral solution	Diclofenac sodium
60408	Naproxen 500mg gastro-resistant tablets (Waymade Healthcare Plc)	Naproxen
60443	Diclofenac sodium 75mg modified-release capsules (DE Pharmaceuticals)	Diclofenac sodium
60510	Nurofen for Children Cold, Pain and Fever Orange Flavour 100mg/5ml oral suspension (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
60666	Diclofenac sodium 75mg modified-release capsules (Actavis UK Ltd)	Diclofenac sodium
60705	Meloxicam 15mg tablets (Niche Generics Ltd)	Meloxicam
60772	Indometacin 25mg/5ml oral solution	Indometacin
60786	Voltarol 50mg dispersible tablets (Sigma Pharmaceuticals Plc)	Diclofenac sodium
60916	Indometacin 75mg modified-release capsules (Kent Pharmaceuticals Ltd)	Indometacin

60930	Indometacin 25mg capsules (Alliance Healthcare (Distribution) Ltd)	Indometacin
61235	Meloxicam 7.5mg tablets (Sigma Pharmaceuticals Plc)	Meloxicam
61469	Fenbufen 300mg capsules (A A H Pharmaceuticals Ltd)	Fenbufen
61581	Mefenamic acid 500mg tablets (Essential Generics Ltd)	Mefenamic acid
61596	Diclofenac sodium 75mg modified-release capsules (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
61695	Naproxen 500mg tablets (Alliance Healthcare (Distribution) Ltd)	Naproxen
61762	Diclofenac 10mg/5ml oral suspension	Diclofenac sodium
61878	Nurofen Express Period Pain 200mg capsules (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen
61953	Ibuprofen 200mg caplets (Wockhardt UK Ltd)	Ibuprofen
62238	Ibuprofen 200mg capsules (Colorama Pharmaceuticals Ltd)	Ibuprofen
62251	Arcoxia 90mg tablets (Sigma Pharmaceuticals Plc)	Etoricoxib
62636	Diclofenac sodium 25mg gastro-resistant tablets (Sterwin Medicines)	Diclofenac sodium
62643	Indometacin 50mg Capsule (Carter Wallace Ltd)	Indometacin
62658	Arcoxia 120mg tablets (Waymade Healthcare Plc)	Etoricoxib
62840	Celebrex 100mg capsules (DE Pharmaceuticals)	Celecoxib
62843	Arcoxia 90mg tablets (Lexon (UK) Ltd)	Etoricoxib
62892	Ibuprofen 200mg tablets (Wockhardt UK Ltd)	Ibuprofen
63036	Ibuprofen 400mg capsules (AM Distributions (Yorkshire) Ltd)	Ibuprofen
63079	Ibuprofen 400mg tablets (Waymade Healthcare Plc)	Ibuprofen
63357	Naproxen 250mg tablets (Almus Pharmaceuticals Ltd)	Naproxen
63843	Naproxen 250mg tablets (Aurobindo Pharma Ltd)	Naproxen
64103	Mefenamic acid 500mg tablets (Almus Pharmaceuticals Ltd)	Mefenamic acid
64245	Celecoxib 200mg capsules (A A H Pharmaceuticals Ltd)	Celecoxib
64297	Nabumetone 500mg tablets (Mylan Ltd)	Nabumetone
64303	Diclofenac sodium 25mg gastro-resistant tablets (DE Pharmaceuticals)	Diclofenac sodium
64521	Arcoxia 90mg tablets (Mawdsley-Brooks & Company Ltd)	Etoricoxib
64759	Diclofenac 50mg/5ml oral solution	Diclofenac sodium
64935	Celecoxib 200mg capsules (Sigma Pharmaceuticals Plc)	Celecoxib
65016	Celecoxib 200mg capsules (Alliance Healthcare (Distribution) Ltd)	Celecoxib
65025	Ibuprofen 400mg tablets (Crescent Pharma Ltd)	Ibuprofen
65121	Fenpaed 100mg/5ml oral suspension (Pinewood Healthcare)	Ibuprofen
65348	Naproxen 250mg gastro-resistant tablets (Genesis Pharmaceuticals Ltd)	Naproxen
65471	Ibuprofen 200mg tablets (Almus Pharmaceuticals Ltd)	Ibuprofen
65514	Ibuprofen 200mg tablets (Boston Healthcare Ltd)	Ibuprofen
65591	Ibuprofen 200mg tablets (Crescent Pharma Ltd)	Ibuprofen
65783	Diclofenac potassium 50mg tablets (DE Pharmaceuticals)	Diclofenac potassium
65877	Diclofenac sodium 75mg modified-release tablets (Mawdsley-Brooks & Company Ltd)	Diclofenac sodium
65952	Naproxen 500mg gastro-resistant tablets (Almus Pharmaceuticals Ltd)	Naproxen
66123	Diclofenac sodium 100mg modified-release tablets (Ethigen Ltd)	Diclofenac sodium
66194	Care Ibuprofen for Children 100mg/5ml oral suspension (Thornton & Ross Ltd)	Ibuprofen
66323	Ebretin 300mg capsules (Ranbaxy (UK) Ltd)	Etodolac

66364	Meloxicam 15mg tablets (Actavis UK Ltd)	Meloxicam
66452	Mefenamic acid 500mg tablets (Waymade Healthcare Plc)	Mefenamic acid
66486	Arcoxia 90mg tablets (DE Pharmaceuticals)	Etoricoxib
66544	Ibuprofen 400mg tablets (DE Pharmaceuticals)	Ibuprofen
66567	Ibuprofen sodium dihydrate 400mg tablets	Ibuprofen sodium dihydrate
66571	Celecoxib 200mg capsules (Actavis UK Ltd)	Celecoxib
66577	Diclofenac sodium 75mg modified-release capsules (Sigma Pharmaceuticals Plc)	Diclofenac sodium
66648	Ibuprofen 400mg tablets (Almus Pharmaceuticals Ltd)	Ibuprofen
66757	Celebrex 200mg capsules (Waymade Healthcare Plc)	Celecoxib
67220	Diclofenac sodium 100mg modified-release tablets (Phoenix Healthcare Distribution Ltd)	Diclofenac sodium
67363	Naproxen 250mg gastro-resistant tablets (Sigma Pharmaceuticals Plc)	Naproxen
67594	Ibuprofen 400mg tablets (Kent Pharmaceuticals Ltd)	Ibuprofen
67608	Piroxicam 20mg dispersible tablets (A A H Pharmaceuticals Ltd)	Piroxicam
67740	Ibuprofen 600mg tablets (Fannin UK Ltd)	Ibuprofen
67756	Indometacin 25mg capsules (Almus Pharmaceuticals Ltd)	Indometacin
67768	Naproxen 250mg tablets (Mylan Ltd)	Naproxen
67786	Vioxx 25mg tablets (Dowelhurst Ltd)	Rofecoxib
67803	Oruvail 200 modified-release capsules (Lexon (UK) Ltd)	Ketoprofen
67815	Feldene Melt 20mg tablets (Waymade Healthcare Plc)	Piroxicam
68018	Ibuprofen 200mg tablets (Mawdsley-Brooks & Company Ltd)	Ibuprofen
68097	Naproxen 250mg tablets (Crescent Pharma Ltd)	Naproxen
68220	Ibuprofen 200mg capsules (Ennogen Healthcare Ltd)	Ibuprofen
68354	Diclofenac sodium 100mg modified-release capsules (Actavis UK Ltd)	Diclofenac sodium
68470	Naproxen 25mg/ml oral suspension sugar free (Orion Pharma (UK) Ltd)	Naproxen
68582	Ibuprofen 200mg tablets (DE Pharmaceuticals)	Ibuprofen
68685	Naproxen 250mg tablets (Waymade Healthcare Plc)	Naproxen
68708	Indometacin 75mg modified-release capsules (DE Pharmaceuticals)	Indometacin
68932	Meloxicam 15mg tablets (Somex Pharma)	Meloxicam
69018	Nurofen Joint & Back Pain Relief 256mg tablets (Reckitt Benckiser Healthcare (UK) Ltd)	Ibuprofen sodium dihydrate
69477	Voltarol Rapid 50mg tablets (DE Pharmaceuticals)	Diclofenac potassium
69582	Voltarol 100mg suppositories (Lexon (UK) Ltd)	Diclofenac sodium
69584	Diclofenac sodium 100mg modified-release tablets (Sigma Pharmaceuticals Plc)	Diclofenac sodium
69645	Naproxen 50mg/ml oral suspension (Thornton & Ross Ltd)	Naproxen
69828	Naproxen 50mg/ml oral suspension (Alliance Healthcare (Distribution) Ltd)	Naproxen

Appendix 5.5: OPCS code list used to define PCI and coronary angiography during the index ACS hospitalisation stay

PCI

OPCS code	Description
K49	Transluminal balloon angioplasty of coronary artery
K49.1	Percutaneous transluminal balloon angioplasty of one coronary artery
K49.2	Percutaneous transluminal balloon angioplasty of multiple coronary arteries
K49.3	Percutaneous transluminal balloon angioplasty of bypass graft of coronary artery
K49.4	Percutaneous transluminal cutting balloon angioplasty of coronary artery
K49.8	Other specified transluminal balloon angioplasty of coronary artery
K49.9	Unspecified transluminal balloon angioplasty of coronary artery
K50	Other therapeutic transluminal operations on coronary artery
K50.1	Percutaneous transluminal laser coronary angioplasty
K50.4	Percutaneous transluminal atherectomy of coronary artery
K50.8	Other specified other therapeutic transluminal operations on coronary artery
K50.9	Unspecified other therapeutic transluminal operations on coronary artery
K75	Percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
K75.1	Percutaneous transluminal balloon angioplasty and insertion of 1-2 drug-eluting stents into coronary artery
K75.2	Percutaneous transluminal balloon angioplasty and insertion of 3 or more drug-eluting stents into coronary artery
K75.3	Percutaneous transluminal balloon angioplasty and insertion of 1-2 stents into coronary artery
K75.4	Percutaneous transluminal balloon angioplasty and insertion of 3 or more stents into coronary artery NEC
K75.8	Other specified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery
K75.9	Unspecified percutaneous transluminal balloon angioplasty and insertion of stent into coronary artery

Coronary angiography

OPCS code	Description
K63.1	Angiocardiography of combination of right and left side of heart
K63.2	Angiocardiography of right side of heart NEC
K63.3	Angiocardiography of left side of heart NEC
K63.4	Coronary arteriography using two catheters
K63.5	Coronary arteriography using single catheter
K63.6	Coronary arteriography NEC
K65.1	Catheterisation of combination of right and left side of heart NEC
K65.2	Catheterisation of right side of heart NEC
K65.3	Catheterisation of left side of heart NEC
K65.8	Catheterisation of left side of heart via atrial transeptal puncture
K65.8	Other specified catheterisation of heart
K65.9	Unspecified catheterisation of heart

Chapter 6.0 appendices

Appendix 6.1: ICD-10 code list used to identify ACS patients within the HES database

ICD 10 Codes	Description
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22	Subsequent myocardial infarction
I22.0	Subsequent myocardial infarction of anterior wall
I22.1	Subsequent myocardial infarction of inferior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I23	Certain current complications following acute myocardial infarction
I23.0	Haemopericardium as current complication following acute myocardial infarction
I23.1	Atrial septal defect as current complication following acute myocardial infarction
I23.2	Ventricular septal defect as current complication following acute myocardial infarction
I23.3	Rupture of cardiac wall without haemopericardium as current complication following acute myocardial
I23.4	Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5	Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6	Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute my
I23.8	Other current complications following acute myocardial infarction

Figure 6.1: Detailed description of the steps involved in identifying the study population

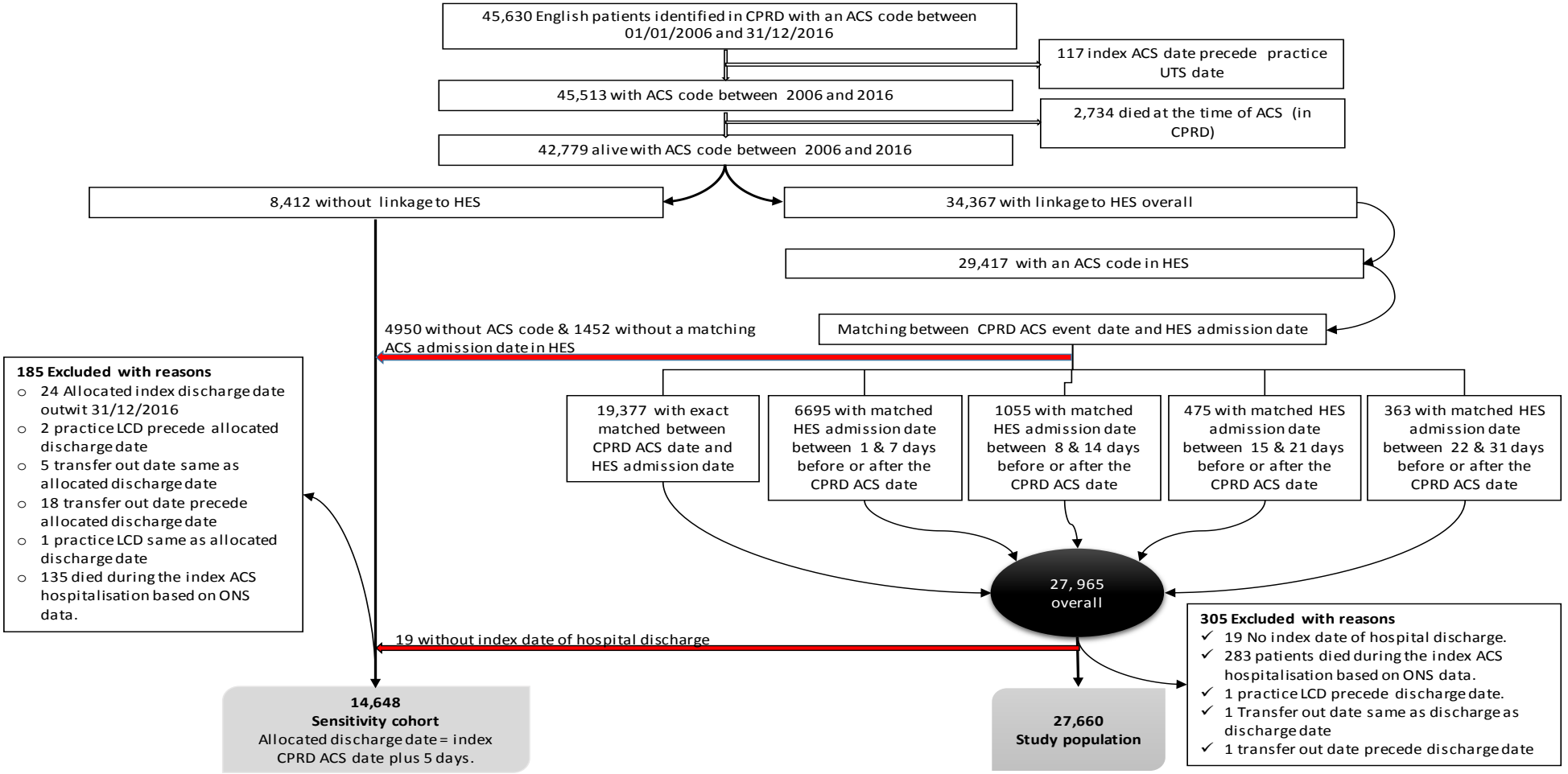

Table 6.1: A detailed description of the combinations of the discharge antithrombotic drugs of the study population

Antithrombotic Drug Combinations	Frequency	Percent (%)
Aspirin only	3867	14.0
Clopidogrel only	2792	10.1
Prasugrel only	109	0.4
Ticagrelor only	186	0.7
Warfarin only	644	2.3
Apixaban only	12	0.0
Dabigatran only	5	0.0
Rivaroxaban only	27	0.1
Aspirin + Clopidogrel	14260	51.6
Aspirin + Prasugrel	730	2.6
Aspirin + Ticagrelor	1480	5.4
Aspirin + Warfarin	340	1.2
Aspirin + Apixaban	5	0.0
Aspirin + Dabigatran	1	0.0
Aspirin + Rivaroxaban	14	0.1
Clopidogrel + Warfarin	239	0.9
Clopidogrel + Apixaban	12	0.0
Clopidogrel + Dabigatran	6	0.0
Clopidogrel + Rivaroxaban	21	0.1
Prasugrel + Warfarin	1	0.0
Ticagrelor + Warfarin	10	0.0
Ticagrelor + Dabigatran	1	0.0
Ticagrelor + Rivaroxaban	2	0.0
Aspirin + Clopidogrel + Warfarin	181	0.7
Aspirin + Clopidogrel + Apixaban	4	0.0
Aspirin + Clopidogrel + Dabigatran	2	0.0
Aspirin + Clopidogrel + Rivaroxaban	14	0.1
Aspirin + Prasugrel + Warfarin	6	0.0
Aspirin + Ticagrelor + Warfarin	8	0.0
Aspirin + Ticagrelor + Apixaban	2	0.0
Aspirin + Ticagrelor + Dabigatran	1	0.0
Aspirin + Ticagrelor + Rivaroxaban	1	0.0
No record	2677	9.7
Total	**27660**	**100.0**

Chapter 7.0 appendices

Table 7.1: Baseline characteristics of patients that experienced bleeding events in the first 12 months following hospital discharge for ACS stratified by age and gender

Demographic characteristics	Bleeding Post-Discharge				
	≤ 65 years (n = 1079)	**66 - 80 years** (n = 1433)	**> 80 years** (n = 1108)	**Males** (n = 2126)	**Females** (n = 1494)
Age (year) (Mean ± SD)				67.2 ± 13.2	74.9 ± 13.0
Age (n, %)					
≤ 65				740 (34.8)	339 (22.7)
66 - 80				871 (41.0)	562 (37.6)
> 80				515 (24.2)	593 (39.7)
Gender (n, %)					
Male	740 (68.6)	871 (60.8)	515 (46.5)		
Female	339 (31.4)	562 (39.2)	593 (53.5)		
BMI (kg/m^2) (n, %)					
Underweight (BMI < 18.50)	8 (1.0)	22 (2.1)	32 (3.9)	15 (1.0)	47 (4.3)
Normal weight (BMI 18.50 to < 25)	208 (27.2)	317 (29.8)	303 (37.3)	447 (28.8)	381 (35.0)
Overweight (BMI 25 to < 30)	275 (35.9)	427 (40.2)	329 (40.5)	669 (43.1)	362 (33.2)
Obese (BMI ≥ 30)	275 (35.9)	297 (27.9)	148 (18.2)	421 (27.1)	299 (27.5)
Smoking Status (n, %)					
Non-smoker	220 (24.6)	405 (32.4)	407 (45.5)	497 (27.1)	535 (44.5)
Ex-smoker	244 (27.3)	616 (49.3)	409 (45.7)	868 (47.3)	401 (33.4)
Current smoker	429 (48.0)	228 (18.3)	78 (8.7)	470 (25.6)	265 (22.1)
Comorbidities					
Diabetes (n, %)	188 (17.4)	386 (26.9)	240 (21.7)	499 (23.5)	315 (21.1)
Hypertension (n, %)	208 (19.3)	472 (32.9)	395 (35.6)	564 (26.5)	511 (34.2)
Heart failure (n, %)	56 (5.2)	136 (9.5)	145 (13.1)	197 (9.3)	140 (9.4)
Cancer (n, %)	97 (9.0)	207 (14.4)	127 (11.5)	289 (13.6)	142 (9.5)
PVD (n, %)	34 (3.2)	77 (5.4)	63 (5.7)	109 (5.1)	65 (4.4)
Gastroduodenal ulcer (n, %)	***	16 (1.1)	11 (1.0)	18 (0.8)	12 (0.8)
COPD (n, %)	206 (19.1)	424 (29.6)	314 (28.3)	536 (25.2)	408 (27.3)
Atrial fibrillation (n, %)	23 (2.1)	114 (8.0)	147 (13.3)	156 (7.3)	128 (8.6)
Hyperlipidaemia (n, %)	663 (61.4)	1064 (74.2)	772 (69.7)	1459 (68.6)	1040 (69.6)
History of bleeding (n, %)	173 (16.0)	304 (21.2)	282 (25.5)	444 (20.9)	315 (21.1)
CKD (eGFR < 60 mL/min/1.73 m^2 (n, %))	106 (9.8)	504 (35.2)	704 (63.5)	663 (31.2)	651 (43.6)
ACS presentation (n, %)					
STEMI	164 (15.2)	177 (12.4)	98 (8.8)	271 (12.7)	168 (11.2)
NSTEMI	329 (30.5)	561 (39.1)	562 (50.7)	812 (38.2)	640 (42.8)
Not otherwise specified	586 (54.3)	695 (48.5)	448 (40.4)	1043 (49.1)	686 (45.9)
Haemoglobin (g/L (Mean ± SD))	145 ± 16.9	135 ± 18.0	126 ± 17.3	140 ± 18.9	128 ± 16.3

Continuation	Bleeding Post-Discharge				
	≤ 65 years (n = 1079)	**66 - 80 years** (n = 1433)	**> 80 years** (n = 1108)	**Males** (n = 2126)	**Females** (n = 1494)
Diastolic (mm Hg (Mean ± SD))	81.6 ± 11.8	76.1 ± 11.1	73.3 ± 11.8	77.6 ± 12.0	76.2 ± 12.0
Systolic (mm Hg (Mean ± SD))	136 ± 19.1	137 ± 19.0	138 ± 20.5	136 ± 18.7	139 ± 20.6
White cell count ($x10^9$/L (Median ± IQR))	7.7 (6.3, 9.5)	7.4 (6.2, 8.9)	7.3 (6.0, 8.8)	7.5 (6.2, 9.0)	7.4 (6.1, 9.1)
In-hospital procedures					
Coronary angiography (only) (n, %)	173 (16.0)	281 (19.6)	113 (10.2)	343 (16.1)	224 (15.0)
PCI (n, %)	532 (49.3)	486 (33.9)	183 (16.5)	793 (37.3)	408 (27.3)
Drug Therapy (n, %)					
Baseline NSAIDs	195 (18.1)	211 (14.7)	94 (8.5)	297 (14.0)	203 (13.6)
Baseline SSRIs	114 (10.6)	125 (8.7)	81 (7.3)	135 (6.3)	185 (12.4)
Discharge antithrombotic					
Single antiplatelet	197 (18.3)	370 (25.8)	341 (30.8)	503 (23.7)	405 (27.1)
Dual antiplatelet	788 (73.0)	810 (56.5)	553 (49.9)	1290 (60.7)	861 (57.6)
Oral anticoagulant	40 (3.7)	145 (10.1)	91 (8.2)	168 (7.9)	108 (7.2)
No record	54 (5.0)	108 (7.5)	123 (11.1)	165 (7.8)	120 (8.0)

**** frequency count is < 5, **SD:** standard deviation, **n:** number of patients in each category, **ACS:** acute coronary syndrome, **STEMI:** ST-elevation myocardial infarction, **NSTEMI:** Non ST-elevation myocardial infarction, **IQR:** interquartile range, **MI:** myocardial infarction, **PVD:** peripheral vascular disease, **COPD:** chronic obstructive pulmonary disease, **CKD:** chronic kidney disease, **eGFR:** estimated glomerular filtration rate, **NSAID:** non-steroidal anti-inflammatory drugs, **SSRI:** selective serotonin re-uptake inhibitors, **PCI:** percutaneous coronary intervention, **BMI:** body mass index.*

Table 7.2: Baseline characteristics of patients that experienced bleeding events in the first 12 months following hospital discharge for ACS stratified by in-hospital management strategy, and discharge antithrombotic therapy

Demographic characteristics	Bleeding Post-Discharge					
	Medically managed (n = 2381)	**PCI** (n = 1201)	**SAPT** (n = 908)	**DAPT** (n = 2151)	**Oral anticoagulant** (n = 276)	**No record** (n = 285)
Age (Mean ± SD)	73.0 ± 13.5	64.5 ± 12.3	72.6 ± 13.3	67.7 ± 13.5	74.6 ± 11.1	73.8 ± 13.9
Age (n, %)						
≤ 65	534 (22.4)	532 (44.3)	197 (21.7)	788 (36.6)	40 (14.5)	54 (18.9)
66 - 80	924 (38.8)	486 (40.5)	370 (40.7)	810 (37.7)	145 (52.5)	108 (37.9)
> 80	923 (38.8)	183 (15.2)	341 (37.6)	553 (25.7)	91 (33.0)	123 (43.2)
Gender (n, %)						
Male	1310 (55.0)	793 (66.0)	503 (55.4)	1290 (60.0)	168 (60.9)	165 (57.9)
Female	1071 (45.0)	408 (34.0)	405 (44.6)	861 (40.0)	108 (39.1)	120 (42.1)
BMI (kg/m^2) (n, %)						
Underweight (BMI < 18.50)	53 (3.0)	8 (1.0)	24 (3.5)	33 (2.1)	***	5 (2.4)
Normal weight (BMI 18.5 to < 25)	571 (32.0)	254 (30.6)	208 (30.7)	489 (31.6)	62 (29.8)	69 (32.9)
Overweight (BMI 25 to < 30)	682 (38.2)	335 (40.4)	268 (39.6)	601 (38.9)	73 (35.1)	89 (42.4)
Obese (BMI ≥ 30)	478 (26.8)	232 (28.0)	177 (26.1)	423 (27.4)	73 (35.1)	47 (22.4)
Smoking Status (n, %)						
Non-smoker	735 (36.7)	287 (28.6)	272 (36.1)	596 (33.0)	80 (33.5)	84 (35.3)
Ex-smoker	866 (43.2)	390 (38.9)	316 (41.9)	724 (40.1)	125 (52.3)	104 (43.7)
Current smoker	404 (20.1)	325 (32.4)	166 (22.0)	485 (26.9)	34 (14.2)	50 (21.0)
Comorbidities						
Diabetes (n, %)	575 (24.1)	232 (19.3)	214 (23.6)	438 (20.4)	82 (29.7)	80 (28.1)
Hypertension (n, %)	748 (31.4)	312 (26.0)	287 (31.6)	603 (28.0)	95 (34.4)	90 (31.6)
Heart failure (n, %)	270 (11.3)	67 (5.6)	89 (9.8)	161 (7.5)	50 (18.1)	37 (13.0)
Cancer (n, %)	260 (10.9)	166 (13.8)	128 (14.1)	241 (11.2)	26 (9.4)	36 (12.6)
PVD (n, %)	122 (5.1)	51 (4.2)	58 (6.4)	70 (3.3)	20 (7.2)	26 (9.1)
Gastroduodenal ulcer (n, %)	28 (1.2)	***	10 (1.1)	9 (0.4)	***	8 (2.8)
COPD (n, %)	670 (28.1)	268 (22.3)	239 (26.3)	524 (24.4)	93 (33.7)	88 (30.9)
Atrial fibrillation (n, %)	231 (9.7)	51 (4.2)	79 (8.7)	96 (4.5)	82 (29.7)	27 (9.5)
Hyperlipidaemia (n, %)	1688 (70.9)	783 (65.2)	659 (72.6)	1432 (66.6)	202 (73.2)	206 (72.3)
History of bleeding (n, %)	559 (23.5)	194 (16.2)	219 (24.1)	380 (17.7)	72 (26.1)	88 (30.9)
CKD (eGFR < 60 mL/min/1.73 m^2 (n, %))	1033 (43.4)	272 (22.6)	398 (43.8)	652 (30.3)	135 (48.9)	129 (45.3)

Continuation	Bleeding Post-Discharge					
	Medically managed (n = 2381)	**PCI** (n = 1201)	**SAPT** (n = 908)	**DAPT** (n = 2151)	**Oral anticoagulant** (n = 276)	**No record** (n = 285)
ACS presentation (n, %)						
STEMI	147 (6.2)	287 (23.9)	85 (9.4)	311 (14.5)	28 (10.1)	15 (5.3)
NSTEMI	1107 (46.5)	333 (27.7)	391 (43.1)	811 (37.7)	127 (46.0)	123 (43.2)
Not otherwise specified	1127 (47.3)	581 (48.4)	432 (47.6)	1029 (47.8)	121 (43.8)	147 (51.6)
Haemoglobin (g/L (Mean ± SD))	132 ± 19.1	141 ± 16.9	132 ± 19.6	138 ± 17.7	134 ± 18.1	130 ± 21.4
Diastolic (mm Hg (Mean ± SD))	76.1 ± 12.2	79.0 ± 11.3	76.3 ± 11.8	77.8 ± 11.9	75.7 ± 11.3	75.9 ± 12.9
Systolic (mm Hg (Mean ± SD))	137 ± 20.0	137 ± 18.3	137 ± 19.8	137 ± 19.2	135 ± 19.5	136 ± 20.4
White cell count ($x10^9$/L (Median ± IQR))	7.4 (6.1, 9.0)	7.5 (6.3, 9.1)	7.4 (6.1, 9.0)	7.4 (6.2, 9.1)	7.4 (6.2, 9.0)	7.5 (6.2, 9.2)
In-hospital procedures						
Coronary angiography (only) (n, %)			154 (17.0)	305 (14.2)	73 (26.4)	35 (12.3)
PCI (n, %)			193 (21.3)	908 (42.2)	59 (21.4)	41 (14.4)
Drug Therapy (n, %)						
Baseline NSAIDs	295 (12.4)	202 (16.8)	118 (13.0)	322 (15.0)	27 (9.8)	33 (11.6)
Baseline SSRIs	236 (9.9)	80 (6.7)	78 (8.6)	190 (8.8)	25 (9.1)	27 (9.5)
Discharge antithrombotic						
Single antiplatelet	691 (29.0)	193 (16.1)				
Dual antiplatelet	1236 (51.9)	908 (75.6)				
Oral anticoagulant	213 (8.9)	59 (4.9)				
No record	241 (10.1)	41 (3.4)				

*** *frequency count is < 5,* ***SD:*** *standard deviation,* ***n:*** *number of patients in each category,* ***ACS:*** *acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***IQR:*** *interquartile range,* ***MI:*** *myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***eGFR:*** *estimated glomerular filtration rate,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***SAPT:*** *single antiplatelet,* ***DAPT:*** *dual antiplatelet.*

Chapter 8.0 appendices

Appendix 8.1: Published paper from the risk factors for bleeding study

ORIGINAL RESEARCH

American Heart Association.

Bleeding After Hospital Discharge Following Acute Coronary Syndrome: Incidence, Types, Timing, and Predictors

Nafiu Ismail, MPH; Kelvin P. Jordan, PhD; Umesh T. Kadam, PhD; John J. Edwards, PhD; Tim Kinnaird, MD; Mamas A. Mamas, PhD

Background—The incidence and predictors of bleeding after acute coronary syndrome are unclear within the real-world setting. Our objective was to determine the incidence, types, timing, and predictors of bleeding complications following hospital discharge after acute coronary syndrome.

Methods and Results—We used the Clinical Practice Research Datalink, with linkage to Hospital Episode Statistics, to determine the incidence, timing, and types of bleeding events within 12 months after hospital discharge for acute coronary syndrome. We assessed independent associations between postdischarge bleeding and baseline patient characteristics using a competing risk regression model, accounting for death as a competing event. Among 27 660 patients surviving to hospital discharge, 3620 (13%) experienced bleeding complications at a median time of 123 days (interquartile range, 45–223 days) after discharge. The incidence of bleeding was 162/1000 person-years (95% CI, 157–167/1000 person-years) within the first 12 months after hospital discharge. Bruising (949 bleeds [26%]) was the most common type of first bleeding event, followed by gastrointestinal bleed (705 bleeds [20%]), whereas intracranial bleed was relatively rare (81 bleeds [2%]). Significant predictors of postdischarge bleeding included history of bleeding complication, oral anticoagulant prescription, history of peripheral vascular disease, chronic obstructive pulmonary disease, and advanced age (>80 years). Predictors for postdischarge bleeding varied, depending on the anatomic site of the bleeding event.

Conclusions—Bleeding complications after hospital discharge for acute coronary syndrome are common. Patients who experience these bleeding events have distinct baseline characteristics, which vary by anatomic site of the bleed. These characteristics can inform risk-benefit considerations in deciding on favorable combination and duration of secondary antithrombotic therapy. **(*J Am Heart Assoc.* 2019;8:e013679. DOI: 10.1161/JAHA.119.013679.)**

Key Words: hemorrhage • incidence • postdischarge • real world • risk factors • sites

The management of acute coronary syndrome (ACS) with antithrombotic medications achieves the desired goal of reducing the risk of future ischemic events. But these reductions are accompanied by bleeding complications.[1]

In clinical trials, the incidence of major bleeding complications is reported to be between 1% and 10%, depending on the bleeding definition used,[2–4] with observational studies reporting incidences of between 2.8%[5] and 11%.[6] However, the emphasis in most of these studies has been on major in-hospital or 30-day bleeding events (a composite of in-hospital and postdischarge events), with little consideration for events in the longer term after hospital discharge. After hospital discharge, patients with ACS often remain on dual antiplatelet therapy for up to a year, and aspirin indefinitely, so their risk of bleeding complications persists in the longer term.[7]

Major in-hospital bleeding has been associated with sociodemographic characteristics, cardiovascular and noncardiovascular comorbidities, and pharmacological and procedural characteristics,[8–10] leading to the development of risk scoring algorithms that stratify patients into risk profiles for these bleeding events.[8–10] However, it is unclear whether these characteristics are also predictive of bleeding events after hospital discharge. For example, procedural characteristics may become less relevant in predicting the risk of postdischarge bleeding events, whereas patient

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Accompanying Data S1 and Tables S1 through S5 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.013679

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Clinical Perspective

What Is New?

- Bleeds after hospital discharge for acute coronary syndrome are common, with bruising and gastrointestinal bleeds the most common.
- History of bleeding complications, chronic obstructive pulmonary disease, peripheral vascular disease, management with oral anticoagulants after hospital discharge, and aged >80 years were the most significant determinants of postdischarge bleeding.
- Predictors for postdischarge bleeding varied, depending on the anatomic site of the bleeding event.

What Are the Clinical Implications?

- These baseline predictors can assist clinicians in identifying patients at risk of bleeding complications after hospital discharge so that longer-term antithrombotic therapy can be tailored to fit an individual patient's risk profile.

characteristics and pharmacological choice may become more important after discharge. The few studies that have reported on characteristics associated with postdischarge bleeding events have mostly been randomized controlled trials,[11–13] where minor bleeding events, high-risk multimorbid "real-world" patients, and those receiving long-term oral anticoagulation (a potential risk factor for bleeding) have been excluded. Therefore, the generalizability of these studies to the wider population with ACS in the real-world setting is unclear.

While the nature of in-hospital bleeds and their predictors have been well described,[8–10,14] the incidence, types, and predictors of bleeding events that occur after hospital discharge are unclear. The first objective of this study was to determine the incidence, timing, and types of bleeding events within 12 months after hospital discharge. The second objective was to determine the predictors of bleeding events and site-specific bleeds after hospital discharge.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Setting

This was a cohort study set within the Clinical Practice Research Datalink (CPRD),[15] with linkage to Hospital Episode Statistics (HES) and Office for National Statistics mortality data. CPRD is a primary care electronic healthcare record database containing anonymized routinely collected consultation records from >670 general practices in the United Kingdom. The CPRD population is representative of the UK population on age, sex, and ethnicity.[15] Practices included in our analysis (n=377, all from England) had to have linked HES and Office for National Statistics mortality data. Practices with and without such linkage are similar in respect of demographic data, years of follow-up, and prescribing.[16] The CPRD data set is described further in Data S1. HES is a secondary care database containing detailed information on diagnosis, procedures, admissions, and discharge dates from National Health Service hospitals or hospitals where the cost of care is reimbursed by the National Health Service. The National Health Service is the main healthcare provider in the United Kingdom that is free at the point of care. The Office for National Statistics mortality data contain records of date of death and the underlying cause of death of all deceased individuals in the United Kingdom. The validity of diagnoses for conditions such as ACS is high in both CPRD and HES.[17,18] The study was approved by the CPRD Independent Scientific Advisory Committee (protocol No. 17_181). The requirement for informed consent was waived because these databases are anonymized following strict confidentiality guidelines before being distributed for research purposes.

Study Population

Patients were included in the study if they were aged ≥18 years, with a primary care record for ACS in CPRD between 2006 and 2016 and a matching ACS record in HES within 1 month of the primary care ACS event, but without a primary care record of ACS in the preceding 2 years. The period of 2 years was selected to identify only incident ACS cases. The index date for each patient was the date of hospital discharge after the matched ACS event in HES. Read codes and *International Classification of Diseases, Tenth Revision* (*ICD-10*) code lists used in defining ACS in CPRD and HES are available at http://www.keele.ac.uk/mrr. Patients were excluded if they did not survive to discharge, they had no discharge date recorded in HES, or their first ACS event preceded the date their registered practice was deemed to have up to standard data in CPRD.

Predictors

We identified potential predictors of bleeding by reviewing previously published risk scores for in-hospital and postdischarge bleeding events,[8–14,19–21] as well as studies that had reported on characteristics associated with bleeding after ACS.[22–26] Nineteen potential predictors were selected for inclusion in the study on the basis of clinical judgement.

These predictors included sociodemographic characteristics, cardiovascular and noncardiovascular comorbidities (recorded in the previous 2 years before the index date, except body mass index, which was defined as last measurement until 30 days after index date to capture the most recent body mass index for a patient), in-hospital procedures, and pharmacological characteristics (recorded in the previous 6 months before the index date in the case of NSAIDs and selective serotonin reuptake inhibitors, or within 90 days after hospital discharge in the case of antithrombotic drugs). See Table S1 for the full list of potential predictors and their baseline definitions.

Bleeding End Point

The outcome of bleeding was defined as having a diagnostic record for bleeding in a patient primary care record or a death record in Office for National Statistics mortality data, with bleeding as the underlying cause within 12 months after the index date. Bleeding events included gastrointestinal bleeding, hematemesis, melena, gastrointestinal ulcers with bleeding, intracranial bleeding, hemoptysis, epistaxis, hemarthrosis, hemopericardium, hematuria, vaginal bleeding, retinal bleeding, anemia caused by blood loss, spontaneous bruising, petechiae, spontaneous ecchymoses, and bleeding not elsewhere classified. Bleeding events were further classified based on site into bruising; respiratory/ears, nose, and throat; gastrointestinal; genitourinary; intraocular; and intracranial. Read codes used to define and classify bleeding events are available at http://www.keele.ac.uk/mrr. Where the date of the bleeding event was the same as the index date, these bleeding events were regarded as in-hospital bleeds and, therefore, excluded.

Follow-Up

For all analyses, patients who were discharged alive were longitudinally followed up for a maximum of 12 months for records of bleeding consultations after hospital discharge for ACS. Follow-up started from the index date (date of hospital discharge) until earliest of first bleeding event or date patient ceased contributing to CPRD because of death or transfer out of practice or practice leaving CPRD or the end of 12 months from the index date of hospital discharge or the date of last data collection at the time of data request.

Statistical Analysis

All analyses were based on a first bleeding event for a patient after hospital discharge for ACS. Baseline sociodemographic characteristics, comorbidities, in-hospital procedures, and pharmacological characteristics were descriptively compared between those who did and those who did not experience bleeding events within the first 12 months after hospital discharge. Continuous variables are presented as mean and SD or median and interquartile range, and they were compared using Student t test or Mann-Whitney test, as appropriate. Categorical variables are presented as frequencies and percentages, and they were compared using χ^2 test.

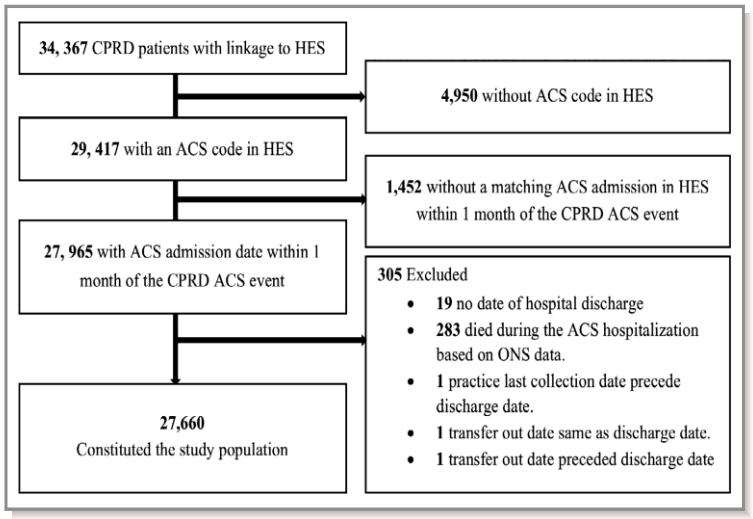

Figure 1. Flow diagram describing the steps involved in identifying the study population. ACS indicates acute coronary syndrome; CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; ONS, Office for National Statistics mortality data.

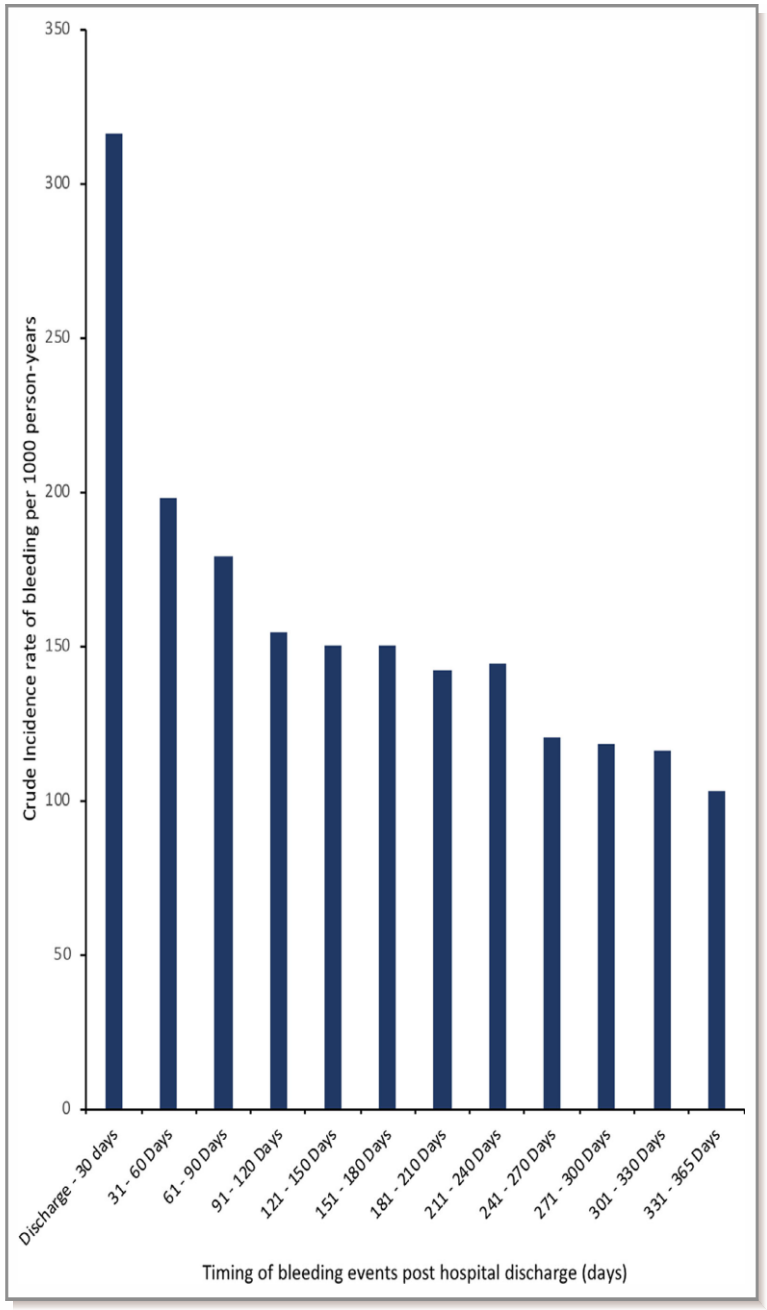

Figure 2. Crude incidence rates (per 1000 person-years) of bleeding within 12 months after hospital discharge by time from the date of hospital discharge.

Fine and Gray competing risk regression model[27] was used to determine univariable and multivariable associations between the outcomes of bleeding (and of each type of bleeding event) with potential predictors, accounting for death as a competing event, and reported using sub–hazard ratios (sHRs) with their corresponding 95% CIs. Death from a non-bleeding cause was selected as a competing event because of the older age of the cohort and will prevent a bleeding event occurring. All multivariable associations were adjusted for year of index hospital discharge, geographic region, and all

other potential predictors. Robust variance estimators were used to account for clustering within general practices. Fractional polynomials were used to determine the functional form of age, and a plot of age against rates of bleeding (per 1000 person-years) was then used to create cut points in categorizing age when the linear form was not appropriate. The proportional hazard assumption was examined by inclusion of time-by-covariate interactions in the final models.

To address missing data in smoking status and body mass index, multiple imputation (10 imputations) was performed.[28] To assess the impact of missing data, a sensitivity analysis was performed (for the outcome of all bleeds) in which only patients with complete data on all variables were included (complete case analysis). Results of the complete case analysis were compared with those from the imputed data analysis. Only results of analyses on the imputed data sets are presented here. Results of the complete case analysis are reported in Data S1. As a subgroup analysis, the predictors for bleeding in patients managed with percutaneous coronary intervention (PCI) during the ACS hospitalization were determined. All comparisons were 2 tailed, and $P<0.05$ was considered statistically significant. All analyses were performed using Stata, version 14.2.

Results

Incidence, Timing, and Types of Postdischarge Bleeding Events

Figure 1 shows the number of patients included in the study, with exclusions. A total of 27 660 patients constituted the study population, of which 3620 (13%) experienced 5041 bleeding events over a median follow-up of 365 days (interquartile range, 246–365 days) after hospital discharge. Of the 3620 patients with bleeding events, 947 (26%) had multiple bleeding events within the first 12 months of hospital discharge. Of those with multiple bleeding events, 69% (n=654) had 2 bleeding events, 21% (n=197) had 3 bleeding events, and 10% (n=96) had ≥4 bleeding events after hospital discharge. The median time to a first bleeding event within the first 12 months was 123 days (interquartile range, 45–223 days). The incidence of bleeding was 162/1000 person-years (95% CI, 157–167/1000 person-years), and bleeding events occurred more frequently in the first 30 days after hospital discharge (Figure 2).

Table 1 shows the incidence, timing, and types of bleeding events (based on first bleed). Bruising was the most common (26% of all first bleeds), followed by gastrointestinal bleeds (20%). The incidence was highest for bruising (42/1000 person-years) and lowest for intracranial bleeding events (3/1000 person-years).

Baseline Characteristics

Table 2 summarizes the baseline characteristics of those who experienced bleeding complications and those who did not within the first 12 months after hospital discharge for ACS. Patients who experienced bleeding complications after hospital discharge were, on average, older (mean, 72 versus 70 years) and more commonly ex-smokers with higher prevalence of baseline hypertension, chronic obstructive pulmonary disease (COPD), anemia, hyperlipidemia, chronic kidney disease, history of bleeding complications (in 2 years before the index date), and a lower level of hemoglobin. Those who experienced bleeding events were also more commonly treated with oral anticoagulants after discharge. The baseline characteristics of the study population, stratified by site-specific bleeding events, are summarized in Table S2. Patients who experienced bruising were, on average, younger (age, 70 years) and more commonly women, whereas those who experienced intracranial bleeds were mostly older (age, 76 years) with a higher prevalence of chronic kidney disease.

Predictors of Bleeding Events

Age violated the linearity assumption of the competing risk model and was, therefore, categorized. Predictors that violated the proportional hazard assumption were included in the relevant models as time-dependent coefficients. The change in risk of bleeding for each predictor that interacted with time, and was significantly associated with bleeding, is reported in Table S3 at 2 time points (at 30 and at 365 days) after hospital discharge.

The crude and adjusted associations of each predictor with bleeding are presented in Table S4. Figure 3 presents the

Table 1. Incidence and Timing of Each (First) Bleeding Event Within 12 Months After Hospital Discharge

Site of Bleed	Bleeding Events, No. (% of All First Bleeds)	Incidence Rate (per 1000 Person-Years) (95% CI)	Timing of Bleed Within 12 Months, Median (IQR), d
All bleeds	3620 (100)	162 (157–167)	123 (45–223)
Bruising	949 (26)	42 (39–44)	126 (49–212)
Gastrointestinal	705 (20)	32 (30–35)	116 (41–230)
Other unclassified	700 (19)	32 (30–35)	118 (41–231)
Respiratory/ENT	582 (16)	27 (25–29)	128 (47–222)
Genitourinary	468 (13)	22 (20–24)	119 (41–226)
Intraocular	135 (4)	6 (5–7)	162 (52–239)
Intracranial	81 (2)	3 (3–4)	117 (42–222)

ENT indicates ears, nose, and throat; IQR, interquartile range.

Table 2. Baseline Characteristics of the Study Population by Bleeding Events Within 12 Months After Hospital Discharge

Demographic Characteristics	Bleeding After Discharge		
	Bleed (n=3620)	No Bleed (n=24 040)	*P* Value
Age, mean±SD, y	72.1±12.9	69.6±13.7	
Age, n (%)			
≤65	1079 (29.8)	9309 (38.7)	<0.001
66–80	1433 (39.6)	8614 (35.8)	
>80	1108 (30.6)	6117 (25.4)	
Sex, n (%)			
Men	2126 (58.7)	15 729 (65.4)	<0.001
Women	1494 (41.3)	8311 (34.6)	
BMI, n (%)			
Underweight (BMI <18.50 kg/m^2)	62 (2.3)	325 (1.9)	0.262
Normal weight (BMI 18.50–<25 kg/m^2)	828 (31.4)	5096 (30.2)	
Overweight (BMI 25–<30 kg/m^2)	1031 (39.0)	6798 (40.3)	
Obese (BMI ≥30 kg/m^2)	720 (27.3)	4647 (27.6)	
Smoking status, n (%)			
Nonsmoker	1032 (34.0)	6428 (33.1)	<0.001
Ex-smoker	1269 (41.8)	7432 (38.2)	
Current smoker	735 (24.2)	5576 (28.7)	
Comorbidities			
Diabetes mellitus, n (%)	814 (22.5)	5002 (20.8)	0.021
Hypertension, n (%)	1075 (29.7)	6028 (25.1)	<0.001
Heart failure, n (%)	337 (9.3)	2184 (9.1)	0.662
Cancer, n (%)	431 (11.9)	2526 (10.5)	0.011
PVD, n (%)	174 (4.8)	776 (3.2)	<0.001
Stroke/TIA, n (%)	249 (6.9)	1326 (5.5)	0.001
COPD, n (%)	944 (26.1)	4616 (19.2)	<0.001
Anemia, n (%)	1123 (31.0)	5535 (23.0)	<0.001
Atrial fibrillation, n (%)	284 (7.8)	1450 (6.0)	<0.001
Hyperlipidemia, n (%)	2499 (69.0)	15 309 (63.7)	<0.001
History of bleeding, n (%)	759 (21.0)	2563 (10.7)	<0.001
CKD (eGFR <60 mL/min per 1.73 m^2), n (%)	1314 (36.3)	7093 (29.5)	<0.001
ACS presentation, n (%)			
STEMI	439 (12.1)	3193 (13.3)	0.003
NSTEMI	1452 (40.1)	8963 (37.3)	
ACS not otherwise specified	1729 (47.8)	11 884 (49.4)	
Hemoglobin, mean±SD, g/L	132±19.8	136±18.7	<0.001
Diastolic blood pressure, mean±SD, mm Hg	76.2±12.1	77.2±12.0	<0.001
Systolic blood pressure, mean±SD, mm Hg	137±19.8	137±19.4	0.872
White cell count (×10^9/L), median (IQR)	7.4 (6.2–8.9)	7.4 (6.2–9.1)	0.305
In-hospital procedures, n (%)			
Coronary angiography (only)	567 (15.7)	3693 (15.4)	0.641

Continued

Table 2. Continued

Demographic Characteristics	Bleeding After Discharge		
	Bleed (n=3620)	No Bleed (n=24 040)	*P* Value
PCI	1201 (33.2)	8484 (35.3)	0.013
Drug therapy, n (%)			
Baseline NSAIDs	500 (13.8)	2983 (12.4)	0.018
Baseline SSRIs	320 (8.8)	1771 (7.4)	0.002
Discharge antithrombotic			
Single antiplatelet	908 (25.1)	6046 (25.1)	<0.001
Dual antiplatelet	2151 (59.4)	14 319 (59.6)	
Oral anticoagulant	276 (7.6)	1283 (5.3)	
No record	285 (7.9)	2392 (10.0)	

Number of patients with missing data: smoking (n=5188), BMI (n=8153), hemoglobin (n=8702), diastolic and systolic blood pressure (n=9592), white cell count (n=8914). ACS indicates acute coronary syndrome; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NSTEMI, non ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SSRI, selective serotonin reuptake inhibitor; STEMI, ST-segment–elevation myocardial infarction; TIA, transient ischemic attack.

independent predictors for bleeding within the first 12 months after hospital discharge. After multivariable adjustment, age >65 years, female sex, history of hypertension, peripheral vascular disease (PVD), COPD, not having a history of heart failure, history of bleeding complications, management with PCI during the ACS hospitalization stay, use of NSAIDs, and treatment with oral anticoagulants or single antiplatelet after hospital discharge were independently associated with 12-month postdischarge bleeding events. The most significant predictors of bleeding were baseline history of bleeding complications (sHR, 1.88; 95% CI, 1.73–2.04), management with oral anticoagulants versus single antiplatelet after hospital discharge (sHR, 1.35; 95% CI, 1.17–1.55), aged >80 years versus aged ≤65 years (sHR, 1.42; 95% CI, 1.22–1.66), COPD (sHR, 1.29; 95% CI, 1.20–1.39), and PVD (sHR, 1.28; 95% CI, 1.09–1.50). The increased risk of bleeding in those managed with PCI or those aged >80 years (compared with those aged ≤65 years) was highest immediately after hospital discharge, but then decreased with time (Table S3).

Results of the sensitivity analysis did not reveal any disparities in findings between the imputed data analysis and the complete case analysis (Table S5). In the subgroup analysis, advanced age (>80 versus age ≤65 years), female sex, history of cancer, PVD, COPD, bleeding complications, and use of NSAIDs were the main predictors of bleeding events within the first 12 months after hospital discharge in patients managed with PCI (Figure 4). Treatment with oral anticoagulant was also associated with an increased risk of bleeding in patients managed with PCI, but this association did not reach statistical significance.

Predictors of Site-Specific Bleeding Events

Characteristics independently associated with each site-specific bleeding event are reported in Table 3. After multivariable adjustment, history of bleeding complications (sHR, 2.22; 95% CI, 1.87–2.64), advanced age (>80 versus ≤65 years) (sHR, 1.29; 95% CI, 1.01–1.65), and COPD (sHR, 1.29; 95% CI, 1.08–1.55) were the independent predictors of gastrointestinal bleeding events. Treatment with single antiplatelet after hospital discharge was also associated with an increased risk of gastrointestinal bleed. History of diabetes mellitus (sHR, 1.77; 95% CI, 1.08–2.89) and bleeding complications (sHR, 1.91; 95% CI, 1.05–3.45) were the main predictors of intracranial bleeds after hospital discharge. Treatment with oral anticoagulants, use of NSAIDs, history of PVD, aged 66 to 80 years, and advanced age (>80 years) were also associated with increased risk of intracranial bleed, but these associations did not reach statistical significance. Risk factors independently associated with each site-specific bleeding event are reported in Table 3.

Discussion

This is the first electronic health record–based study to examine the incidence, timing, and types of postdischarge bleeding events and their predictors from a primary care perspective. Our study reports that bleeding complications after hospital discharge are common and occur in ≈1 in 10 patients within the first 12 months after hospital discharge, with bruising and gastrointestinal bleeds the most common. We report that the median time to a first bleeding event was

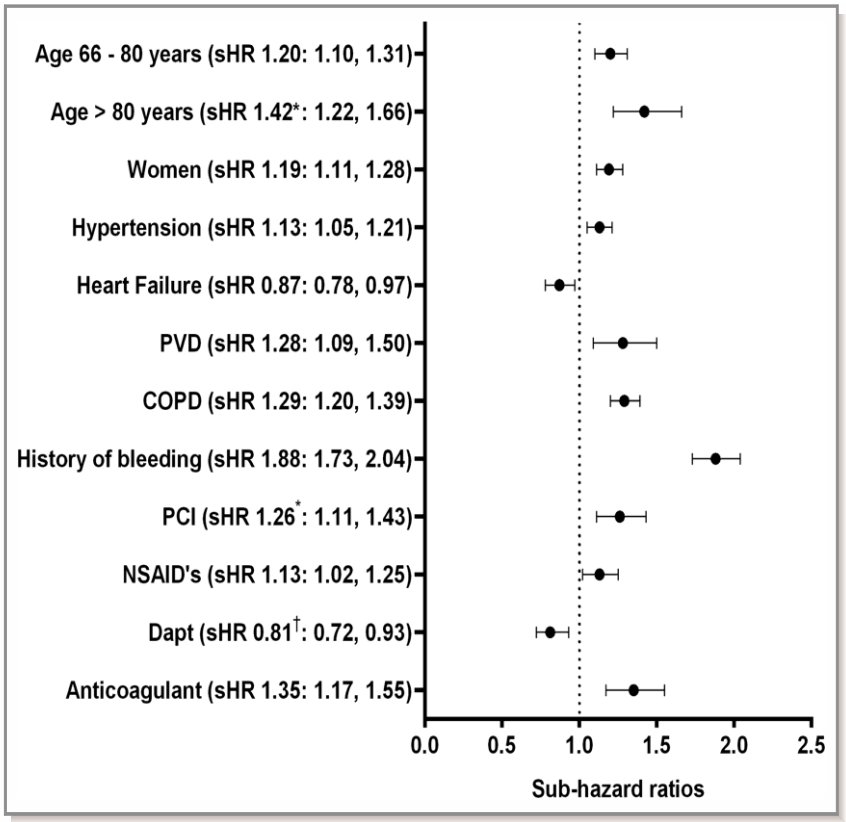

Figure 3. Characteristics associated with bleeding events within 12 months after hospital discharge for acute coronary syndrome. *Included as time-dependent coefficient: estimated sub–hazard ratio (sHR) at day of hospital discharge but decreases with time after discharge. †Included as time-dependent coefficient: estimated sHR at day of hospital discharge but increases with time after discharge. COPD indicates chronic obstructive pulmonary disease; Dapt, dual antiplatelet; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

123 days, with bleeding events more commonly occurring in the first 30 days after hospital discharge. Our analysis found that history of bleeding complications in 2 years before hospital discharge, management with oral anticoagulants after hospital discharge, COPD, PVD, and advanced age (>80 years) were the major predictors of bleeding complications in the first 12 months after hospital discharge. Predictors for postdischarge bleeding varied, depending on the anatomic site of the bleeding event. We report that characteristics, such as COPD, use of NSAIDs, and history of cancer, which have not been previously examined in a population with ACS, may carry greater risk for bleeding complications after hospital discharge.

The results of our study add granularity to the growing body of literature evaluating the risk of bleeding complications after hospital discharge. The finding that 13% of patients had experienced bleeding complications in the year after discharge was higher than those reported in the ADAPT-DES (Assessment of Dual Antiplatelet Therapy With Drug-Eluting Stents) study[29] and other previous studies in the postdischarge setting (range, 2.5%–7.9%).[30,31] This higher incidence likely reflects differences in the definition of bleeding used, as the emphasis in previous studies has been on major bleeding events. The higher incidence may also be because of the primary care population with elderly multimorbid patients, which were mostly excluded from randomized controlled trials. Our study did not capture bleeding events that are not actionable and did not cause patients to seek medical advice. This highlights that the actual incidence of postdischarge bleeding events may be higher than what we have reported. Our study and previous studies[25,26] have identified the first 30 days of hospital discharge as the period for greater vulnerability for these bleeding complications and highlight the time when resources can be better used to improve longer-term patient prognosis, such as by personalization of antithrombotic drugs at the time of hospital discharge. We

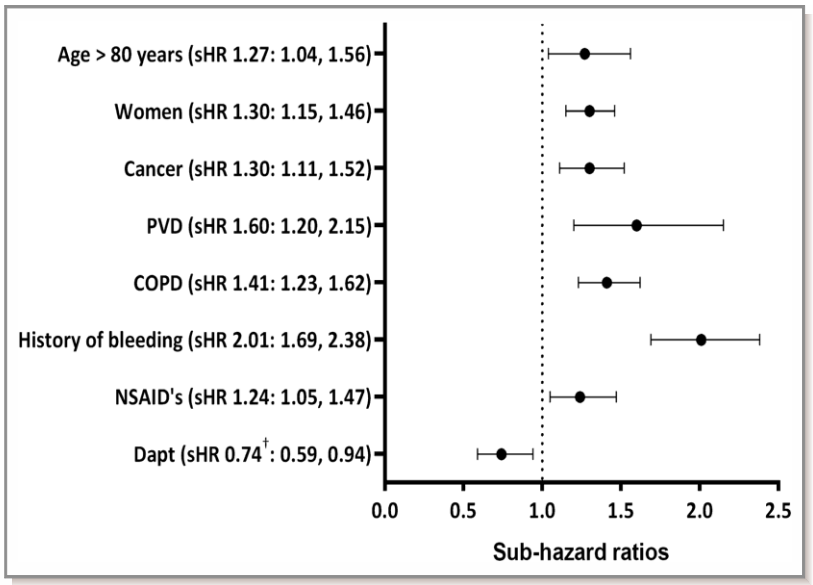

Figure 4. Characteristics associated with bleeding events within 12 months after hospital discharge for acute coronary syndrome in patients managed with percutaneous coronary intervention. †Included as time-dependent coefficient: estimated sub–hazard ratio (sHR) at day of hospital discharge but increases with time after discharge. COPD indicates chronic obstructive pulmonary disease; Dapt, dual antiplatelet; PVD, peripheral vascular disease.

report that bruising was the most common type of bleeding complication after hospital discharge. These types of bleeding events, which have mostly been neglected in previous studies, can be detrimental. Bruising may impact on patient quality of life, leading to discontinuation of antithrombotic therapy, which can have indirect adverse consequences.[32,33]

We found that the predictors (eg, age, hypertension, PVD, history of bleeding, management with PCI during ACS hospitalization, and use of oral anticoagulants)[8–10,14] for in-hospital bleeding have some overlap with those for postdischarge bleeding events. But characteristics, such as those related to ACS presentation, may carry less impact on risk of postdischarge bleeding. Although there was some overlap between the predictors for in-hospital and postdischarge bleeding events, the predictors for site-specific bleeds vary, depending on the anatomic site of the bleeding event.

A novel finding of this study in reviewing the predictors of site-specific bleeding complications was that, although characteristics such as advanced age (>80 years) and prior history of bleeding complications were predictive of all types of bleeding events (except bruising), some predictors were more associated with certain types of bleeds. We found that the female sex was only predictive of nuisance bruising, and not major bleeds (eg, gastrointestinal or intracranial bleeds), contrary to that reported by in-hospital studies.[8,9,14] This finding is consistent with most studies of bleeding in the postdischarge setting, which showed a lack of association between female sex and major bleeding events.[21,34]

Another novel finding from our analysis was that COPD is a strong predictor of bruising, respiratory, gastrointestinal, and genitourinary bleeding events. Most contemporary studies in the ACS setting have either not included COPD as a potential predictor or not recorded its diagnosis. Our finding on the effect of COPD on the occurrence of bleeding suggests that COPD should be taken into account when evaluating future risk of bleeding complications. COPD is characterized by local and systemic inflammation.[35] Patients with COPD are exposed to oxidative stress via chronic hypoxia and increased release of reactive oxygen species by leukocytes.[36] This damages gastric mucosa[37] and may predispose to peptic ulcer bleeds.[38] Patients with COPD are often treated with steroids to control lung inflammation. Steroids may delay peptic ulcer healing,[39] thus increasing the risk of perforation and bleeding complications.[40] The association of COPD with bleeding events should be explored further to confirm the result of our study.

Our study found cancer to be a strong predictor of respiratory bleeding events and a modest nonsignificant increased risk of gastrointestinal bleeds. Malignancy has been an exclusion criterion in previous studies, such as the CRUSADE (Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early

Table 3. Characteristics Independently Associated With Site-Specific Bleeding Events Within 12 Months After Hospital Discharge for ACS

Risk Factors	Bruising (n=949)*	Respiratory/ ENT Bleeds (n=582)*	Gastrointestinal Bleeds (n=705)*	Genitourinary Bleeds (n=468)*	Intraocular Bleeds (n=135)*	Intracranial Bleeds (n=81)*
Demographics						
Age, y						
≤65	1.00	1.00	1.00	1.00	1.00	1.00
66–80	0.98 (0.84–1.14)	1.27 (1.01–1.60)†	1.05 (0.86–1.29)	1.37 (1.05–1.79)†	2.02 (1.26–3.25)†	1.81 (0.86–3.83)
>80	0.81 (0.65–1.03)	1.60 (1.21–2.12)†	1.29 (1.01–1.65)†	1.65 (1.21–2.24)†	1.49 (0.81–2.75)	2.31 (0.92–5.79)
Women	2.11 (1.85–2.41)†	0.94 (0.79–1.12)	0.97 (0.82–1.13)	0.84 (0.67–1.06)	0.78 (0.55–1.11)	1.13 (0.74–1.73)
BMI, kg/m^2						
Normal weight (18.50–<25)	1.00	1.00	1.00	1.00	1.00	1.00
Underweight (<18.50)	1.16 (0.73–1.87)	2.02 (0.89–4.58)‡	0.94 (0.49–1.79)	0.73 (0.26–2.04)	0.93 (0.23–3.70)	1.14 (0.34–3.80)
Overweight (25–<30)	1.10 (0.93–1.31)	0.93 (0.75–1.16)	1.23 (0.84–1.81)‡	0.95 (0.74–1.22)	0.74 (0.45–1.21)	0.59 (0.34–1.02)
Obese (≥30)	0.99 (0.81–1.21)	0.91 (0.71–1.17)	1.03 (0.82–1.31)	1.12 (0.82–1.51)	0.81 (0.49–1.33)	0.42 (0.20–0.88)†
Smoking status						
Nonsmoker	1.00	1.00	1.00	1.00	1.00	1.00
Ex-smoker	0.97 (0.80–1.17)	1.13 (0.90–1.43)	0.95 (0.77–1.17)	1.10 (0.88–1.38)	1.07 (0.71–1.61)	1.15 (0.69–1.92)
Current smoker	0.87 (0.71–1.07)	0.96 (0.74–1.24)	0.99 (0.79–1.25)	0.97 (0.72–1.30)	0.94 (0.52–1.68)	0.79 (0.37–1.68)
Comorbidities						
Diabetes mellitus	0.73 (0.61–0.88)†	0.91 (0.73–1.13)	0.92 (0.77–1.10)	0.96 (0.76–1.19)	1.10 (0.73–1.65)	1.77 (1.08–2.89)†
Hypertension	1.02 (0.88–1.18)	1.43 (1.20–1.72)†	1.11 (0.94–1.31)	0.98 (0.79–1.22)	1.43 (1.02–2.02)†	1.01 (0.62–1.66)
Heart failure	0.75 (0.59–0.96)†	1.09 (0.82–1.43)	0.87 (0.67–1.13)	0.80 (0.57–1.11)	1.10 (0.42–2.91)‡	0.36 (0.13–0.97)†
Cancer	0.97 (0.79–1.19)	1.86 (1.26–2.74)†,‡	1.17 (0.94–1.46)	1.10 (0.84–1.45)	0.77 (0.43–1.37)	0.78 (0.38–1.63)
PVD	1.20 (0.82–1.76)	1.30 (0.90–1.87)	1.06 (0.72–1.54)	1.33 (0.85–2.08)	1.03 (0.46–2.30)	1.31 (0.49–3.55)
COPD	1.21 (1.04–1.40)†	1.66 (1.36–2.01)†	1.29 (1.08–1.55)†	1.26 (1.01–1.58)†	1.02 (0.64–1.63)	1.11 (0.64–1.93)
CKD (eGFR <60 mL/ min per 1.73 m^2)	1.10 (0.93–1.31)	0.81 (0.66–1.00)	1.12 (0.95–1.33)	0.93 (0.73–1.18)	1.71 (1.11–2.65)†	1.06 (0.61–1.84)
Hyperlipidemia	1.09 (0.93–1.26)	1.15 (0.94–1.40)	0.94 (0.73–1.22)§	1.00 (0.83–1.20)	1.32 (0.88–1.95)	0.74 (0.45–1.23)
History of bleeding	1.11 (0.79–1.56)§	2.06 (1.70–2.49)†	2.22 (1.87–2.64)†	2.79 (2.26–3.44)†	2.11 (1.34–3.34)†	1.91 (1.05–3.45)†
ACS presentation						
STEMI	1.00	1.00	1.00	1.00	1.00	1.00
NSTEMI	1.13 (0.92–1.39)	0.89 (0.69–1.15)	0.82 (0.65–1.04)	1.18 (0.85–1.64)	1.07 (0.59–1.93)	0.75 (0.40–1.42)
Not otherwise specified	1.01 (0.83–1.22)	0.85 (0.65–1.11)	0.83 (0.65–1.05)	1.21 (0.89–1.63)	1.09 (0.62–1.94)	0.69 (0.37–1.30)
In-hospital procedure						
PCI	1.24 (1.06–1.44)†	1.87 (1.37–2.54)†,‡	1.04 (0.87–1.26)	1.03 (0.81–1.30)	1.20 (0.77–1.86)	1.01 (0.58–1.77)
Drug therapy						
Baseline NSAIDs	1.06 (0.89–1.27)	1.29 (1.04–1.59)†	1.12 (0.89–1.42)	1.26 (0.95–1.66)	0.96 (0.58–1.59)	1.95 (0.71–5.32)‡
Baseline SSRIs	1.23 (1.00–1.50)†	0.93 (0.68–1.28)	1.12 (0.88–1.42)	1.23 (0.90–1.68)	1.64 (0.97–2.77)	1.03 (0.48–2.19)
Single antiplatelet	1.00	1.00	1.00	1.00	1.00	1.00
Dual antiplatelet	1.34 (1.14–1.57)†	0.75 (0.54–1.04)§	0.67 (0.49–0.91)†,§	1.17 (0.93–1.48)	2.10 (1.27–3.45)†	1.03 (0.62–1.72)

Continued

Table 3. Continued

Risk Factors	Bruising (n=949)*	Respiratory/ ENT Bleeds (n=582)*	Gastrointestinal Bleeds (n=705)*	Genitourinary Bleeds (n=468)*	Intraocular Bleeds (n=135)*	Intracranial Bleeds (n=81)*
Oral anticoagulant	1.18 (0.90–1.56)	1.61 (1.15–2.25)†	1.15 (0.83–1.59)	1.61 (1.11–2.34)†	3.64 (1.90–6.98)†	1.45 (0.25–8.46)‡
No record	0.49 (0.34–0.68)†	0.60 (0.43–0.85)†	1.26 (0.98–1.60)	0.96 (0.66–1.39)	1.33 (0.63–2.82)	6.53† (2.35–18.12)

Data are given as sub–hazard ratio (95% CI). ACS indicates acute coronary syndrome; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ENT, ears, nose, and throat; NSTEMI, non ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SSRI, selective serotonin reuptake inhibitor; STEMI, ST-segment–elevation myocardial infarction.

*Adjusted for year of hospital discharge, geographic region, general practice, and all listed characteristics in the table.

†Statistically significant predictors of bleeding at the 5% threshold.

‡Included as time-dependent coefficient: estimated sub–hazard ratio at day of hospital discharge but decreases with time after discharge (1.00=reference category).

§Included as time-dependent coefficient: estimated sub–hazard ratio at day of hospital discharge but increases with time after discharge.

implementation of the ACC/AHA guidelines), DAPT (Dual antiplatelet therapy study), and Trilogy-ACS (Targeted platelet inhibition to clarify the optimal strategy to medically manage acute coronary syndromes).[8,12,13] Cancers that are systemic, such as those emanating from the gastroesophageal tract, are more likely to increase bleeding complications. Therefore, thoughtful consideration should be given to this group of patients when deciding on secondary management strategy after ACS. We found dual antiplatelet therapy to be associated with a decreased risk of gastrointestinal bleed in the immediate period after hospital discharge. The decreased risk of gastrointestinal bleed with dual antiplatelet may be caused by an element of confounding by indication, with patients deemed to be at highest risk for this type of bleed only prescribed single antiplatelet at the time of hospital discharge.

We found treatment with oral anticoagulants to be associated with higher risk of respiratory, genitourinary, and intraocular bleeding events after hospital discharge. Of patients in our study, 6% were prescribed oral anticoagulants, with most (92%) given warfarin at discharge. Replacing warfarin with the newer oral anticoagulants that have a more favorable safety profile may mitigate the bleeding complications in this group of patients.[41,42] In patients managed with PCI, who have an indication for oral anticoagulants, such as those with atrial fibrillation who are at increased risk of stroke, secondary management involving an antiplatelet (eg, clopidogrel) and a newer oral anticoagulant, as stipulated in the updated American Heart Association guideline for the management of patients with atrial fibrillation, will reduce the risk of late bleeding events.[43] For patients prescribed triple therapy (aspirin plus P2Y12 inhibitor plus an oral anticoagulant), the duration of this therapy should be minimized to a period of 4 to 6 weeks and dual therapy (a P2Y12 inhibitor plus an oral anticoagulant) should be considered thereafter,[43] to minimize the risk of bleeding.

The findings of this study should be interpreted in light of some limitations. First, bleeding events were not independently adjudicated. The observational design of the study does not preclude residual confounding. The definition for bleeding did not include laboratory parameters, such as decrease in hemoglobin measurements and/or receipt of blood transfusion. Classifying bleeding on the basis of severity (major and minor) was, therefore, not possible. The study was not adequately powered to examine the independent predictors of some types of bleeding events, such as intracranial and intraocular bleeds that occurred relatively rarely. Thus, findings in relation to these bleeding events should be viewed as exploratory. Reporting bias may be a cause for concern in our study because not all patients who experience minor and nuisance bleeding events (eg, nose bleeds and bruising) will seek medical advice. Therefore, the incidence of bleeding is likely to have been underreported, although more significant bleeds may have been likely recorded. Prasugrel, ticagrelor, and the newer oral anticoagulants became available during the study period, but most patients (90%) were mostly treated with aspirin, clopidogrel, or warfarin after discharge. We restricted our study to people in England. Thus, the generalizability of our results outside of England is unclear. Finally, we were unable to examine the impact of dosing and duration of discharge antithrombotic drugs and those of emerging risk factors, such as frailty and genetic factors, on risk of future bleeding events.

In summary, bleeding complications after hospital discharge are common and occur more frequently in the first 30 days after hospital discharge. Patients who experience these bleeding events have distinct baseline characteristics. These characteristics differ, depending on the anatomic site of the bleeding event. Identification of these characteristics is an important step toward developing a real-world risk stratification tool that can facilitate a more patient-centered approach in deciding on favorable combination and duration of secondary antithrombotic therapy after ACS.

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Disclosures

None.

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Table 8.1: Risk factors univariably associated with serious bleeds, non-serious bleeds, early bleeds and each site-specific bleeding event post-hospital discharge for ACS

Risk factors	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Bruising** (n = 949)	**Respiratory bleeds** (n = 582)	**Gastrointestinal bleeds** (n = 705)	**Genitourinary bleeds** (n = 468)	**Intraocular bleeds** (n = 135)	**Intracranial bleeds** (n = 81)
Demographics	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***
Age (years)									
≤65	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
66 - 80	**1.53 (1.37, 1.71)**	**1.26 (1.12, 1.41)**	**1.56 (1.31, 1.85)**	1.13 (0.98, 1.30)	**1.45 (1.18, 1.80)**	**1.21 (1.02, 1.45)**	**1.47 (1.16, 1.87)**	**2.50 (1.67, 3.75)**	**2.21 (1.11, 4.39)**
> 80	**1.79 (1.60, 2.01)**	**1.30 (1.14, 1.49)**	**2.00 (1.67, 2.39)**	1.04 (0.87, 1.24)	**1.71 (1.38, 2.12)**	**1.54 (1.28, 1.85)**	**1.72 (1.37, 2.16)**	**2.04 (1.29, 3.22)**	**3.82 (1.97, 7.40)**
Female	**1.15 (1.06, 1.25)**	**1.62 (1.48, 1.79)**	**1.34 (1.15, 1.57)**	**2.04 (1.80, 2.30)**	1.06 (0.90, 1.25)	1.11 (0.96, 1.29)	0.95 (0.78, 1.15)	0.99 (0.70, 1.39)	**1.53 (1.05, 2.23)**
BMI (kg/m2)									
Normal weight *(18.50 to < 25)*	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Underweight *(< 18.50)*	0.99 (0.69, 1.43)	1.24 (0.83, 1.85)	0.95 (0.51, 1.77)	1.31 (0.82, 2.10)	1.23 (0.70, 2.17)	0.99 (0.51, 1.90)	0.74 (0.27, 2.02)	0.94 (0.24, 3.70)	1.32 (0.40, 4.42)
Overweight *(25 to <30)*	0.88 (0.78, 1.00)	0.99 (0.87, 1.13)	0.87 (0.72, 1.05)	1.04 (0.88, 1.23)	0.90 (0.73, 1.11)	0.97 (0.78, 1.20)	0.90 (0.71, 1.14)	0.78 (0.48, 1.25)	**0.52 (0.31, 0.88)**
Obese *(≥ 30)*	0.94 (0.83, 1.07)	0.92 (0.79, 1.07)	0.82 (0.65, 1.03)	0.98 (0.80, 1.19)	0.88 (0.70, 1.12)	0.99 (0.79, 1.23)	1.04 (0.79, 1.37)	0.87 (0.55, 1.37)	**0.36 (0.18, 0.73)**

Continuation	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Bruising** (n = 949)	**Respiratory bleeds** (n = 582)	**Gastrointestinal bleeds** (n = 705)	**Genitourinary bleeds** (n = 468)	**Intraocular bleeds** (n = 135)	**Intracranial bleeds** (n = 81)
	sHR (95% CI)	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***
Smoking Status									
Non smoker	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Ex-smoker	1.07 (0.96, 1.19)	0.97 (0.84, 1.12)	0.99 (0.82, 1.19)	0.88 (0.73, 1.05)	1.19 (0.95, 1.49)	0.96 (0.79, 1.17)	1.13 (0.91, 1.41)	1.07 (0.71, 1.62)	1.02 (0.62, 1.68)
Current smoker	**0.84 (0.74, 0.95)**	**0.79 (0.68, 0.93)**	**0.80 (0.66, 0.98)**	0.85 (0.71, 1.03)	0.85 (0.66, 1.09)	0.86 (0.70, 1.05)	0.81 (0.63, 1.06)	0.69 (0.40, 1.18)	0.55 (0.29, 1.07)
Comorbidities									
Diabetes	**1.30 (1.18, 1.43)**	**0.84 (0.74, 0.95)**	1.05 (0.87, 1.25)	**0.76 (0.65, 0.90)**	1.01 (0.82, 1.23)	1.08 (0.91, 1.27)	1.09 (0.89, 1.34)	1.34 (0.91, 1.97)	1.55 (0.97, 2.48)
Hypertension	**1.29 (1.18, 1.42)**	**1.19 (1.06, 1.35)**	**1.29 (1.09, 1.53)**	1.09 (0.94, 1.26)	**1.55 (1.30, 1.86)**	**1.23 (1.05, 1.45)**	1.07 (0.86, 1.32)	**1.65 (1.16, 2.34)**	1.15 (0.71, 1.86)
Heart failure	1.15 (1.00, 1.32)	0.85 (0.71, 1.02)	1.11 (0.88, 1.41)	**0.74 (0.58, 0.95)**	1.28 (0.97, 1.68)	1.05 (0.82, 1.33)	0.96 (0.69, 1.33)	0.63 (0.32, 1.25)	0.51 (0.19, 1.34)
Cancer	**1.24 (1.09, 1.41)**	1.01 (0.88, 1.17)	**1.47 (1.22, 1.76)**	0.94 (0.76, 1.15)	**1.32 (1.06, 1.64)**	**1.32 (1.07, 1.64)**	1.27 (0.98, 1.66)	0.91 (0.52, 1.59)	0.91 (0.45, 1.85)
PVD	**1.59 (1.30, 1.94)**	**1.33 (1.02, 1.73)**	1.23 (0.85, 1.76)	1.15 (0.80, 1.65)	**1.56 (1.08, 2.25)**	1.23 (0.85, 1.79)	1.54 (0.99, 2.39)	1.39 (0.63, 3.08)	1.52 (0.56, 4.07)
COPD	**1.55 (1.41, 1.70)**	**1.34 (1.20, 1.50)**	**1.36 (1.14, 1.63)**	**1.24 (1.08, 1.43)**	**1.83 (1.52, 2.21)**	**1.46 (1.24, 1.71)**	**1.46 (1.18, 1.81)**	1.20 (0.77, 1.89)	1.34 (0.80, 2.24)
CKD (eGFR < 60 mL/min/1.73 m^2)	**1.48 (1.36, 1.60)**	**1.18 (1.06, 1.32)**	**1.54 (1.33, 1.79)**	1.13 (0.98, 1.31)	1.14 (0.96, 1.35)	**1.38 (1.19, 1.60)**	1.22 (1.00, 1.49)	**2.09 (1.46, 3.00)**	**1.75 (1.14, 2.68)**

Continuation	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Bruising** (n = 949)	**Respiratory bleeds** (n = 582)	**Gastrointestinal bleeds** (n = 705)	**Genitourinary bleeds** (n = 468)	**Intraocular bleeds** (n = 135)	**Intracranial bleeds** (n = 81)
	sHR (95% CI)	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***
Hyperlipidaemia	**1.32 (1.21, 1.44)**	**1.16 (1.04, 1.31)**	1.10 (0.94, 1.28)	1.09 (0.95, 1.26)	**1.29 (1.07, 1.55)**	**1.35 (1.16, 1.57)**	1.14 (0.96, 1.37)	**1.68 (1.15, 2.45)**	0.90 (0.58, 1.41)
History of bleeding	**2.52 (2.26, 2.80)**	**1.64 (1.45, 1.86)**	**2.17 (1.82, 2.60)**	**1.41 (1.19, 1.67)**	**2.31 (1.91, 2.78)**	**2.47 (2.09, 2.91)**	**3.05 (2.50, 3.73)**	**2.40 (1.56, 3.69)**	**2.49 (1.48, 4.20)**
ACS presentation									
STEMI	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
NSTEMI	**1.32 (1.15, 1.52)**	1.01 (0.85, 1.19)	**1.39 (1.06, 1.83)**	1.08 (0.89, 1.31)	0.99 (0.77, 1.27)	0.94 (0.75, 1.19)	1.32 (0.96, 1.80)	1.19 (0.68, 2.07)	1.02 (0.54, 1.89)
ACS not otherwise specified	1.13 (0.98, 1.30)	0.94 (0.80, 1.10)	1.23 (0.94, 1.59)	0.99 (0.83, 1.19)	0.90 (0.70, 1.16)	0.85 (0.68, 1.07)	1.24 (0.92, 1.66)	1.09 (0.63, 1.88)	0.82 (0.45, 1.50)
In-hospital procedure									
PCI	**0.81 (0.73, 0.89)**	1.09 (0.98, 1.21)	0.89 (0.76, 1.04)	**1.15 (1.01, 1.32)**	0.96 (0.80, 1.15)	0.90 (0.77, 1.06)	0.90 (0.74, 1.10)	1.02 (0.71, 1.44)	0.66 (0.40, 1.11)
Drug Therapy									
Baseline NSAIDs	1.10 (0.97, 1.24)	1.14 (0.98, 1.32)	0.92 (0.73, 1.16)	1.12 (0.94, 1.34)	**1.25 (1.01, 1.53)**	1.08 (0.86, 1.36)	1.23 (0.93, 1.61)	0.94 (0.57, 1.55)	0.55 (0.24, 1.23)
Baseline SSRIs	**1.22 (1.05, 1.41)**	**1.26 (1.07, 1.48)**	1.18 (0.90, 1.53)	**1.42 (1.17, 1.73)**	1.03 (0.75, 1.40)	**1.27 (1.01, 1.61)**	1.33 (0.99, 1.79)	1.61 (0.97, 2.66)	1.18 (0.55, 2.52)

Continuation	**Serious bleeds** (n = 2126)	**Non-serious bleeds** (n = 1494)	**Early bleeds** (n = 698)	**Bruising** (n = 949)	**Respiratory bleeds** (n = 582)	**Gastrointestinal bleeds** (n = 705)	**Genitourinary bleeds** (n = 468)	**Intraocular bleeds** (n = 135)	**Intracranial bleeds** (n = 81)
	sHR (95% CI)	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***	***sHR (95% CI)***
Discharge antithrombotic									
Single antiplatelet	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Dual antiplatelet	0.90 (0.81, 1.00)	**1.17 (1.03, 1.32)**	**0.66 (0.56, 0.79)**	**1.30 (1.11, 1.52)**	0.94 (0.79, 1.13)	0.92 (0.77, 1.10)	1.03 (0.83, 1.29)	**1.76 (1.09, 2.85)**	0.89 (0.53, 1.50)
Anticoagulant	**1.42 (1.18, 1.71)**	**1.39 (1.12, 1.73)**	1.22 (0.90, 1.65)	1.14 (0.87, 1.51)	**1.66 (1.19, 2.31)**	1.20 (0.87, 1.65)	**1.67 (1.15, 2.41)**	**3.82 (2.00, 7.28)**	0.50 (0.12, 2.13)
No record	1.08 (0.92, 1.25)	**0.61 (0.48, 0.77)**	1.17 (0.92, 1.48)	**0.49 (0.35, 0.69)**	**0.63 (0.45, 0.90)**	**1.31 (1.04, 1.67)**	1.01 (0.70, 1.45)	1.36 (0.64, 2.86)	**3.26 (1.77, 6.00)**

sHR: *subhazard ratio,* ***CI:*** *confidence interval,* ***eGFR:*** *estimated glomerular filtration rate,* ***ACS****: acute coronary syndrome,* ***STEMI:*** *ST-elevation myocardial infarction,* ***NSTEMI:*** *Non ST-elevation myocardial infarction,* ***PVD:*** *peripheral vascular disease,* ***COPD:*** *chronic obstructive pulmonary disease,* ***CKD:*** *chronic kidney disease,* ***NSAID:*** *non-steroidal anti-inflammatory drugs,* ***SSRI:*** *selective serotonin re-uptake inhibitors,* ***PCI:*** *percutaneous coronary intervention,* ***BMI:*** *body mass index,* ***1.00:*** *reference category,* ***Bold text:*** *indicates statistically significant risk factors for bleeding at the 5% threshold.*

Table 8.2: The change in hazard of bleeding for each statistically significant risk factor that was included as a time dependent coefficient in the competing risk model for any bleed, serious bleed and each site-specific bleeding event

Outcome	Predictors	Baseline Hazard *(sHR (95% CI)*	Change in baseline hazard for each day post hospital discharge *(sHR (95% CI)*	Risk of bleeding at 30 days after hospital discharge (sHR (95% CI)	Risk of bleeding at 365 days after hospital discharge (sHR (95% CI)
Any bleed	Age > 80 years	1.42 (1.22, 1.66)	0.99921 (0.99839, 1.00003)	1.39 (1.16, 1.67)	1.06 (0.67, 1.68)
	PCI	1.26 (1.11, 1.43)	0.99907 (0.99840, 0.99974)	1.22 (1.05, 1.41)	0.89 (0.62, 1.30)
	Dual antiplatelet	0.81 (0.72, 0.93)	1.00211 (1.00134, 1.00289)	0.87 (0.74, 1.01)	1.76 (1.16, 2.44)
Serious bleeds	PCI	1.19 (1.01, 1.40)	0.99889 (0.99799, 0.99979)	1.15 (0.95, 1.39)	0.79 (0.48, 1.31)
	Dual antiplatelet	0.73 (0.61, 0.86)	1.00237 (1.00139, 1.00335)	0.78 (0.64, 0.96)	1.73 (1.02, 2.65)
Respiratory/ENT bleeds	Cancer	1.86 (1.26, 2.74)	0.99659 (0.99383, 0.99934)	1.68 (1.05, 2.69)	0.53 (0.13, 2.20)
	PCI	1.87 (1.37, 2.54)	0.99674 (0.99494, 0.99853)	1.69 (1.18, 2.43)	0.57 (0.22, 1.55)
Gastrointestinal bleeds	Dual antiplatelet	0.67 (0.49, 0.91)	1.00281 (1.00103, 1.00460)	0.73 (0.50, 1.05)	1.86 (0.71, 4.25)

Outcome	Predictors	Baseline Hazard *(sHR (95% CI)*	Change in baseline hazard for each day post hospital discharge *(sHR (95% CI)*	Risk of bleeding at 7 days after hospital discharge (sHR (95% CI)	Risk of bleeding at 30 days after hospital discharge (sHR (95% CI)
Early bleeds	Hypertension	1.69 (1.27, 2.24)	0.97226 (0.95299, 0.99193)	1.38 (0.91, 2.11)	0.73 (0.30, 1.86)
	Current smoking	1.54 (1.04, 2.27)	0.97098 (0.94782, 0.99470)	1.25 (0.72, 2.19)	0.64 (0.21, 2.01)

sHR: *subhazard ratio,* ***CI:*** *confidence interval,* ***PCI:*** *percutaneous coronary intervention,* ***Hx:*** *history,* ***NSAIDs:*** *non-steroidal anti-inflammatory drugs.*

Table 8.3: The change in hazard of bleeding for each statistically significant risk factor that was included as a time dependent coefficient in the competing risk model in the subgroup analyses

Outcome	Predictors	Baseline Hazard *(sHR (95% CI)*	Change in baseline hazard for each day post hospital discharge *(sHR (95% CI)*	Risk of bleeding at 30 days after hospital discharge (sHR (95% CI)	Risk of bleeding at 365 days after hospital discharge (sHR (95% CI)
≤ 65 years	PCI	1.26 (1.01, 1.57)	0.99877 (0.99763, 0.99991)	1.21 (0.94, 1.57)	0.80 (0.42, 1.53)
66 - 80 years	Hyperlipidaemia	0.80 (0.66, 0.97)	1.00206 (1.00092, 1.00320)	0.85 (0.68, 1.07)	1.69 (0.92, 2.82)
> 80 years	Dual antiplatelet	0.74 (0.60, 0.92)	1.00280 (1.00146, 1.00415)	0.81 (0.62, 1.04)	2.06 (1.02, 3.68)
Men	Age > 80 years	1.77 (1.42, 2.20)	0.99873 (0.99751, 0.99995)	1.70 (1.31, 2.20)	1.11 (0.57, 2.17)
	Current smoking	1.28 (1.03, 1.60)	0.99822 (0.99702, 0.99942)	1.22 (0.94, 1.57)	0.67 (0.35, 1.31)
	Dual antiplatelet	0.74 (0.62, 0.87)	1.00287 (1.00186, 1.00389)	0.80 (0.66, 0.98)	2.10 (1.22, 3.20)
PCI	Dual antiplatelet	0.74 (0.59, 0.94)	1.00214 (1.00068, 1.00359)	0.79 (0.60, 1.04)	1.62 (0.76, 3.11)
Medically managed	Age 66 - 80 years	1.43 (1.18, 1.73)	0.99889 (0.99795, 0.99984)	1.38 (1.11, 1.72)	0.95 (0.56, 1.63)
	Age > 80 years	1.56 (1.27, 1.91)	0.99858 (0.99757, 0.99959)	1.49 (1.18, 1.89)	0.93 (0.52, 1.67)
	Dual antiplatelet	0.85 (0.73, 0.99)	1.00202 (1.00112, 1.00291)	0.90 (0.76, 1.08)	1.78 (1.10, 2.62)

sHR: *subhazard ratio,* ***CI:*** *confidence interval,* ***COPD:*** *chronic obstructive pulmonary disease,* ***PCI:*** *percutaneous coronary intervention.*