Use of invasive strategies in the management of non-ST elevation acute myocardial infarction and clinical outcomes

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Publications

Publications arising directly from this PhD thesis are as follow

1. Rashid M, Lawson C, Potts J, Kontopantelis E, Kwok CS, Bertrand OF, Shoaib A, Ludman P, Kinnaird T, de Belder M, Nolan J, Mamas MA. Incidence, Determinants, and Outcomes of Left and Right Radial Access Use in Patients Undergoing Percutaneous Coronary Intervention in the United Kingdom: A National Perspective Using the BCIS Dataset. JACC Cardiovasc Interv. 2018 Jun 11;11
2. Rashid M, Fischman DL, Gulati M, Tamman K, Potts J, Kwok CS, Ensor J, Shoaib A, Mansour H, Zaman A, Savage MP, Mamas MA. Temporal trends and inequalities in coronary angiography utilization in the management of non-ST-Elevation acute coronary syndromes in the U.S. Sci Rep. 2019 Jan 18;9(1):240
3. Rashid M, Fischman DL, Martinez SC, Capers Q 4th, Savage M, Zaman A, Curzen N, Ensor J, Potts J, Mohamed MO, Kwok CS, Kinnaird T, Bagur R, Mamas M. Temporal trends and predictors of time to coronary angiography following non-ST-elevation acute coronary syndrome in the USA. Coron Artery Dis. 2019 May;30(3):159-170
4. Rashid M, Kontopantelis E, Kinnaird T, Curzen N, Gale CP, Mohamed MO, Potts J, Myint PK, Kwok CS, Nolan J, Zaman MJ, Timmis AD, Mamas MA. association between Hospital Cardiac Catheter Laboratory Status, Utilization of an Invasive Coronary Strategy and In-hospital Outcomes for the Management of Non-ST Elevation Acute Myocardial Infarction in the United Kingdom (In submission)

5. Rashid M, Kontopantelis E, Kinnaird T, Curzen N, Gale CP, Mohamed MO, Potts J, Myint PK, Kwok CS, Shoaib A, Timmis AD, Mamas MA. Baseline Risk and Timing of Invasive Strategy for 137,265 Patients Presenting with Non-ST elevation Acute Myocardial Infarction: Level of Compliance with International Guidelines (in submission)

Other publications

In addition to above publications, there are several other publications which I have led or contributed during the course of my PhD as follows.

1. Rashid M, Sperrin M, Ludman PF, O'Neill D, Nicholas O, de Belder MA, Mamas MA, Impact of operator volume for percutaneous coronary intervention on clinical outcomes: what do the numbers say? Eur Heart J Qual Care Clin Outcomes. 2016 Jan 1;2(1):16-22.
2. Rashid M, Kwok CS, Pancholy S, Chugh S, Kedev SA, Bernat I, Ratib K, Large A, Fraser D, Nolan J, Mamas MA, Radial Artery Occlusion After Transradial Interventions: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2016 Jan 25;5(1)
3. Rashid M, Kwok CS, Gale CP, Doherty P, Olier I, Sperrin M, Kontopantelis E, Peat G, Mamas MA, Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis. Eur Heart J Qual Care Clin Outcomes. 2017 Jan 1;3(1):20-36
4. Rashid M, Rushton CA, Kwok CS, Kinnaird T, Kontopantelis E, Olier I, Ludman P, De Belder MA, Nolan J, Mamas MA, Impact of Access Site Practice on Clinical Outcomes in Patients Undergoing Percutaneous Coronary Intervention Following Thrombolysis for ST-Segment Elevation Myocardial Infarction in the United Kingdom: An Insight From the British Cardiovascular

Intervention Society Dataset, JACC Cardiovasc Interv. 2017 Nov 27;10(22):2258-2265.

5. Rashid M, Ludman PF, Mamas MA. British Cardiovascular Intervention Society registry framework: a quality improvement initiative on behalf of the National Institute of Cardiovascular Outcomes Research (NICOR). Eur Heart J Qual Care Clin Outcomes. 2019 May 3. pii: qcz02
6. Noman A, Balasubramaniam K, Alhous MHA, Lee K, JesudasoP, Rashid M, Mamas MA, Zaman AG, Mortality after percutaneous coronary revascularization: Prior cardiovascular risk factor control and improved outcomes in patients with diabetes mellitus. Catheter Cardiovasc Interv. 2017 Jun 1;89(7):1195-1204.
7. Kwok CS, Bagur R, Rashid M, Lavi R, Cibelli M, de Belder MA, Moat N, Hildick-Smith D, Ludman P, Mamas MA, Aortic stenosis and non-cardiac surgery: A systematic review and meta-analysis, Int J Cardiol. 2017 Aug 1;240:145-153.
8. Ul Haq MA, Rashid M, Kwok CS, Wong CW, Nolan J, Mamas MA. Hand dysfunction after transradial artery catheterization for coronary procedures. World J Cardiol. 2017 Jul 26;9(7):609-619
9. Olier I, Sirker A, Hildick-Smith DJR, Kinnaird T, Ludman P, de Belder MA, Baumbach A, Byrne J, Rashid M, Curzen N, Mamas MA; Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention, Heart. 2018 Feb 2. pii: heartjnl-2017-312366
10. Kwok CS, Kontopantelis E, Kinnaird T, Potts J, Rashid M, Shoaib A, Nolan J, Bagur R, de Belder MA, Ludman P, Mamas MA, Retroperitoneal Hemorrhage After Percutaneous Coronary Intervention: Incidence, Determinants, and Outcomes as Recorded by the British Cardiovascular Intervention Society, Circ Cardiovasc Interv. 2018 Feb;11(2).
11. Kwok CS, Potts J, Gulati M, Alasnag M, Rashid M, Shoaib A, Ul Haq MA, Bagur R, Mamas MA, Effect of Gender on Unplanned Readmissions After Percutaneous Coronary Intervention (from the Nationwide Readmissions Database), Am J Cardiol. 2018 Apr 1;121(7):810-817.
12. Kwok CS, Rao SV, Potts JE, Kontopantelis E, Rashid M, Kinnaird T, Curzen N, Nolan J, Bagur R, Mamas MA, Burden of 30-Day Readmissions After Percutaneous Coronary Intervention in 833,344 Patients in the United States:

Predictors, Causes, and Cost: Insights From the Nationwide Readmission Database, JACC Cardiovasc Interv. 2018 Apr 9;11(7):665-674

13. Jackson M, Austin D, Kwok CS, Rashid M, Kontopantelis E, Ludman P, de Belder M, Mamas MA, Zaman A. The impact of diabetes on the prognostic value of left ventricular function following percutaneous coronary intervention: Insights from the British Cardiovascular Intervention Society. Catheter Cardiovasc Interv. 2018 Nov 15;92(6)
14. Kwok CS, Rao SV, Gilchrist I, Martinez SC, Al Ayoubi F, Potts J, Rashid M, Kontopantelis E, Myint PK, Mamas MA. Relation Between Age and Unplanned Readmissions After Percutaneous Coronary Intervention (Findings from the Nationwide Readmission Database). Am J Cardiol. 2018 Jul 15;122(2):220-228
15. Muhammad Ayyaz Ul Haq, Sheraz A. Nazir, Muhammad Rashid, Chun Shing Kwok, Syed Mubashiruddin, Zaheer Alisiddiq, Ahmed Shoaib, Karim Ratib, Mamas A. Mamas, James Nolan, Accelerated Patent Haemostasis Using a Procoagulant Disk; A Protocol Designed to Minimise the Risk of Radial Artery Occlusion Following Cardiac Catheterisation,CRM (Inpress)
16. Kwok CS, Bell M, Anderson HV, Al Shaibi K, Gulati R, Potts J, Rashid M, Kontopantelis E, Bagur R, Mamas MA, Discharge Against Medical Advice After Percutaneous Coronary Intervention in the United States. JACC Cardiovasc Interv. 2018 Jul 23;11(14)
17. Potts J, Kwok CS, Ensor J, Rashid M, Kadam U, Kinnaird T, Curzen N, Pancholy SB, Van der Windt D, Riley RD, Bagur R, Mamas MA. Temporal Changes in Co-Morbidity Burden in Patients Having Percutaneous Coronary Intervention and Impact on Prognosis, Am J Cardiol. 2018 Sep 1;122(5):712-722
18. Olier I, Carr M, Curzen N, Ludman P, Baumbach A, Kinnaird T, de Belder MA, Hildick-Smith D, Sirker A, Kwok CS, Rashid M, Nolan J, Kontopantelis E, Mamas MA, Changes in Periprocedural Bleeding Complications Following Percutaneous Coronary Intervention in The United Kingdom Between 2006 and 2013 (from the British Cardiovascular Interventional Society). Am J Cardiol. 2018 Sep 15;122(6):952-960.
19. Potts J, Sirker A, Martinez SC, Gulati M, Alasnag M, Rashid M, Kwok CS, Ensor J, Burke DL, Riley RD, Holmvang L, Mamas MA, Persistent sex disparities in clinical outcomes with percutaneous coronary intervention:

Insights from 6.6 million PCI procedures in the United States. PLoS One. 2018 Sep 4;13(9):e0203325

20. Ayyaz Ul Haq M, Rashid M, Gilchrist IC, Bertrand O, Kwok CS, Wong CW, Mansour HM, Baghdaddy Y, Nolan J, van Leeuwen MAH, Mamas MA, Incidence and Clinical Course of Limb Dysfunction Post Cardiac Catheterization - A Systematic Review. Circ J. 2018 Oct 25;82(11):2736-2744
21. Potts JE, Iliescu CA, Lopez Mattei JC, Martinez SC, Holmvang L, Ludman P, De Belder MA, Kwok CS, Rashid M, Fischman DL, Mamas MA, Percutaneous coronary intervention in cancer patients: a report of the prevalence and outcomes in the United States. Eur Heart J. 2018 Nov 30
22. Shoaib A, Farag M, Nolan J, Rigby A, Patwala A, Rashid M, Kwok CS, Perveen R, Clark AL, Komajda M, Cleland JGF. Mode of presentation and mortality amongst patients hospitalized with heart failure? A report from the First Euro Heart Failure Survey. Clin Res Cardiol. 2018 Oct 25.
23. Shoaib A, Kinnaird T, Curzen N, Kontopantelis E, Ludman P, de Belder M, Rashid M, Kwok CS, Nolan J, Zaman A, Mamas MA, Outcomes Following Percutaneous Coronary Intervention in Non-ST-Segment-Elevation Myocardial Infarction Patients With Coronary Artery Bypass Grafts, Circ Cardiovasc Interv. 2018 Nov;11(11).
24. Shoaib A, Mamas MA, Ahmad QS, McDonagh TM, Hardman SMC, Rashid M, Butler R, Duckett S, Satchithananda D, Nolan J, Dargie HJ, Clark AL, Cleland JGF, Characteristics and outcome of acute heart failure patients according to the severity of peripheral oedema, Int J Cardiol. 2019 Mar 15, pii: S0167-5273(18)34755-7. doi: 10.1016/j.ijcard.2019.03.020 [In press]
25. Chun Shing Kwok, Binita Shah, Jassim Al-Suwaidi, David L. Fischman, Lene Holmvang, Chadi Alraies, Rodrigo Bagur, Vinayak Nagaraja, Muhammad Rashid, Mohamed Mohamed, Glen P. Martin, Evan Kontopantelis, Tim Kinnaird, Mamas Mamas, Timing and Causes of Unplanned Readmissions After Percutaneous Coronary Intervention: Insights From the Nationwide Readmission Database, JACC: Cardiovascular Interventions, 2019, ISSN 1936-8798 doi.org/10.1016/j.jcin.2019.02.007. [in Press]

26. Mohamed MO, Kinnaird T, Anderson R, Rashid M, Martin GP, Freeman P, Kwok CS, Myint PK, Zaman AG, Mamas MA, Combinations of bleeding and ischemic risk and their association with clinical outcomes in acute coronary syndrome. Int J Cardiol. 2019 May 21. pii: S0167-5273(18)36498-2

Presentations

Poster or oral presentations arising from this thesis are

1. Rashid M, Fischman DL, Gulati M, Tamman K, Potts J, Kwok CS, Ensor J, Shoaib A, Mansour H, Zaman A, Savage MP, Mamas MA. Trends and outcomes of use of coronary angiography in management of non-ST-Elevation acute coronary syndromes (NSTEACS), a population based cohort study. European Heart Journal 39, 1082-1082 (**Presented as oral presentation in the high impact clinical abstract session at European Society of Cardiology conference, August 2018, Munich, Germany**)
2. Rashid M, Fischman DL, Martinez SC, Capers Q 4th, Savage M, Zaman A, Curzen N, Ensor J, Potts J, Mohamed MO, Kwok CS, Kinnaird T, Bagur R, Mamas M. Temporal trends and predictors of time to coronary angiography following non-ST-elevation acute coronary syndrome in the USA. Journal of the American College of Cardiology 73 (9 Supplement 1), 124 (**Presented as a moderated poster at American College of Cardiology conference, New Orleans, USA, March 2019).**
3. Rashid M, Kontopantelis E, Kinnaird T, Curzen N, Gale CP, Mohamed MO, Potts J, Myint PK, Kwok CS, Nolan J, Zaman MJ, Timmis AD, Mamas MA. association between Hospital Cardiac Catheter Laboratory Status, Utilization of

an Invasive Coronary Strategy and In-hospital Outcomes for the Management of Non-ST Elevation Acute Myocardial Infarction in the United Kingdom. Journal of the American College of Cardiology 73 (9 Supplement 1), 125. **(Presented as a moderated poster at American College of Cardiology conference, New Orleans, USA, March 2019).**

Abstract

Non-elevation acute myocardial infarction (NSTEMI) is one of the commonest phenotype of acute coronary syndrome (ACS) and associated with significant morbidity and mortality at the short and long term. An invasive strategy in the form of coronary angiography (CA) or percutaneous coronary intervention (PCI) allows an early assessment of coronary anatomy, identify culprit lesions and plan further management. While the effectiveness of the invasive strategy is well documented in clinical trials, there is limited data regarding the changes in demographics, risk profile and comorbidity burden of patients receiving invasive strategy in contemporary practice. Furthermore, the opinion is divided regarding the optimal timing of invasive strategy in this cohort and it is unclear how risk stratification guides the utilisation of invasive strategy in a real world setting.

Consequently, this thesis was designed to determine, 1) changes in characteristics, risk profile and comorbidity burden of patients admitted with a diagnosis of an NSTEMI and how this relates to the use of an invasive strategy in different subgroups of patients 2) optimal timing of invasive strategy in different subgroups of patients 3) guidelines recommended risk stratification and how this translates into the use of invasive strategy 4) availability of cardiac catheter laboratory facilities, use of invasive strategy and clinical outcomes and 5) optimal access site practice to perform invasive strategy.

This thesis addresses the aforementioned aims in mainly three parts. Part 1 relates to results in chapter 4 and 5 which systematically looked at the use of an invasive strategy in different subgroups of patients. Chapter 4 demonstrates a temporal

increase in the utilisation of invasive strategy albeit slower adoption was noted in older, women and more comorbid patients. Furthermore, the results from chapter 5 showed that despite the increase in the use of early invasive strategy within 24hours, there were significant disparities in utilisation of an early invasive strategy in Women, African Americans, admission day and older patients. Part 2 of the thesis shows that an invasive strategy for management of NSTEMI is not delivered according to international guidelines recommendations. Specifically, the disconnect between baseline risk and utility of invasive strategy increases with increasing risk and women achieve even slower access than men to the invasive strategy, so that overall their care is even more discrepant with the guidelines. Chapter 7 highlights important differences in both the utilisation of invasive strategy and subsequent management of NSTEMI patients according to admitting hospital cardiac catheter laboratory facilities. These variations are important particularly in the high-risk NSTEMI where patients admitted to 'diagnostic' hospitals had a greater risk of in-hospital mortality. Finally, part 3 of the thesis showed that left radial access offers a very safe and effective alternative access site route for performing invasive strategy and may also help to reduce procedure related stroke complications.

Overall, this thesis has demonstrated that there are significant inequalities in the use of invasive strategy in clinical practice in that elderly, women, ethnic minorities, and more comorbid patients. Furthermore, there is a significant disconnect between guidelines recommended risk stratification criteria and use of invasive strategy. There are also significant institutional variations in the adoption of an invasive strategy which may be associated with poor outcomes in high-risk patients. Clinical implications and further areas of research are discussed in detail.

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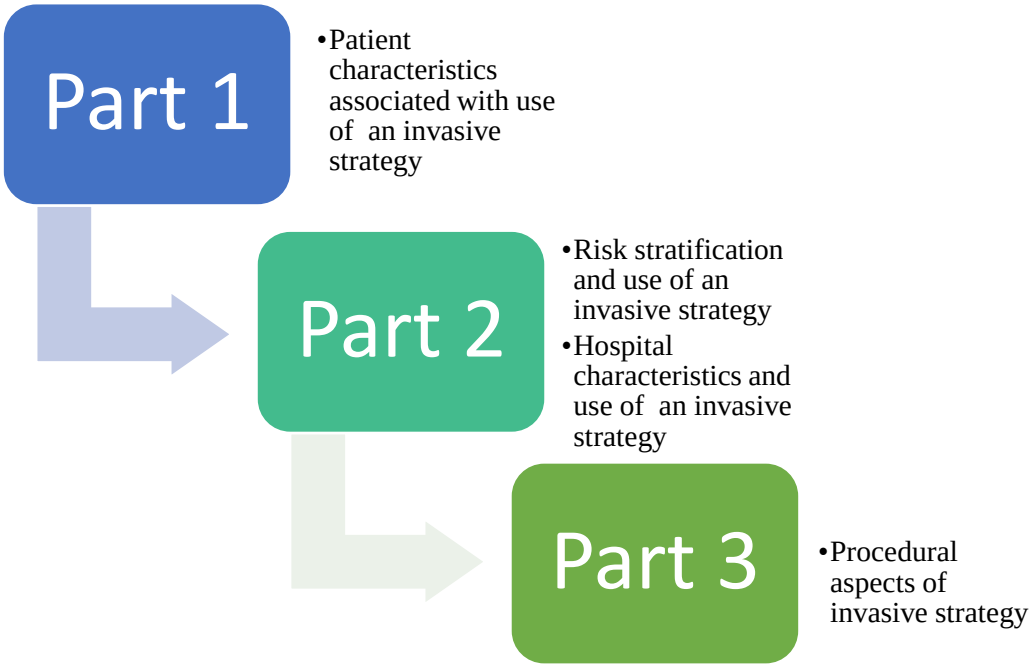
Chapter 1

This chapter sets the objectives of this thesis and provides a brief outline of the content of each chapter

1.1 Introduction:

This thesis is concerned with the invasive management of Non-ST Elevation Acute Myocardial Infarction (NSTEMI) and investigates various factors associated with utilisation of an invasive strategy in the form of Coronary Angiography (CA) or Percutaneous Coronary Intervention (PCI) in this cohort. On the whole, the thesis is divided into three parts, in order to study the three main aspects of the use of an invasive strategy in the management of NSTEMI as illustrated in Figure 1.1.

Figure 1.1 Pictorial demonstration of the three main phases of the thesis.



1.2 Objectives

The main objectives of this thesis were to investigate the following:

- The utilisation of an invasive strategy in the form of CA or PCI in the management of patients admitted with a diagnosis of NSTEMI and its association with clinical outcomes.
- Trends in the utilisation of an invasive strategy at different time points from admission and association with clinical outcomes.

- Appropriate use of guidelines recommended risk stratification in clinical practice and its relationship with the use of an invasive strategy.
- Influence of hospital cardiac catheterisation facilities on the use of an invasive strategy in patients admitted with the diagnosis of NSTEMI and association with clinical outcomes.
- Radial access and access site choice in patients undergoing an invasive strategy (PCI) following admission with NSTEMI and its association with clinical outcomes.

1.3 Chapter 2

The chapter reviews the pathophysiology, clinical presentation and overall management of different types of Acute Coronary Syndrome (ACS). Furthermore, various aspects of invasive management of ACS patients are discussed and gaps in the literature are identified.

1.4 Chapter 3

This chapter describes the datasets used in this PhD, namely, National Inpatient Sample (NIS), Myocardial Ischaemia National Audit Project (MINAP) and the British Cardiovascular Intervention Society (BCIS) dataset. In addition to cohort selection, the general methodology used in this thesis for descriptive analyses and complex modelling strategies is described in detail.

1.5 Chapter 4

This chapter addresses the objective one of the thesis. In this chapter, temporal trends in the characteristics of patients receiving an invasive strategy are examined. I also explored the secular trends in the use of an invasive strategy and differences in the use

of an invasive strategy in NSTEMI patients stratified according to age, sex, ethnicity, comorbidity burden and hospital characteristics.

1.6 Chapter 5

This chapter addresses objective two of the thesis. In this chapter, I studied the temporal trends in timing to an invasive strategy and also described the changes in the profile of patients undergoing early, intermediate and late invasive strategy following admission with an NSTEMI over the past decade in the United States.

1.7 Chapter 6

Objective three of this thesis was studied in this chapter, to study the adoption of guidelines recommended risk stratification in clinical practice and association with the use of an invasive strategy.

1.8 Chapter 7

This chapter addresses objective four of the thesis, to examine the relationship between the presence of different types of cardiac catheter laboratory facilities and utilisation of an invasive strategy in patients admitted with the diagnosis of NSTEMI.

1.9 Chapter 8

In line with objective four of the thesis, this chapter studies the procedural aspect of an invasive strategy. Current practice is to perform PCI using radial access but there is limited data on the difference between using right or left radial access. Therefore, this chapter investigated the differences between the use of left and right radial access in performing PCI, and clinical outcomes in all patients admitted following ACS. Furthermore, access site crossover practice was described in patients receiving the first procedure from right radial access.

1.10 Chapter 9

This chapter summarises the overall findings of the thesis and the potential clinical implications of these findings in relation to future research, clinical practice, and guidelines.

Chapter 2

This chapter provides an introduction to Acute Coronary Syndromes and overview of invasive strategies used in the management of Acute Coronary Syndromes.

2.1 Acute coronary syndrome

This thesis focuses on the invasive management of NSTEMI, the most common presentation of ACS. ACS, an umbrella term that denotes the presence of acute myocardial injury and raised cardiac biomarkers in the setting of acute myocardial ischemia or infarction[1]. Pathologically, the majority of ACS is caused by atherothrombotic coronary artery disease and are usually precipitated by an acute plaque rupture or erosion culminating in prolonged myocardial ischemia and myocardial cell death. This type is also referred as type 1 Myocardial Infarction (MI), however, there are 4 other types of MIs which may occur due to a variety of reasons ranging from oxygen supply/demand imbalance (type 2 MI) to procedure-related MI (type 3-5 MI)[1]. Hereafter, all the discussion in this thesis is related to ACS or type 1 MI.

For clinical purposes and allocation of appropriate treatment strategies, all types of ACS are mainly divided into two groups, namely ST-elevation Acute Myocardial Infarction (STEMI) and NSTEMI. STEMI occurs when there is complete occlusion of one or more coronary vessels and is diagnosed by the presence of an acute ST-segment elevation in two contiguous leads or a new bundle branch block on the electrocardiogram (ECG) in presence of cardiac chest pain. As the artery is completely occluded and diagnosis is evident on the ECG, the treatment is therefore based on the principle “time is muscle” i.e. open the blocked artery soon as possible by performing a procedure called PCI in order to minimise the irreversible myocardial injury. PCI is an invasive procedure, where an interventional cardiologist injects contrast dye into the coronary arteries using a small catheter, to establish if there is any narrowing/ blockages inside the arteries and can then treat them with balloons or metal tubes (stents) during the procedure if necessary. In contrast, NSTEMI usually occurs due to a sudden reduction in blood supply to the heart muscle from rupture of a plaque without complete

occlusion of the coronary vessel. Therefore, diagnosis is often reliant on carrying a number of investigations such as ECG and blood tests (cardiac enzyme biomarkers) to detect damage to the myocardium. As the artery is only partially blocked, performing immediate intervention in the form of PCI is usually not mandated and these patients are often managed by giving appropriate combination of medications such as antiplatelets, (aspirin, clopidogrel etc), antithrombotics (heparin, glycoprotein 2b3a inhibitors) before a decision about an invasive strategy is made. As such, the use of an invasive strategy is determined by various patient and hospital level factors, which will be discussed in details later on in this chapter.

2.2 Management of NSTEMI

The management of NSTEMI entails a detailed assessment of the patient's presentation, risk-stratification using validated risk scores such as Global Registry of Acute Coronary Events (GRACE) risk score[2], pharmacological treatment including administration of antiplatelets, anticoagulants, antithrombotics and invasive strategies in the form of invasive CA followed by the PCI or Coronary Artery Bypass Graft (CABG) surgery if indicated[3,4]. The overall goal of all these treatment strategies is to minimise further myocardial muscle damage, prevent future adverse events and improve survival in patients admitted with NSTEMI.

2.2.1 *Risk stratification*

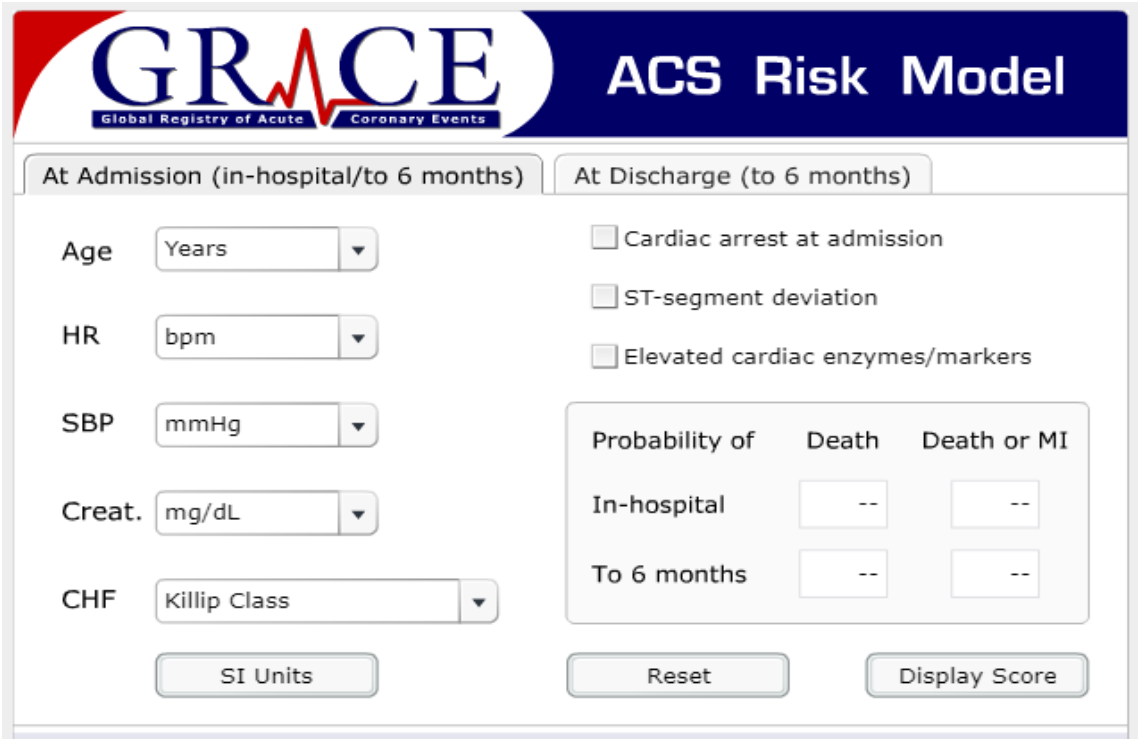
As described earlier, patients presenting with STEMI usually have complete occlusion of one or more coronary arteries affecting a larger territory of the myocardium. Therefore, in contemporary practice, patients presenting with chest pain and diagnosed with STEMI are now urgently triaged to hospitals having facilities to perform urgent primary PCI (PPCI) in order to open the blocked artery and restore myocardial perfusion within the recommended timeframe of 90 minutes from the first medical

contact[3,4]. However, when PPCI facilities are not readily available or located beyond the recommended timeframe of 90 minutes, thrombolytic therapy is administered[5-7]. Thrombolytic therapy, also known as clot-busting therapy, includes administration of potent blood thinners in the form of tissue plasminogen activator to allow immediate desolation of thrombus inside the coronary arteries[6]. These patients may then be transferred to a PCI capable hospital to perform invasive CA followed by PCI or CABG if required. Immediate risk stratification in STEMI patients is infrequent particularly due to the widespread use of PPCI to treat these patients. Regional pathways now offer urgent PPCI once clinical and diagnostic criteria of ECG is met, therefore it is unlikely that a STEMI risk stratification score would alter decision making and treatment offered. Guidelines from national bodies also encourage rapid assessment, early diagnosis and transfer to a PPCI capable hospital to minimise the delays and improve outcomes[3,4].

In contrast to STEMI, the treatment pathways for patients admitted with an NSTEMI are more diverse. National bodies emphasise the use of a pharmaco-invasive approach for NSTEMI patients which includes an initial period of intense medical therapy with antiplatelet, anti-coagulant and anti-ischemic agents followed by an invasive strategy in the form of an invasive CA with adjuvant PCI or CABG if indicated [3,4,8]. Compared to STEMI, the patients presenting with an NSTEMI are also likely to be much more complex, older and comorbid, making them challenging to diagnose and treat[9-11]. Therefore, a quantitative risk stratification plays a pivotal role in enabling physicians to identify patients at higher risk of adverse events and target treatments accordingly[2]. Risk stratification is a predictive tool based on a number of independent factors of patients on presentation which are used to calculate a score to help physicians stratify the patients. A number of risk stratification scores have been reported in the literature

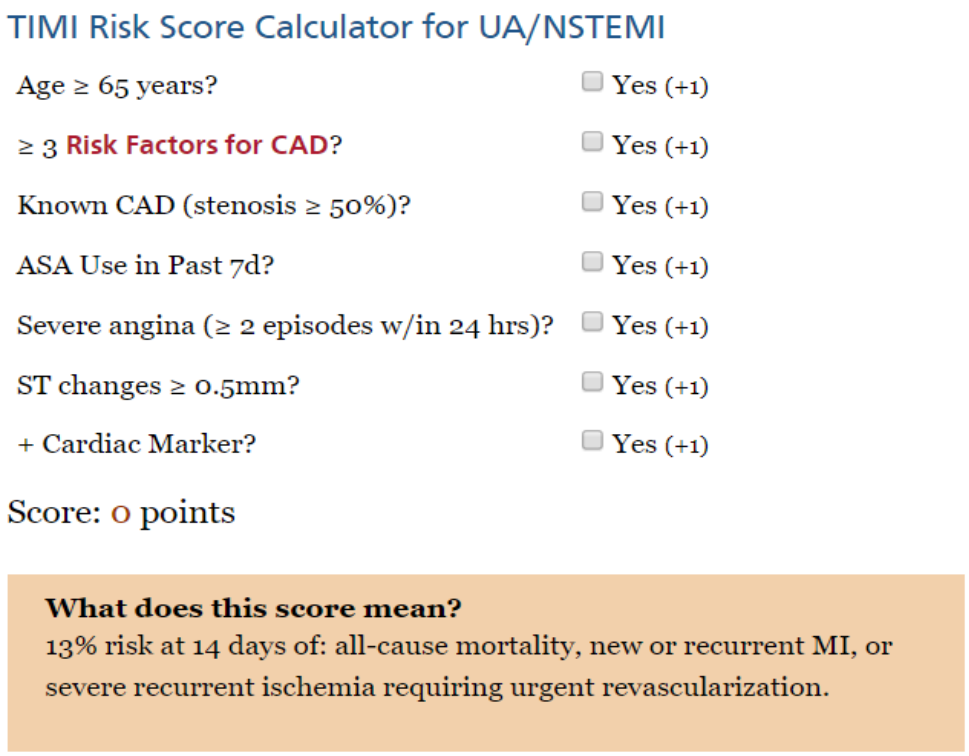
but the two most widely used in daily practice are the GRACE risk score and TIMI (Thrombolysis In Myocardial Infarction) scores[2,12]. The GRACE risk score is a scoring system to risk stratify patients diagnosed with ACS to estimate their in-hospital and 6-month to 3-year mortality[2]. The GRACE risk score clinical application tool is a web-based downloadable application and is available at http://www.outcomes-umassmed.org/grace. The GRACE risk score is based on the patient's age, heart rate or pulse, systolic blood pressure, creatinine, cardiac arrest at admission, ST-segment changes on the ECG, elevated cardiac enzymes and the Killip class, which is a surrogate for the degree of acute heart failure. An overall score is then calculated by imputing all these parameters, which is then divided into three different risk categories, low risk (score <109), intermediate risk (score 109-140) and high-risk (score >140). Depending upon the risk profile of the patient, the risk of in-hospital death ranges from 0-2% in low-risk GRACE to more than 20% in high-risk GRACE category [2](Figure 2.3).

Figure 2.1 GRACE ACS risk and mortality calculator (adapted from https://www.outcomes-umassmed.org)



The second most commonly used risk score for risk stratification of NSTEMI patients is TIMI score. This score is also derived using patient factors such as age, presence of 3 or more coronary artery disease risk factors, known coronary artery disease, aspirin use in the past seven days, severe angina defined as two or more episodes in last 24 hours, ST-segment changes on the ECG and elevated cardiac enzymes [12]. One point is given for the presence of each factor and totals score ranges from 0-7, which is then used to predict the risk of in-hospital death, new or recurrent myocardial infarction, or severe recurrent ischemia requiring urgent revascularisation in the first 14-days of admission (Figure 2.4). Although both scores are widely used in clinical practice, GRACE score is preferred over TIMI score due to its superior discriminative accuracy and accurate risk stratification both on admission and discharge[13,14].

Figure 2.2 TIMI risk calculator for NSTEMI/UA (adapted from HTTP:// www.timi.org)



2.2.2 *Pharmacological treatments*

The pharmacological treatment of NSTEMI includes administration of anti-ischemic, antiplatelets and lipid lower agents in all patients. After the acute phase, a continuation of these medications is also recommended as secondary prevention beyond the acute phase[3,4,15]. The main goal of anti-ischemic medications is to relieve the symptoms of

ischemia by reducing the myocardial oxygen demand or increase the oxygen supply to the myocardium. Beta-blockers and nitrates have excellent anti-ischemic properties, whereas administration of oxygen is also recommended particularly in patients with oxygen saturation lower than 90%[4]. Antiplatelet medications such as aspirin, clopidogrel, ticagrelor and prasugrel are pivotal in inhibition of platelet activation and aggregation and prevent thrombus formation after acute plaque rupture[16-19]. Current guidelines advocate administration of aspirin along with one of the P2Y12 inhibitors such as clopidogrel or ticagrelor or prasugrel for up to 12 months. It is also recommended that lipid-lowering statin therapy should be initiated in all patients soon after the admission and continued beyond the discharge[3,4].

2.2.3 *Invasive strategy*

An invasive strategy in the context of NSTEMI is defined as an initial assessment of coronary anatomy using a procedure called "coronary angiography (CA)" followed by revascularisation in the form of PCI or CABG if indicated. CA is a non-surgical procedure, where a catheter is inserted into the coronary arteries via either the femoral or radial artery, allowing the operator to visualise the extent of coronary obstruction by injecting a contrast dye into the coronary arteries under x-ray guidance. CA is the most commonly performed medical procedure, to investigate the extent of coronary disease and identify the culprit lesions in the vessel that contributed to the NSTEMI. More importantly, the information from CA helps to decide the further course of treatment in the form of medical management, PCI or surgical revascularisation in the form of CABG surgery. As described earlier, PCI includes treating the narrowing in the coronary arteries mechanically either with a balloon or a stent. In the context of STEMI, the majority of the patients end up needing PCI in order to achieve coronary reperfusion as soon as possible. However, in NSTEMI patients, the decision to undertake an

invasive strategy in the form of CA or PCI requires a careful assessment of patient's clinical presentation, comorbidities, risk stratification as outlined in 1.2.1, the risk associated with the invasive procedure and prognostic impact of any potential treatment on patient's survival[3,4]. Nevertheless, very often a proportion of patients receive CA and PCI as one procedure instead of a staged procedure depending upon the availability of facilities of admitting hospital and clinical indication. In this thesis, from hereafter, an invasive strategy is defined use of either coronary angiography or PCI.

2.3 Determinants of use of an invasive strategy in NSTEMI

As described earlier, an invasive strategy plays a central role in the invasive management of patients admitted with NSTEMI. The information obtained from the CA helps physicians to confirm the diagnosis of ACS, identify the culprit lesions and establish the indication of revascularisation in the form of PCI or CABG. However, given the invasive nature of the procedure and associated complications, the decision to undertake an invasive strategy must also be weighed against the potential risks of the procedure, costs, resource utilisation and impact on patient outcomes. There are several factors which may influence the utilisation of an invasive strategy and clinical outcomes in NSTEMI patients as discussed below.

2.3.1 *Patient-related factors*

Patient characteristics such as age, gender, ethnicity and presence of comorbidities are known determinants of receipt of an invasive strategy [20-24]. It is widely reported in the literature that younger patients admitted with NSTEMI are more likely to receive an invasive strategy compared to older patients. A similar bias towards the lower threshold to adopt an invasive strategy in men compared to women has been reported[25]. This is probably because physicians are likely to opt for a more conservative approach in complex and higher-risk patients such as elderly and women compared to lower-risk

young and male patients. Presence of comorbidities is also an important determinant of the use of an invasive strategy. Due to changes in population demographics, a significant proportion of patients with NSTEMI are older and have cardiac and non-cardiac comorbidities[9,11]. Presence of these comorbidities not only influence outcomes of patients but are also likely to play a major role in decision making and planning treatments. For instance, current guidelines place special emphasis on the early use of an invasive strategy in patients with known cardiovascular risk factors such as the history of diabetes, chronic renal disease, heart failure and hypertension[3,4,15]. Whilst cardiovascular risk factors such as hypertension, hyperlipidemia, smoking, diabetes are prevalent in patients presenting with NSTEMI, with the changing population demographics, these patients often have a broad spectrum of cardiac and non-cardiac comorbidity conditions[9]. It is not clear how clustering of multiple chronic comorbidities influence decision making in terms of the use of an invasive strategy in patients admitted with NSTEMI. In order to study the association between clustering of the different comorbid condition and use of an invasive strategy, it is important to focus on an overall comorbidity burden of the patient using a recognised measure. The Charlson comorbidity index (CCI) is a well-recognised measure of quantifying the prognostic impact of 22 comorbidity conditions individually by means of a score, which can then be used to estimate the prognosis of the patients with these conditions. In a previously published meta-analysis, I reported that every point increase in CCI score was associated with an increased risk of mortality in patients with ACS and a two-fold increase in the risk of mortality in patients with a CCI score of 2 or more[9]. However, it is not clear what factors drive the increased risk of mortality with an increasing burden of comorbidities. It is plausible that patients with multiple comorbidities are less likely to receive an invasive strategy and more likely to be managed conservatively.

Similarly, sex differences in clinical outcomes of patients presenting with NSTEMI are widely reported in the literature[26-31]. The unfavourable outcomes in women have often been attributed to the delayed or atypical presentation, older age, less aggressive management and higher comorbidity burden [9,32-35]. However, more contemporary data suggest that differences in clinical characteristics and presentation only partially contribute towards the higher mortality amongst women[36,37]. A recent analysis of the Myocardial Infarction National Audit Project (MINAP) registry showed that women in England and Wales were less likely to receive guidelines indicated care and had significantly higher mortality than men following AMI. These data highlight the need for greater understanding of factors driving these differences in outcomes and optimising the therapeutic strategies such as the use of an invasive strategy in women to improve survival[38].

2.3.2 *Healthcare system-related factors*

Healthcare system related factors such as the presence of cardiac catheter laboratory facilities is another important factor, which may influence the utilisation of an invasive strategy in patients with NSTEMI. Patients meeting the diagnostic criteria of STEMI are usually transferred immediately to the nearest PCI capable hospital for urgent reperfusion in the form of PPCI. Evidence from multiple randomised control trials, suggests that PPCI performed in a timely fashion improves outcomes in this cohort of patients by reducing mortality by approximately 30% and is the current gold standard treatment modality[39,40]. Consequently, there has been a great expansion in the provision of PCI programmes in the majority of the healthcare systems across Europe, UK and USA. For example, the use of thrombolysis for treatment of STEMI has steadily declined in the UK to almost less than 1% of the total STEMI cohort in 2014[41].

In contrast, the use of an invasive strategy in patients admitted with NSTEMI may be different across hospitals with different types of cardiac catheter laboratory facilities. For instance, patients admitted to a hospital without on-site cardiac catheter laboratory facilities may be less likely to receive an invasive strategy or have to wait longer before being transferred to another hospital with facilities to perform CA or PCI. Conversely, previous studies have shown that patients admitted to hospital with onsite cardiac catheter laboratory facilities are more likely to receive invasive coronary procedures[42,43]. However, the use of an invasive strategy may be variable according to different types of cardiac catheter laboratory facilities at the first admitting hospital. For example, patients admitted to hospitals with facilities to perform diagnostic coronary angiography only, may receive CA locally but then will need to be transferred to PCI capable hospital in case of needing PCI, whereas this may not be relevant to patients admitted directly to the PCI capable hospitals. It is also not known if different types of cardiac catheter laboratory facilities at the admitting hospital influence outcomes in NSTEMI cohort.

2.3.3 *Timing of an invasive strategy*

As discussed earlier, STEMI usually develops because of acute plaque rupture or erosion, triggering platelet aggregation and fibrin deposition and leading to the formation of an occlusive thrombus and complete vessel occlusion. Therefore, patients presenting with STEMI are treated with an immediate invasive strategy to minimise myocardial injury and improve patient outcomes. STEMI care pathways are designed around 24/7 emergency services to minimise time delays and offer PCI in the recommended time of fewer than 90 minutes [3,4,15]. Health services have been structured in a way to offer immediate PCI 24/7 and there is little variation in services offered / access to PCI either nationally or internationally.

In contrast, the timing of an invasive strategy for patients with NSTEMI varies greatly according to national and regional practices. For example, in UK practice, National Institute of Clinical Excellence (NICE) recommends that an invasive strategy in the form of CA should be undertaken within 96 hours following admission with NSTEMI[8]. In contrast, the European Society of Cardiology (ESC) advocates offering an invasive strategy within 72 hours to low-risk patients and within 24 hours to patients with high-risk features defined as GRACE score >140 [4]. Lastly, the American Heart Association/ American College of Cardiology (AHA/ACC) has also recommended three different points for performing CA whilst acknowledging the fact that optimal timing to an invasive strategy remains inconclusive[3]. An immediate invasive strategy (within 2 hours) is recommended by both ESC and AHA/ACC guidelines in patients with hemodynamic instability, signs of new heart failure or recurrent angina despite maximum medical therapy, early approach (within 24h) for patients with changes in cardiac biomarker or ECG changes and a late approach for patients with low GRACE score (109-140). However, the integration of guidelines into clinical practice is variable and often delayed due to a variety of potential barriers such as clinician's bias, lack of infrastructure or financial restraints [44-46]. Therefore, it is important to describe the utilisation of an invasive strategy based on guidelines recommended risk and whether the receipt of an invasive strategy is based on guidelines-based risk criteria.

There is also strong evidence that the time/day of presentation does not influence outcomes in patients following STEMI, due to the fact that STEMI care pathways are designed around a 24/7 emergency service where an ECG meeting the diagnostic criteria of STEMI will trigger the same pathway regardless the time or day of presentation[47,48]. As a result, the patients are directly taken to the catheter laboratory for immediate revascularisation regardless of their time or day of presentation whereas

patient admitted after NSTEMI are usually admitted and treated medically first before a decision is made about further invasive strategy or conservative management. Therefore, optimal timing to an invasive strategy in patients admitted following NSTEMI remains inconclusive as reflected in heterogeneity in current national practices and national societies guideline recommendations[3,4]. In general, there are two viewpoints regarding optimal timing to perform an invasive strategy; early invasive (i,e within 24 hours of admission) or delayed invasive (i,e within 72 hours of admission). The use of an early invasive approach in the form of CA followed by revascularisation is supported by some, but not all[49-51] randomised control trials (RCT) data that has shown that an early invasive strategy reduces the risk of adverse events and improves long-term survival largely by reducing the risk of severe recurrent angina[52], late myocardial infarction[53] and death[54]. Additionally, an early invasive strategy also facilitates early risk stratification, timely treatment in the form PCI or CABG and speedy discharge but this can also place greater logistic demands on limited resources of a healthcare system. The early invasive strategy is also associated with increased risk of procedure-related complications such as major bleeding, stroke and procedure-related myocardial infarction [55]. To minimise this hazard, a second expert consensus is to passivate plaque activity by means of extended medical therapy for up to 72 hours before undertaking any invasive intervention[56]. The delayed strategy obviously has disadvantages in that it increases the risk of further complications of NSTEMI such as re-infarction that could ensue during medical therapy and longer hospital stays. Therefore, optimal timing to an invasive strategy in patients admitted following NSTEMI remains an area of uncertainty and it is unclear whether it should be offered as early as possible after admission or it could be delayed safely until patient receives medical therapy to allow plaque passivation[57-59]. An earlier meta-analysis of four RCTs

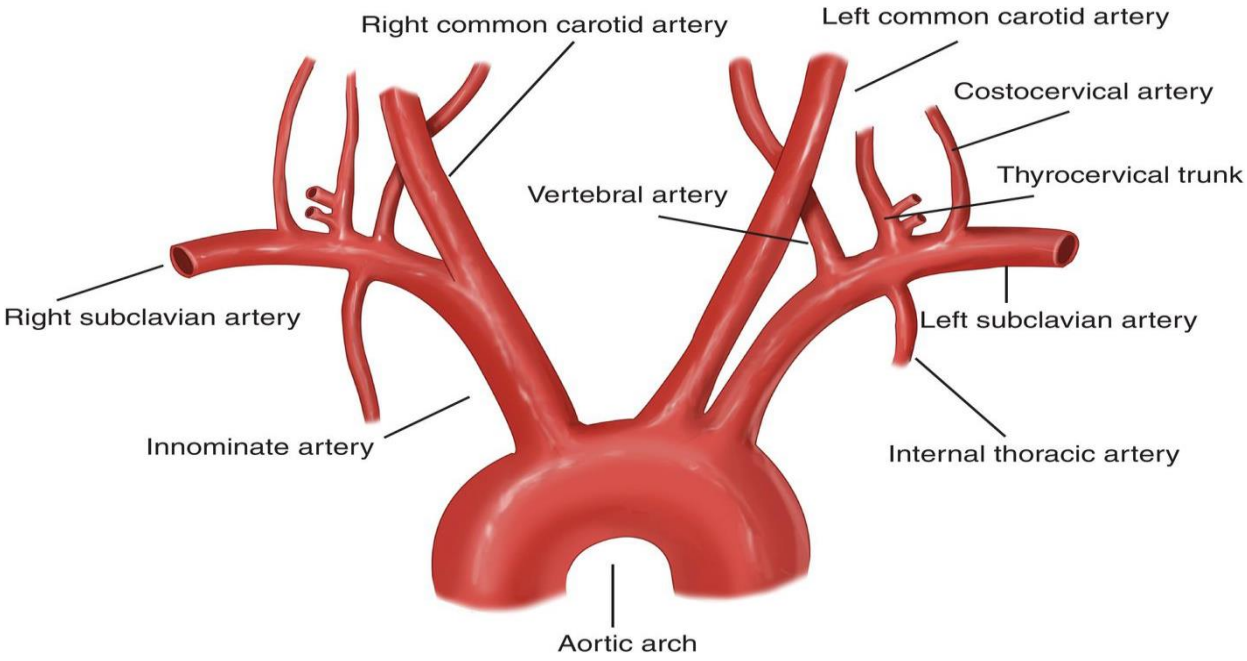
illustrated that an early invasive strategy was superior in preventing recurrent ischemia and reducing major bleeding complications. However, this protective impact of early invasive therapy did not translate into any significant benefit in reducing mortality or major cardiovascular events[59]. A very recent updated meta-analysis of all the 10 RCTs conducted to date on this subject showed that patients undergoing an early invasive strategy have less recurrent ischemia or refractory angina but no overall survival benefit in reducing mortality and adverse cardiovascular events [60]. The confidence intervals around estimates of mortality and myocardial infarction were very wide despite the fact that 3 more trials (almost 1,000) were added in the latest meta-analysis. This is an important limitation of current literature highlighting the fact that randomised trials have so far failed to provide a conclusive answer to the question of whether one strategy is better than other. In conclusion, the currently available evidence does not provide definitive evidence around the optimal timing of performing an invasive strategy in patients admitted with NSTEMI.

2.3.4 *Procedural aspects of the invasive strategy*

Transradial and transfemoral access are the two commonest access sites used in the performing CA and PCI. In transradial access, the operator punctures the radial artery in the wrist of the patient to get access to coronary arteries whereas, in transfemoral access, one of the femoral arteries is used as an access site. The radial artery is much smaller in diameter and easily compressible against the distal radius bone, hence much easier to achieve haemostasis and has lesser propensity to bleed compared to the femoral artery. The adoption of transradial access has increased significantly over the past decade and is certainly a default access site in many countries such as UK, Europe and many countries in Asia[61-63]. Data from randomised control trials and observational studies also show that transradial access is associated with reduced risk of major

adverse cardiac events, mortality, major bleeding, access site related complications[64-73]. However, transradial access is not without challenges such as difficult technique, longer learning curve, radial artery spasm and occlusion[74,75]. I have previously published a large meta-analysis of 68 studies summarising the incidence of radial artery occlusion in patients undergoing PCI[75]. The results showed that the rate of radial occlusion varied from <1% to 33% depending upon the timing of assessment of radial artery patency after the procedure. Nevertheless, once the radial artery is occluded, it precludes the use of radial access for any future intervention and the operator may need to perform the following procedure via the femoral artery. Given the aforementioned benefits of radial access over the femoral access, it is not only important to minimise the occurrence of radial artery occlusion but may also need to explore alternatives access site such as left radial access instead of switching to femoral access. Previous studies comparing the use of left radial access with right radial access report that use of left radial access may be associated with reduced procedure time, radiation dose and quicker learning[76-79]. This may be due to more favourable anatomy of subclavian artery on the left side compared to the right side. The right common carotid artery which supplies blood to the brain originates from the right innominate artery whereas on the left common carotid artery originates directly from the aortic arch as shown in Figure 2.5. Therefore, on the right side, the catheter needs to manipulated from the right subclavian artery into the innominate artery and aortic arch which requires more manipulation and an increased theoretical risk of plaque embolisation into the right common carotid artery which in return may also increase the risk of procedure-related stroke. It is plausible that using left radial access may result in reduced risk of procedure-related stroke compared to right radial access.

Figure 2.3 Illustration of arterial circulation of the aortic arch



2.4 Gaps in Evidence and rationale for thesis

NSTEMI is the commonest manifestation of ACS. An invasive strategy in the form of coronary angiography remains a gold standard investigation, to investigate the cause of NSTEMI and plan further management. Due to a large diversity in underlying pathophysiology, clinical presentation and risk of adverse events in patients presenting with NSTEMI, it is very difficult to tailor the use of an invasive strategy in these patients. Furthermore, due to changing population demographics, patients presenting with an NSTEMI are getting older, multimorbid and they are at increased risk of adverse events. There are several limitations of current literature which are summarised below,

1. There is a significant change in population demographics and comorbidity burden of the patients over the past decade. My previous work illustrates the rising burden of co-existing comorbidities in all patients presenting with ACS[9]. These changes in population demographics may relate to differences in receipt of an invasive strategy in different subgroups of patients admitted following NSTEMI. It is therefore important to study if there are any systematic biases in

the utilisation of an invasive strategy in particular subgroups of patients. This thesis will study the secular trends in the use of an invasive strategy based on age, gender, ethnicity, comorbidity burden and types of admitting hospital.

2. Despite the fact that the best treatment option for most patients with an NSTEMI is angiography guided revascularisation, regardless of the primary success of medical treatment, the optimal timing for the invasive strategy remains unclear and opinion remains divided amongst the interventional cardiology community. Current guidelines advocate different time points about the time of invasive angiography depending upon the patient's baseline risk on presentation.[3,4]. It is therefore important to study if there are any inequalities in the timing of an invasive strategy and whether the timing of invasive strategy is related to the baseline risk as defined by the guidelines in real-world practice. Further studies will also be framed to investigate if there is any relationship between the timing of invasive strategy and outcomes in patients with an NSTEMI in this thesis.
3. Availability of services is an important driver of the utilisation of resources. For instance, the presence of on-site cardiac catheter laboratory facilities has been noted to have a positive association with increased utilisation of invasive cardiac procedures. However, it is not known how different types of cardiac catheter facilities may influence the physician's decision making and use of an invasive strategy. It is also not known if these differences are associated with differences in outcomes in patients admitted with NSTEMI to hospitals with different types of cardiac catheter laboratory facilities.
4. Finally, despite the fact the radial access is the preferred the choice of access site in patients undergoing coronary angiography, there is limited regarding the association between choice of the radial access site and clinical outcomes.

Furthermore, in order to further increase the uptake of radial access and encourage

the best procedural practices in routine use of an invasive strategy, it is important to study the alternative access site in these patients. Therefore, the research question about whether the left radial access offers a similar procedural and clinical safety compared to right radial access will also be investigated in the thesis.

In summary, the main rationale for this thesis is to describe different patient, hospital and procedural factors influencing the use of an invasive strategy and how they are related to outcomes in the real world population admitted following an NSTEMI.

Chapter 3

Description of datasets and general methodology.

3.1 Introduction

This chapter describes each dataset utilised to study different aspects of invasive management of patients admitted with NSTEMI. Firstly, a brief description of the source of each dataset, the context in which information is collected in the dataset, type of coding system, description of variables used and strengths and limitations of the dataset. Secondly, an outline of the general methodology used in this thesis and an overview of statistical methods is described. As each chapter has its own specific aims and study material, full details of methods will be discussed specifically in the relevant section of subsequent chapters.

3.2 Study datasets

3.2.1 *Myocardial Infarction National Audit Project (MINAP) dataset*

Myocardial Infarction National Audit Project (MINAP) is a comprehensive national clinical database of patients hospitalised with an ACS in England and in Wales. Participation in the audit is mandated by the Department of Health for all National Health Service (NHS) acute hospitals in England and in Wales. Data are collected prospectively at each participating hospital and encrypted electronically before transfer to central database servers at the National Institute for Cardiovascular Research Outcomes (NICOR). It captures consecutive patients admitted with a diagnosis of an ACS across all the acute NHS hospitals in England and in Wales. MINAP amasses almost 85 000 episodes of patients with an overall sample size of close to a million records in 2018[41]. Data entry is subject to routine error checking such as range and consistency checks. In addition, a mandatory annual data validation exercise is conducted where participating hospitals are requested to re-enter data for 20 fields from 20 randomly selected patients using a data validation tool. The completeness of 20 key fields including the NHS number, patient's demographics, discharge diagnosis, hospital

mortality and secondary medication at discharge is closely monitored and is generally above 95%. In other fields, the completeness of data entry, as recorded in 2008, was generally over 80% and has been improving constantly since MINAP's inception[80].

All patients in the dataset are identified and tracked from their unique NHS number, which is pseudo-anonymised to protect the patient's identity. MINAP does not record patient's full postal address but does record other patient identifiers such as hospital numbers, dates of birth and postcodes area. These are encrypted before transmission to the central database. Researchers do not have access to the patient's sensitive data, and hospital identity is also strictly protected. However, age at the time of the index event is provided and eastings and northings of the centroid of the output area of residence, shared between one and 80 addresses, can be made available for geographical mapping with the necessary permissions.

The MINAP dataset contains 123 separate fields under the groups of; patient demographics, medical history mainly encompassing known cardiovascular risk factors, drug treatment before admission, admission method/route, clinical characteristics and important relevant cardiac investigations carried out whilst being in-patient, in-hospital drug treatments, primary reperfusion treatment details, interventional treatments, clinical complications, in-hospital outcomes, diagnosis on discharge and discharge (secondary prevention) treatments. Thus each entry provides a complete overview of the patient journey from the first contact to medical services, in-hospital treatment and discharge. Follow up data is not collected in the dataset and the linkage to the Office of National Statistics (ONS) for long term mortality is only available for audit purposes due to recent changes in data governance. Therefore, the outcome of interest will be restricted to in-hospital all-cause mortality, cardiac mortality, major bleeding and re-infarction complications. Ethical approval for using this dataset for research is not

required as secondary use of anonymised MINAP dataset for research purposes is authorised under the NHS research governance arrangements and further supported under section 251 of NHS act 2006 (NIGB: ECC1-06(d)/2011), which allows researchers to use patient information collected within the dataset for medical research without patient consent. The size and national reach of the MINAP registry underpin its value as an audit and research tool. The representativeness to the whole of England and Wales is a key strength and provides an excellent first time opportunity to study the invasive management of patients admitted with NSTEMI within the scope of this PhD. Using the detailed information around the time of admission, time of invasive procedures, patient clinical characteristics and risk profile, the association between the presence of onsite hospital cardiac catheterisation facilities and clinical outcomes were examined. Furthermore, the granularity of data around the patient's risk profile and laboratory results allowed to study implications of guidelines recommended risk stratification and timing of invasive management of patients admitted with an NSTEMI in a national cohort.

3.2.2 *British Cardiovascular Intervention Society (BCIS) dataset*

The BCIS dataset is an obligatory national audit, which collects information about almost every PCI procedure performed across all NHS hospitals in the UK. Although private hospitals are not obliged to participate in the registry, some of the private hospitals also contribute to the data collection. Overall, BCIS captures >99% PCI activity within UK[81]. All consecutive patients undergoing PCI for treatment of coronary artery disease are recorded in the dataset. The data collected in the BCIS registry have the same section 251 approval of NHS Act 2006 as MINAP, thus allowing the use of dataset for medical research and audit purposes without seeking patient consent. Full details about the data protection and security are available at

(www.ucl.ac.uk/nicor/patients/security). The audit project is funded by the central government through the Department of Health (DoH), however, the funding is now managed by the Healthcare Quality Improvement Partnership (HQIP). The logistic support, data monitoring and analysis are managed by a project manager along with a team of support staff, analyst and statisticians at NICOR under the supervision of an audit lead from BCIS[82].

All patients within the dataset are tracked by using their unique NHS number which is a unique 10-digit number issued to all patients registered within NHS, with an exception of Scotland where name and date of birth are used for tracking. Some other relevant patient identifiers such as date of birth, postcode, hospital number and present or past geographical location are also collected within the dataset. These identifiers are then encrypted before transmission to the central database. Although NICOR has access to these patient identifiers and is able to contact patients for audit and research purposes, these data fields are protected from access to researchers.

The BCIS registry is designed to collect data of all consecutive adults undergoing PCI for stable angina or ACS in the UK from time of admission to discharge. The information about diagnostic CA is not collected as the main aim of BCIS registry to improve the quality of PCI activity in the UK. There are approximately 113 variables in the BCIS dataset which collect information about patient's baseline demographics, presentation, important cardiovascular risk factors, previous cardiac intervention, indication for PCI, details about technical aspects of PCI, access site, pharmacology, operator details and any in-hospital adverse outcomes. In addition to in-hospital mortality, particular emphasis is placed on the recording of peri-procedural complications such as stroke, myocardial infarction, bleeding, access site related complications and stent thrombosis. BCIS endeavours to collect information about

every single PCI procedure undertaken in the United Kingdom and the nationwide participation from all NHS hospitals in the UK adds to its national representation[81]. With close to a million PCI procedure records in the dataset, the BCIS dataset offers a great opportunity for the researchers to study procedural aspects, access site practice and some of the rare complications of PCI procedures and compare treatments/ strategies in a different cohort of patients which will not be possible in a randomised control trial. I utilised these strengths of the BCIS registry to study the procedural aspects such as optimal access site strategy to perform PCI in patients admitted following ACS in the United Kingdom.

3.2.3 *National Inpatient Sample (NIS) dataset*

National Inpatient Sample also formally called the Nationwide Inpatient Sample (NIS) database is one of the largest publically available all-payer inpatient healthcare database in the United States. It is developed by Healthcare Cost and Utilization Project (HCUP)[83] and sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS contains information about the inpatient hospital stays which is gleaned from billing data submitted by hospitals to state-wide data organizations. This information in the inpatient data includes clinical and resource use information which can easily be derived from discharge level abstracts. NIS collects discharge level data from approximately 1000 hospitals, including 20% of all community hospitals in the US, with over 7 million unweighted hospital admissions added each year making it truly one the largest datasets of its kind worldwide. Discharge weights are used to determine national estimates and weighted data contains over 35 million hospital records representative of a large national sample. NIS is a publically available database with no identifiable patient, state or hospital level information; therefore, ethical approval is not

needed. However, HCUP requires a data user agreement and mandatory online training completion from all research applicants.

Each record within NIS contains granularity of information about patient demographics, ethnicity, primary payer, 29 Elixhauser comorbidity conditions, in-patient procedure information, in-hospital complications such as bleeding, stroke, cardiac complications, mortality, length of stay and cost on hospitalisation. The data elements are stored using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Additionally, HCUP has developed a Clinical Classification of Software (CCS) scheme which contains over 14,000 diagnosis and 3,900 procedure codes condensed into small categories. The CCS scheme is also based on ICD-9-CM codes, however, it enables the analysis of a much larger number of diagnosis or procedures more efficiently and accurately. For instance, all the ICD-9-CM codes for any type of in-hospital gastrointestinal bleeding are collapsed into a single CCS diagnosis code.

Although NIS contains comprehensive information around medical history, comorbidity burden, in-patient procedural treatment and in-hospital outcomes, it lacks information about pharmacology and lab results. Nevertheless, NIS offers an excellent opportunity to study secular trends, changes in patient's characteristics, comorbidity burden, invasive procedural aspects of patients admitted with a diagnosis of an NSTEMI in the United States over a decade.

3.3 Statistical methods

As described above, this thesis has used three different data sources and each chapter aimed to investigate a specific aspect of invasive management of patients admitted with the diagnosis of an NSTEMI. As each chapter has its own comprehensive details of relevant methods, therefore specifics of methods are not discussed here. Rather, this

chapter aims to describe an overview of the general methodology and different statistical methods used.

3.3.1 *Data cleaning*

Before starting the analysis of each dataset, I examined the data for completeness, accuracy and consistency, to identify the scope of and the limitations of data analysis. After evaluating descriptive statistics for each variable, erroneous values for individual data were checked by evaluating frequency distributions and checking lower and upper outliers for entries beyond the acceptable range. For instance, the age variable with age defined > 110 years or <18years were removed. Similarly, unknown gender was excluded. Any patients with duplicate admission during the study time period were excluded from the analysis to prevent survivorship bias both in MINAP and BCIS dataset analyses. However, as the NIS lack information on individual patient ID and merely represents records of each hospitalisation with ACS, individual patient level analyses were not done from NIS.

3.3.2 *Descriptive methods*

After the initial exploratory analyses and cleaning, the total number of admissions with a diagnosis of NSTEMI in each dataset were identified. Study variables were finalised based on literature search, prior clinical knowledge and supervisory team input.

Data for continuous variables were presented as either means (with standard deviation) if normally distributed or medians with interquartile ranges if not normally distributed. To assess the normality of the continuous data, distribution curves and quantile-quantile (QQ) plots were used. Similarly, categorical or ordinal variables are reported as numbers and percentages. Where the interest lay in comparing the two means, student's t-tests were used for normally distributed continuous variables based on the assumption

that observations are normally distributed with equal variance[84,85]. However, when observations were not normally distributed or with equal variance, Mann Whitney or Wilcoxon Rank sum tests were used[84,85]. In the instance of comparing more than two groups, one-way analysis of variances (ANOVA) for normally distributed data was used whereas or when data was not uniformly or normally distributed Kruskal-Wallis tests were used.

The categorical variables were compared using Pearson's Chi-Squared test. Due to the large sample size, clinically important effects and association rather than sole statistical significant p values were described[86].

3.3.3 *Framework for dealing with missing data*

Following on from descriptive analysis, multivariable models were developed to predict the outcomes of interest based on the aims and objectives of each study chapter. It is, however, important to deal with the missing data. Therefore, the missing data for each variable has been reported in the relevant section of each chapter with a consideration of whether there are significant variations based on outcome variables. In order to deal with the missing data, multiple imputations using chained equations (MICE) were used, wherein all variables used in the analytic models, as well as the outcomes of interest, were included. Patient age, gender, exposure and outcomes variables were included in the MICE after removing missing information. Multiple imputation techniques are used to account for the missing data and protect against the biases arising from missing data[87,88]. One of the fundamental assumptions of multiple imputations is that the data are missing at random (MAR)[87] which were examined by using data distributions curves of each variable included in the analysis. Although levels of missingness are high for certain variables, it has been previously shown that multiple imputation frameworks are robust even when levels of missingness are extremely high, while they

can offer some protection when data are missing not at random (MNAR)[89]. During this process, missing values in each variable were replaced with predictions from multiple imputation model plus a random error by using multivariable regression models. Overall, three different types of models namely logistic regression for binary variables, linear regression for continuous variables and ordinal or multinomial logistic regression for ordinal variables were used. Ten imputed datasets were generated in this process. Full details of variables and models are discussed in the methodology of the relevant chapters. In the instances where missing information was very low, complete case analyses were undertaken as a sensitivity analysis to confirm the findings.

3.3.4 *Modelling strategy*

In this thesis, the study outcomes were binary therefore multivariable logistic regression models were used to study the associations between exposure variables and study outcomes. Firstly, data quality, distribution, missingness, prior clinical knowledge and prognostic relevance of each variable was used to determine model covariates. All variables were included in the models in order to fully adjust for all potential confounders This method is widely recommended and practised in conducting large scale epidemiology studies[90,91]. However, as a sensitivity analysis, a backward stepwise approach was used where a non-significant variable was removed from the model at a time to reach a final model and the final results were compared with the first full model. The goodness of fit for each model was assessed using the area under the curve and likelihood ratio tests[92]. Multi-collinearity between the variables was assessed using Variance Inflation factors. All results are reported as odds ratios (OR) along with their associated 95% confidence intervals and p values. More specifics of study design, statistical approaches and methods are discussed in the relevant chapters.

Chapter 4

Utilisation of an invasive strategy in the management of Non-ST Elevation Acute Myocardial Infarction

4.1 Introduction

This chapter addresses the first research question set in part one of the thesis by investigating the patient's level factors associated with the use of invasive strategy. The findings from this chapter were published in the Scientific Reports- Nature journal (impact factor 4.12)[93].

NSTEMI including unstable angina is estimated to account for almost two-thirds of the total hospital admissions for ACS in the United States and Europe[94-97]. Although patients with the STEMI have a worse prognosis in the short term, the long-term outcomes of NSTEMI are worse [20,98-100]. The most likely explanation for this is an ageing population, increased burden of comorbidities and variation in the use of an early invasive strategy in this cohort of patients[9,21,101,102]. Consequently, despite improvements in treatments and the provision of guideline-recommended care, NSTEMI remains the most vulnerable phenotype of ACS.

As described in the introduction chapter (1.0) of this thesis, an invasive strategy in the form of CA is an important tool to diagnose the extent and severity of obstructive coronary artery disease and enable treatment of the underlying lesions that has contributed to the NSTEMI through PCI or CABG surgery. Guidelines from national bodies emphasise the use of an invasive strategy in patients presenting with an NSTEMI particularly in clinically unstable or high-risk patients[4,103] with data from observational and randomised control trials forming the evidence basis of improved outcomes in patients receiving an early invasive strategy[57,104-106].

Despite the established benefit of an early invasive strategy in this cohort, significant variations in the utilisation of an invasive strategy both at regional and national level remain[107,108]. These variations may be related to hospital level factors such as the

availability of cardiac catheterisation laboratory facilities (which will be explored further in chapter 7.0 of this thesis) or patient level factors. The decision to undertake an invasive strategy followed by revascularisation requires careful consideration of the patient's baseline risk profile and coexisting comorbidities[3,4]. In order to answer the first research question as set out in part 1 of this thesis, it is important to investigate how the patient's baseline risk profile and coexisting comorbidities have changed over time, and in particular how these are related to the utilisation of an invasive strategy in the management of patients admitted with an NSTEMI in a real-world setting.

4.2 Objectives

The main objectives of this chapter are to study

I. Overall secular trends in utilisation of an invasive strategy in a national cohort of patients admitted with a diagnosis of an NSTEMI in the United States.
II. Investigate the receipt of an invasive strategy in contemporary practice in different subgroups of patients stratified according to age, sex, ethnicity, and comorbidity burden and hospital characteristics.
III. Compare the characteristics of patients receiving an invasive strategy to those receiving medical management and how these have changed over time.
IV. Examine the independent predictors of receipt of an invasive strategy.
V. Study the association between use of an invasive strategy and in-hospital clinical outcomes.

4.3 Methods

National Inpatient Sample (NIS) dataset was used for this study. Full details about the NIS dataset are already described in chapter 3.

4.3.1 *Study design*

This study is a retrospective cohort study of the prospectively collected NIS dataset.

4.3.2 *Study population*

Within NIS dataset, all patients admitted with a diagnosis of an NSTEMI age >18years between 1st January 2004 to 31st December 2014 were included in the study. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of 4111 and 4107 were used to identify all admissions with a primary diagnosis of an NSTEMI during the study period. Patients admitted with the records of elective admission were excluded as these are unlikely to represent a true diagnosis of an NSTEMI. Elective admissions were also excluded as they were likely to be patients admitted for a different diagnosis or procedure electively and then they may have had a diagnosis of NSTEMI whilst as an inpatient. A typical example of this would be a patient admitted for elective knee arthroscopy and who may have suffered from an NSTEMI. These records don't represent the patients admitted with a primary diagnosis of an NSTEMI and are likely to confound the analysis. This approach has been utilised in previous studies using NIS for research about ACS[109-113]. Similarly, the diagnosis field was only limited to primary diagnosis within the NIS dataset to represent the true diagnosis of NSTEMI. These inclusion criteria were rationalised on the basis of previous studies using the NIS database and Agency of Healthcare Research and Quality (AHRQ) recommendations[83,114-119].

4.3.3 *Study outcomes*

The main outcomes of interest were in-hospital all-cause mortality, Major Adverse Cerebrovascular Complications (MACCE), adverse cardiac complications, major bleeding, and any vascular complications. Adverse cardiac complications were a composite of cardiac tamponade, pericardiocentesis, iatrogenic cardiac complication requiring emergency coronary artery bypass graft (CABG) surgery and hemopericardium. Major bleeding was a composite of gastrointestinal, retroperitoneal,

intracranial or unspecified haemorrhage, and requirement of blood transfusion. Vascular complications were defined as procedure-related vascular injury. MACCE was a composite of acute ischemic stroke, in-hospital mortality and adverse cardiac complications. All complications were identified using ICD-9-CM codes in any of the secondary diagnosis fields within the NIS database (Table 4.1). The ICD-9-CM codes utilised in this study were based on a thorough literature search of previous studies using NIS dataset[10,114,116,120-126]. In order to maximise the capture of accurate codes, all the clinical conditions extracted from NIS dataset were also searched in the ICD-9-CM database at www.findacode.com to look for any additional unpublished codes. After extracting the information from the NIS database using these codes, the estimates for all main conditions such as diagnosis of NSTEMI were matched with national discharged estimates published at AHRQ website (https://www.ahrq.gov/).

Table 4.1 ICD-9-CM codes used for driving post procedural complications

Post-procedural Complication	ICD-9-CM or CCS codes
Bleeding complication	
Gastrointestinal	CCS 153
Unspecified haemorrhage	459.0
Retroperitoneal haemorrhage	568.81, 998.1
Intracranial haemorrhage	430-432x
Post-op haemorrhage requiring transfusion	99.0 (procedure)
Blood transfusion	V58.2
Vascular complications	
Vascular injury	900-904, 998.2, 447, 868.04, 999.7 (diagnosis) 39.31, 39.41, 39.49, 39.52, 39.53, 39.56 - 39.59 39.79 (procedure)
Cardiac complications	
Iatrogenic cardiac complications	997.1
Pericardial complications	423.0, 423.3 (diagnosis) 47.0 (procedure)
Coronary artery dissection	414.12

Requiring CABG surgery	36.1x, 36.2, 36.31, 36.32, 36.9x

CABG= coronary artery bypass graft surgery

4.3.4 *Study covariates*

Use of an invasive strategy was derived from procedure codes provided in the NIS dataset. NIS captures up to 15 procedure codes in the dataset. Invasive strategy in the form of CA was defined as ICD-9-CM procedure codes 88.53, 88.54, 88.55, 88.56 37.22 and 37.23, with or without PCI (ICD-9-CM procedure codes 00.66, 360.1, 360.2, 360.5, 360.6 and 360.7[114,124-128]. Data regarding patient baseline demographics including age, sex, race, primary expected payer, admission day of the week and cardiovascular risk factors (known coronary artery disease (CAD), family history of premature CAD, smoking, dyslipidaemias, previous myocardial infarction (MI), history CABG, previous PCI, previous stroke or transient ischemic attack) and chronic hypertension were also collected. The ICD-9-CM codes or clinical classification software (CCS) codes used to identify any additional comorbidities are provided in Table 4.2.

Table 4.2 List of the ICD-9-CM and clinical classification software (CCS) codes used for identifying additional comorbidities

Comorbidities	Source	Codes
Dyslipidaemias	CCS	53
Coronary artery disease	ICD-9-CM	414.00-414.07
Family history of IHD	ICD-9-CM	V17.3
Previous stroke or transient ischemic attack	ICD-9-CM	V12.54x
Previous CABG	ICD-9-CM	V45.81x
Previous PCI	ICD-9-CM	V45.82x
Cardiogenic	ICD-9-	785.51

shock	CM	
Use of inotropic agents	ICD-9-CM	00.17
Use of inotropic assist device	ICD-9-CM	376, 97.44
Smoking	ICD-9-CM	V15.82, 305.1
Dementia	ICD-9-CM	290.xx,294.1x,294.2x,294.8,331.0,331.12,331.82,797

IHD= ischemic heart disease, CABG= coronary artery bypass graft, PCI= percutaneous coronary intervention

The overall comorbidity burden was defined as per the Charlson Comorbidity Index (CCI) which was determined using information from 29 Elixhauser comorbidities as defined by AHRQ in the NIS[129]. The CCI is a recognized measure of comorbidity burden and quantifies the prognostic impact of 22 comorbid conditions based on their number and individual prognostic impact by means of a score[130]. It is a useful tool for estimating prognosis in patients with multiple co-existing illnesses. CCI was derived using a point-based system with scores ranging from 1 to 6, with each value weighted depending on the prognostic impact of the comorbidity[130]. These scores were then summated to classify overall comorbidity burden into mild, moderate and severe categories with CCI score of 0,1,2 and 3 or more respectively[131,132] (Table 4.3).

Table 4.3 Deyo's modification of Charlson's comorbidity index (CCI)

Reported ICD-9 codes	Condition	Charlson score
412	Previous myocardial infarction	1
428 – 428.9	Congestive heart failure	1
433.9, 441 – 441.9, 785.4 V43.4	Peripheral vascular disease	1
V12.54, 438.x	Previous cerebrovascular disease	1
290 – 290.9	Dementia	1
490 – 496, 500 –505, 506.4	Chronic pulmonary disease	1
710.0, 710.1, 710.4, 714 – 714.2, 714.81, 725	Rheumatologic disease	1

531 – 534.9	Peptic ulcer	1
571.2, 571.5, 571.6, 571.4 – 571.49	Mild liver disease	1
250 – 250.3, 250.7	Diabetes	1
250.4 – 250.6	Diabetes with chronic complications	2
344.1, 342 – 342.9	Hemiplegia or paraplegia	2
582 – 582.9, 583 – 583.7, 585, 586, 588 – 588.9	Renal Disease	2
140 – 172.9, 174 –195.8, 200 – 208.9	Any malignancy including leukaemia and lymphoma	2
572.2 – 572.8	Moderate or severe liver disease	3
196 – 199.1	Metastatic solid tumour	6
042 – 044.9	Acquired immune deficiency syndromes (AIDS)	6

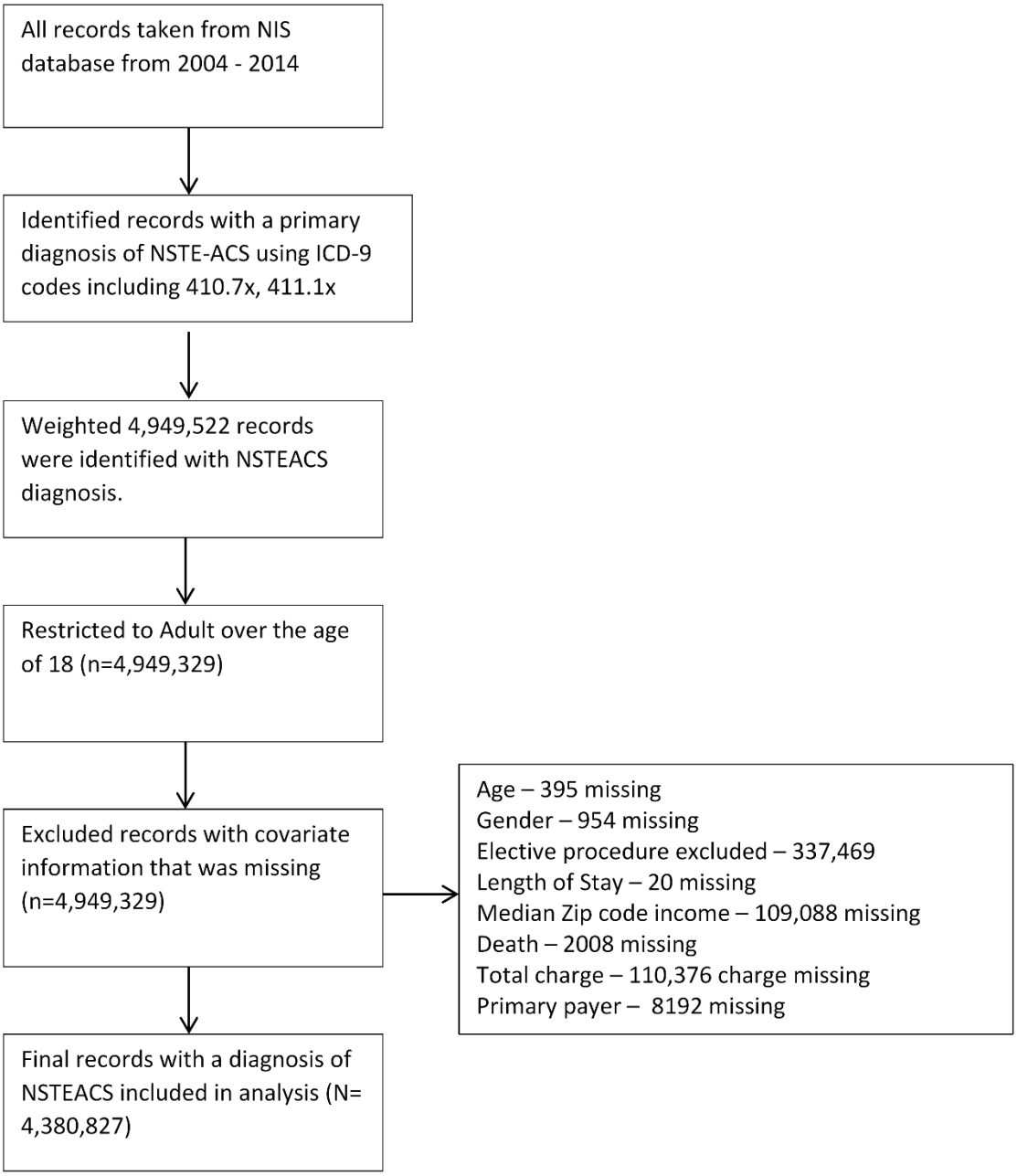
Finally, data regarding the hospital characteristics including the bed size, location, region and teaching status were also collected. The hospital bed size within NIS are defined using different regions of the US and ranges from 1-249 beds for a small hospital, 25-449 for a medium hospital and 50+ to 450+ for a large size hospital.

4.3.5 *Statistical analysis*

All statistical analyses were conducted using Stat 14.0 (College Station, Texas, USA). Complete case analysis strategy was used in this study as the missing information in the study variables were less than 3%. Given the overall sample size of close to 4.3 million patients, it was felt that using multiple imputations to account for a small proportion of patients with missing data information is unlikely to change the findings. Records with missing information on the age (n=395), gender (n=954), length of stay (n=20), Median Zip code (n=109,088) and in-hospital mortality (n=2008) were excluded. The total number of records which were excluded from the main analysis were only n=112,465 which is approximately 2.3% of the total sample size. The elective admissions were not

excluded due to missing information but due to the reason explained above (elective admissions are unlikely to represent true admissions with NSTEMI). (Figure 4.1).

Figure 4.1 Flow diagram of included/excluded records



Descriptive statistics were used to compare differences in baseline demographics, hospital characteristic and crude outcome rates of patients who received an invasive strategy compared to those managed medically. For all analyses, the survey estimation

commands were used (by using the svy prefix in analyses conducted in Stata), this followed the recommendations from AHRQ for analysis of survey data to account for the complex survey design of the NIS database. The use of sampling weights is required because the design of the study means that different observations may have different probabilities of selection. Due to records being sampled by hospitals rather than individuals, clustering of records within hospitals was taken into account in the survey estimation. This was done by defining each hospital to be the primary sampling unit. For calculation of national estimates and correct variances, sampling weights for each individual discharge that were provided by the AHRQ were used.

Continuous variables were reported as median and interquartile ranges to account for the skewness of data. Categorical variables were presented as a number and a percentage. Chi-square and t-tests were used to determine the statistical difference between patients who received an invasive strategy compared to those who were managed medically for categorical or continuous variables respectively, while the "nptrend" package was used to assess the statistical significance of changes in the trend across ordered groups. Multivariable analyses were undertaken to determine the association between the use of an invasive strategy and outcomes of interest. Logistic regression models were fitted using maximum likelihood estimation and were adjusted for all potential and measured confounders including age, sex, year of procedure, 29 Elixhasuer comorbidities, ethnicity, median income, weekend/weekday admission, cardiovascular risk factors and hospital characteristics. In order to better control for any differences in the baseline characteristics of the patients in the two groups, a sensitivity analysis using the propensity score matching was conducted. The average treatment effects (ATE) were calculated using the "teffects" package and included all the variables as described in the multivariable logistic regression models. Full details of

multivariable logistic and propensity score matching algorithm have been described in the methodology (chapter 3).

4.4 Results

4.4.1 *Patient and hospital characteristics*

A total of 4,380,827 patients were admitted with a primary diagnosis of an NSTEMI between 2004 and 2014 out of which 2,518,704 (57.5%) received an invasive strategy as an in-patient. Baseline difference between patients receiving an invasive strategy compared to those managed medically are presented in Table 1. Patients receiving an invasive strategy, in general, were younger (median age 65 vs 72 years, p<0.001), had worse cardiovascular profile such as history of smoking (37.9% vs 22.4%, p<0.001), dyslipidaemia (56.4% vs 37.5%, p<0.001), previous history of PCI (11.5% vs 7.7%, p<0.001) and IHD (81.7% vs 42.6%, p<0.001). Conversely, medically managed patients were more likely to be female (51.3% vs 39.3%, p<0.001), had higher proportions of co-existing comorbidities as defined by CCI (CCI ≥3 53.9% vs 46.1%, p<0.001) and were likely to be admitted on weekend (26.8% vs 25.0%, p<0.001). Patients admitted to a small hospital were more likely to be medically managed (16.3% vs 8.0%, p<0.001), compared to the patients admitted to large hospitals who were more likely to receive an invasive strategy (70.3% vs 55.4%, p<0.001). Similar trends were noted based on the location/teaching status of the hospitals where patients admitted to rural hospitals were more likely to be medically managed (18.0% vs 6.6%, p<0.001) and patients admitted to urban teaching hospitals had higher rates of receipt of an invasive strategy (54.4% vs 34.8%, p<0.001). Medically managed patients had higher unadjusted in-hospital mortality (6.6% vs 1.9%, p<0.001) and bleeding complications (11.9% vs 10.7%, p<0.001). However, patients receiving an invasive strategy had higher rates of procedure related vascular (1.4% vs 0.3%, p<0.001) and cardiac complications (2.1% vs

0.5%, p<0.001). The median length of stay was similar in both groups (3 (IQR 2-6) days)) whereas receipt of the invasive strategy was associated with greater costs compared to medically managed patients. (Median total charge $51433 (IQR $31694-$85583) vs $18078 (IQR $9841-$34417)).

Table 4.4 Baseline characteristics of patients receiving medical management compared to those receiving an invasive strategy

	Patients receiving medical management	**Patients receiving invasive strategy**
Number of Cases weighted (%age)	1,862,123 (42.5%)	2,518,704 (57.5%)
Age (year), Median IRQ)	72 (63-85)	65 (46-75)
Men %	49.7%	61.7%
Ethnicity		
White	63.2%	63.3%
Black	10.0%	9.0%
Hispanic	6.4%	6.2%
Asian/Pacific Islander	1.8%	1.6%
Native American	0.4%	0.5%
Other	2.2%	2.7%
Missing Race	16.0%	16.7%
Weekend admission	26.8%	25.0%
Primary expected payer, %		
Medicare	72.2%	53.3%
Medicaid	5.7%	6.6%
Private Insurance	16.2%	30.3%
Self-pay	3.6%	6.2%
No charge	0.3%	0.7%
other	1.9%	2.9%
Median Household Income (percentile)		
0-25th	30.2%	29.2%
26-50th	27.0%	27.7%
51-75th	22.7%	23.9%
76-100th	20.1%	19.2%
Comorbidities, %		
Dyslipidaemia	37.5%	56.4%

Smoking	22.4%	37.9%
Previous AMI	9.5%	9.4%
Previous PCI	7.7%	11.5%
Previous CABG	10.1%	5.8%
Previous CVA	4.0%	3.1%
Family history of CAD	3.7%	8.0%
Valvular heart disease	0.4	0.1
Peripheral vascular disease	11.9%	11.9%
Use of assist devise or IABP	0.5%	4.2%
Shock	2.2%	2.6%
AIDS	0.12%	0.13%
Alcohol abuse	2.4%	2.9%
Deficiency anaemias	20.3%	13.2%
Chronic Blood loss anaemia	1.6%	0.8%
RA/collagen vascular diseases	2.4%	2.2%
Congestive heart failure	1.3%	0.5%
Chronic pulmonary disease	25.4%	20.6%
Coagulopathy	4.4%	4.2%
Depression	7.8%	6.8%
Diabetes	30.1%	30.3%
Diabetes with complications	7.5%	6.1%
Drug abuse	1.8%	2.2%
Hypertension	68.2%	70.9%
Hypothyroidism	12.6%	9.4%
Liver disease	1.4%	1.2%
Lymphomas	0.7%	0.4%
Fluid and electrolyte disturbances	25.1%	16.1%
Other neurological disorders	9.1%	4.0%
Obesity	9.1%	14.6%
Paralysis	2.6%	1.2%
Psychoses	2.7%	1.9%
Pulmonary circulation disorder	0.2%	0.06%
Renal failure (chronic)	24.8%	15.0%
Peptic ulcer disease	0.05%	0.04%
Weight loss	3.2%	1.5%

Solid tumour without Mets	2.0%	1.1%
Metastatic cancer	1.5%	0.4%
Dementia	12.9%	2.5%
Charlson Comorbidity Index		
0	23.0%	34.5%
1	31.5%	32.8%
2	24.6%	19.5%
≥3	20.9%	13.1%
Hospital bed size		
Small	16.3%	8.0%
Medium	28.3%	21.7%
Large	55.4%	70.3%
Hospital Region		
Northeast	25.8%	17.9%
Midwest	20.1%	24.4%
South	38.8%	42.4%
West	15.2%	15.3%
Location/ Teaching status		
Rural	18.0%	6.6%
Urban-non teaching	47.2%	39.0%
Urban- teaching	34.8%	54.4%
Length of stay, Median (IQR)	3 (2-6)	3 (2-6)
Total charge,$, Median (IQR)	18078 (9841-34417)	51433 (31694-85583)
Bleeding complications	11.9%	10.7%
Vascular complications	0.3%	1.4%
Cardiac complication	0.5%	2.1%
In-hospital mortality	6.6%	1.9%

IQR=interquartile range, AIDS= acquired immunodeficiency syndrome, AMI=acute myocardial infarction, CVA= cerebrovascular accident, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CAD= coronary artery disease, IABP= intra-aortic balloon pump, RA= rheumatoid arthritis.

4.4.2 *Temporal trends*

There was a significant increase in the utilisation of an invasive strategy from 48.5% in 2004 to 65.1% (P_{trend} <0.001) in 2014 (Figure 4.2). PCI procedures performed in this population increased from 23.5% in 2004 to 35.3% (p trend<0.001) in 2014, whilst

CABG procedures declined from 8.6% to 7.7% during the same period (P_{trend} <0.001) (Figure 4.3).

Figure 4.2 Temporal trends in utilisation of an invasive strategy from 2004-2014.

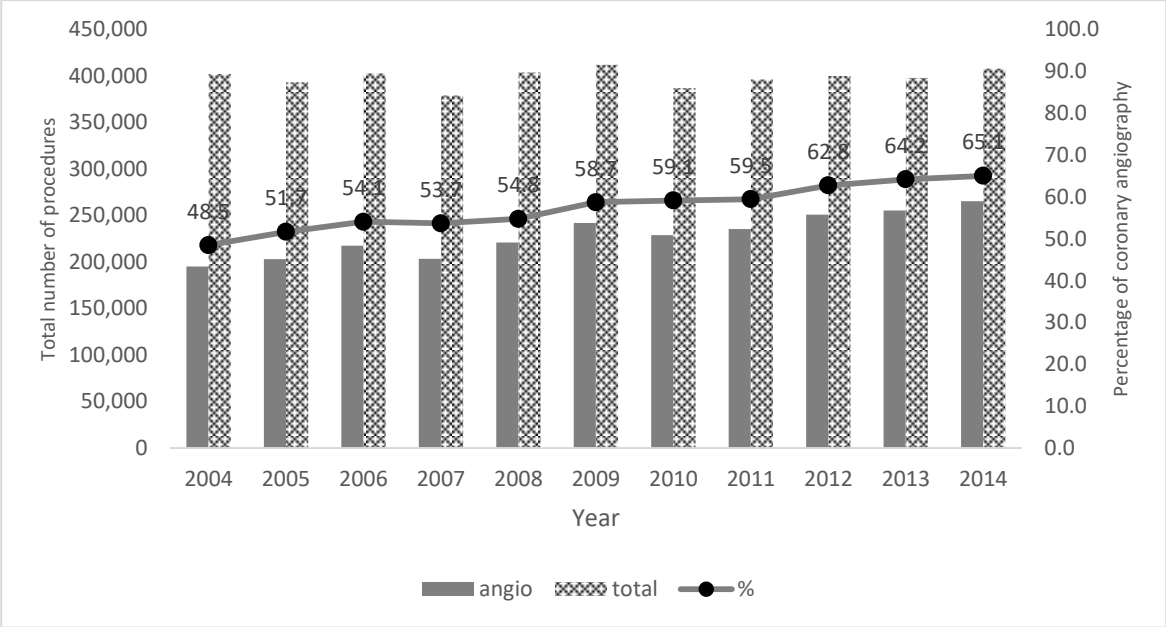


Figure 4.3 Temporal trends in utilisation of invasive strategy, percutaneous coronary intervention and coronary artery bypass procedures from 2004-2014

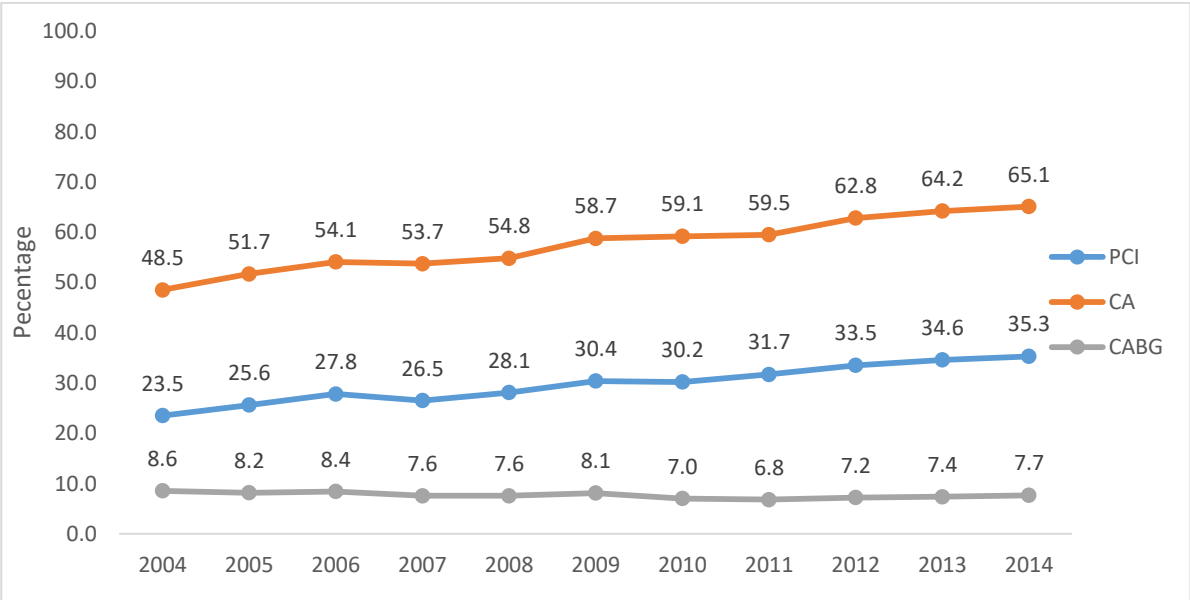


Table 4.5 and 4.6 present the temporal changes in baseline demographics and hospital characteristics, comorbidities and crude outcomes in patients receiving an invasive strategy and those who were medically managed respectively. The prevalence of risk

factors for coronary artery disease such smoking, dyslipidemia, previous AMI, previous PCI, hypertension, previous CABG and peripheral vascular disease has increased in both groups however a greater proportional increase was observed in the invasive strategy group from 2004 to 2014. Patients receiving an invasive strategy were consistently younger and less comorbid across all years compared to medically managed patients. Crude in-hospital mortality decreased from 2.2% in 2004 to 1.9% (P_{trend} <0.001) in 2014. Conversely, in addition to increasing age, a greater proportional increase in the non-cardiac comorbidities was observed in medically managed patients. For instance, the prevalence of renal failure increased from 10.8% to 34.0%, (P_{trend}<0.001) and prevalence of dementia increased from 8.9% to 15.4%, (P_{trend}<0.001) during the study period.

The unadjusted in-hospital mortality decreased from 2.2% in 2004 to 1.9% in 2014, (P_{trend} <0.001) in patients receiving invasive strategy, whilst it remained static in the medically managed group during the study period (6.8% to 6.7%, P_{trend} =0.84).

Table 4.5: Demographics of patients receiving invasive strategy for each year included in the study, from 2004 – 2014.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of records	195,071	203,011	217,748	203,537	221,160	241,979	228,890	235,603	251,015	255,390	265,300
Age (year), Median IRQ	66 (56-76)	66 (55-76)	65 (55-76)	65 (55-76)	65 (55-76)	65 (55-75)	65 (55-75)	65 (56-75)	65 (56-75)	65 (56-75)	66 (56-75)
Men %	60.1%	61.3%	61.5%	61.0%	61.0%	61.5%	61.7%	61.8%	62.1%	62.5%	62.5%
Ethnicity											
White	56.4%	58.1%	55.8%	54.5%	59.4%	62.3%	65.4%	66.4%	70.8%	70.3%	71.0%
Black	7.3%	5.6%	7.1%	8.0%	7.8%	8.2%	10.6%	10.5%	10.7%	10.6%	10.6%
Hispanic	4.8%	5.7%	5.8%	5.6%	5.3%	5.9%	6.4%	6.6%	7.0%	7.7%	7.4%
Asian/Pacific Islander	1.1%	1.2%	1.1%	1.6%	1.6%	1.6%	1.7%	1.6%	1.8%	2.0%	2.0%
Native American	0.2%	0.3%	0.3%	0.6%	0.9%	0.5%	0.8%	0.4%	0.6%	0.4%	0.5%
Other	2.0%	2.5%	2.7%	2.2%	3.1%	3.0%	2.1%	3.1%	3.3%	2.8%	2.9%
Missing Race	28.2%	26.6%	27.2%	27.3%	21.8%	18.5%	13.1%	11.4%	5.8%	6.2%	5.5%
Weekend admission	24.0%	24.4%	24.2%	24.3%	25.0%	24.7%	25.7%	25.7%	25.0%	25.9%	25.6%
Primary expected payer											
Medicare	53.3%	54.0%	52.2%	51.9%	51.7%	52.2%	51.8%	54.5%	54.7%	55.0%	55.0%
Medicaid	5.7%	6.1%	5.7%	5.5%	6.1%	6.1%	7.2%	6.9%	6.9%	6.9%	8.8%
Private Insurance	32.8%	31.8%	32.8%	32.5%	32.3%	30.2%	30.7%	28.5%	27.5%	27.2%	27.8%
Self-pay	5.0%	5.2%	5.4%	6.0%	6.0%	6.8%	6.8%	6.4%	7.0%	7.0%	5.2%
No charge	0.6%	0.6%	0.7%	0.7%	0.6%	0.6%	0.5%	0.7%	0.6%	0.8%	0.6%

other	2.6%	2.4%	3.0%	3.4%	3.3%	3.1%	3.0%	2.9%	3.2%	3.1%	2.5%
Median Household Income (percentile											
0-25th	26.4%	28.3%	26.4%	28.2%	28.3%	28.8%	31.1%	29.5%	32.1%	30.7%	30.3%
26-50th	28.1%	26.2%	26.6%	27.3%	29.4%	28.9%	28.0%	26.0%	26.5%	27.7%	29.5%
51-75th	23.3%	25.6%	25.1%	24.1%	22.9%	24.3%	23.2%	25.8%	22.8%	23.6%	22.5%
76-100th	22.2%	19.9%	21.9%	20.4%	19.3%	18.0%	17.7%	18.7%	18.6%	18.0%	17.7%
Comorbidities, %											
Dyslipidaemia	46.7%	48.6%	50.4%	53.1%	54.3%	56.9%	58.7%	60.7%	61.5%	62.1%	61.8%
Smoking	27.8%	30.7%	32.0%	33.8%	35.1%	38.6%	39.1%	40.9%	42.7%	44.1%	46.7%
Previous AMI	7.8%	7.6%	8.1%	8.3%	8.5%	9.4%	9.7%	10.4%	10.8%	11.0%	11.4%
History of IHD	80.8%	80.5%	80.6%	80.4%	82.0%	83.3%	82.3%	83.1%	82.3%	81.6%	81.0%
Previous PCI	7.3%	7.7%	8.9%	9.4%	10.0%	11.3%	12.2%	13.7%	13.8%	14.4%	15.3%
Previous CABG	5.6%	5.3%	5.3%	5.1%	5.4%	5.5%	5.6%	6.3%	6.2%	6.3%	6.5%
Previous CVA	No data	No data	No data	0.5%	2.8%	3.8%	4.2%	4.9%	4.7%	5.2%	5.5%
Family history of CAD	5.0%	6.4%	5.9%	6.5%	6.8%	8.2%	9.4%	9.2%	9.3%	9.7%	10.0%
Valvular heart disease	0.2%	0.2%	0.2%	0.1%	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%
Peripheral vascular disease	9.7%	9.5%	10.6%	11.6%	12.1%	12.6%	11.5%	13.1%	12.8%	13.0%	13.1%
Use of assist devise or IABP	4.1%	4.4%	4.0%	4.1%	4.5%	4.3%	4.2%	4.2%	4.3%	3.9%	3.9%
Shock	1.8%	2.0%	2.1%	2.1%	2.5%	2.7%	2.7%	3.0%	2.9%	2.9%	3.2%
AIDS	0.1%	0.1%	0.13%	0.13%	0.11%	0.16%	0.14%	0.16%	0.12%	0.14%	0.14%

Alcohol abuse	2.3%	2.3%	2.7%	2.7%	2.8%	2.9%	3.2%	3.1%	3.2%	3.3%	3.4%
Deficiency anaemias	8.9%	9.3%	10.0%	12.2%	13.5%	14.2%	13.9%	15.8%	15.0%	14.9%	14.9%
Chronic Blood loss anaemia	1.1%	1.1%	1.1%	1.2%	1.0%	1.0%	0.7%	0.7%	0.7%	0.6%	0.6%
RA/collagen vascular Diseases	1.6%	1.8%	1.9%	2.0%	2.2%	2.2%	2.2%	2.5%	2.4%	2.6%	2.6%
Congestive heart failure	0.7%	0.6%	0.6%	0.4%	0.4%	0.5%	0.6%	0.5%	0.5%	0.4%	0.4%
Chronic pulmonary disease	18.7%	20.1%	20.2%	20.9%	20.1%	20.5%	19.8%	21.1%	21.4%	21.4%	21.8%
Coagulopathy	3.1%	3.2%	3.2%	3.3%	3.6%	4.2%	4.5%	5.1%	5.0%	5.3%	5.2%
Depression	4.0%	4.6%	5.0%	5.5%	6.3%	6.8%	7.2%	7.8%	8.3%	8.4%	8.7%
Diabetes	26.7%	26.5%	27.8%	28.3%	29.7%	30.0%	30.6%	32.2%	32.8%	33.2%	33.2%
Diabetes with complications	4.5%	4.8%	4.9%	5.6%	5.6%	5.8%	6.1%	6.8%	7.1%	7.3%	7.7%
Drug abuse	1.3%	1.5%	1.9%	2.1%	1.9%	2.0%	2.2%	2.4%	2.5%	2.7%	2.8%
Hypertension	62.0%	62.6%	66.2%	67.1%	70.0%	70.9%	72.6%	74.6%	75.5%	76.5%	77.2%
Hypothyroidism	6.9%	7.1%	7.4%	8.3%	9.1%	9.5%	9.5%	10.7%	10.8%	11.0%	11.5%
Liver disease	0.7%	0.8%	0.8%	1.0%	1.1%	1.1%	1.2%	1.3%	1.5%	1.5%	1.8%
Lymphomas	0.4%	0.4%	0.4%	0.4%	0.5%	0.4%	0.4%	0.5%	0.5%	0.5%	0.5%
Fluid and electrolyte disturbances	10.9%	12.1%	12.8%	13.9%	15.3%	15.9%	16.5%	18.1%	18.4%	19.3%	20.1%

Other neurological disorders	2.8%	3.0%	3.3%	3.7%	4.0%	4.2%	3.9%	4.5%	4.5%	4.8%	4.9%%
Obesity	8.9%	9.7%	9.9%	11.7%	13.7%	15.1%	14.6%	16.9%	18.1%	19.1%	19.9%
Paralysis	0.9%	0.9%	1.0%	1.0%	1.4%	1.2%	1.2%	1.3%	1.2%	1.2%	1.3%
Psychoses	1.2%	1.2%	1.2%	1.4%	2.0%	2.0%	2.0%	2.3%	2.3%	2.5%	2.5%
Pulmonary circulation disorder	0.03%	0.03%	0.03%	0.04%	0.1%	0.1%	0.1%	0.08%	0.07%	0.06%	0.07%
Renal failure (chronic)	6.4%	8.0%	12.7%	14.4%	14.4%	15.7%	16.5%	18.2%	17.8%	18.3%	19.1%
Peptic ulcer disease	0.07%	0.04%	0.06%	0.04%	0.04%	0.02%	0.02%	0.04%	0.03%	0.03%	0.02%
Weight loss	0.6%	0.8%	0.9%	1.0%	1.4%	1.7%	1.6%	2.1%	2.1%	2.1%	2.0%
Solid tumour without Mets	0.9%	1.0%	1.0%	1.1%	1.1%	1.2%	1.0%	1.1%	1.1%	1.2%	1.1%
Metastatic cancer	0.3%	0.3%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
Dementia	1.7%	1.8%	1.9%	2.1%	2.4%	2.8%	2.6%	3.1%	3.1%	3.0%	2.9%
Comorbidities - Charlson Comorbidity Index											
0	38.4%	38.6%	38.4%	37.2%	35.6%	34.7%	34.2%	32.2%	31.6%	31.1%	30.2%
1	33.9%	33.9%	33.9%	33.7%	34.0%	32.8%	32.9%	31.8%	32.1%	31.3%	31.6%
2	18.4%	18.2%	18.2%	18.6%	19.0%	19.3%	19.8%	20.3%	20.4%	21.0%	21.0%
≥3	9.3%	9.3%	9.3%	10.5%	11.4%	13.2%	13.1%	15.6%	15.9%	16.6%	17.2%
Hospital bed size											
Small	8.1%	3.6%	8.7%	8.0%	7.5%	5.9%	8.6%	7.0%	8.4%	8.4%	12.7%

Medium	19.6%	21.5%	21.4%	22.1%	20.0%	18.5%	18.8%	21.2%	24.3%	24.2%	28.9%
Large	72.3%	74.9%	69.9%	69.9%	72.5%	75.6%	72.6%	71.8%	67.3%	67.4%	58.3%
Hospital Region											
Northeast	22.0%	20.9%	18.8%	18.3%	16.4%	17.5%	17.4%	16.1%	16.7%	16.3%	17.0%
Midwest	24.1%	23.2%	22.2%	24.3%	25.3%	23.9%	26.1%	23.6%	23.8%	23.9%	24.1%
South	39.1%	40.7%	44.3%	40.4%	42.5%%	42.7%	38.8%	42.7%	42.9%	43.0%	42.2%
West	14.8%	15.3%	14.7%	17.0%	15.7%	15.9%	17.7%	17.6%	16.6%	16.8%	16.7%
Location/ Teaching status											
Rural	5.2%	5.2%	4.4%	7.3%	7.8%	7.2%	10.1%	5.8%	6.8%	7.1%	5.7%
Urban-non teaching	38.2%	42.5%	39.6%	39.0%	40.5%	40.1%	40.3%	41.7%	38.2%	37.9%	27.5%
Urban- teaching	56.6%	52.3%	56.0%	53.7%	51.7%	52.7%	49.6%	52.5%	55.0%	55.0%	66.8%
Length of stay, Median (IQR)	4(2-7)	4(2-7)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)
Total charge,$, Median (IQR)	39109 (24353-64456)	41941 (25513-68775)	44175 (27482-71955)	43589 (27582-73160)	49439 (31005-81857)	50217 (31771-83747)	53105 (33083-88071)	56973 (36373-94044)	57393 (36054-94376)	62263 (39014-101723)	64487 (40537-105371)
Bleeding complications	11.5%	11.6%	11.3%	11.8%	11.7%	12.2%	10.5%	10.5%	10.0%	9.2%	8.5%
Vascular complications	1.4%	1.7%	1.5%	1.6%	1.5%	1.5%	1.1%	1.4%	1.1%	1.2%	1.1%
Cardiac complication	2.5%	2.5%	2.3%	2.3%	2.6%	2.3%	2.0%	1.7%	1.8%	1.8%	1.9%
In-hospital	2.2%	2.1%	2.0%	2.0%	2.0%	2.0%	1.8%	1.7%	1.8%	1.7%	1.9%

mortality

IQR=interquartile range, AIDS= acquired immunodeficiency syndrome, AMI=acute myocardial infarction, CVA= cerebrovascular accident, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CAD= coronary artery disease, IABP= intra aortic balloon pump, RA= rheumatoid arthritis.

Table 4.6: Demographics of patients not receiving invasive strategy for each year included in the study, from 2004 – 2014.

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number of records	207,084	189,955	184,979	175,428	182,214	169,948	158,144	160,538	148,900	142,474	142,455
Age (year), Median IRQ	75(61-84)	76(62-85)	76(62-84)	76(62-85)	77 (64-86)	77 (63-86)	77 (64-86)	77 (64-86)	77 (64-86)	77 (64-86)	76 (64-86)
Men %	49.0%	49.2%	49.4%	49.2%	49.3%	49.9%	49.3%	49.6%	50.0%	50.8%	51.2%
Ethnicity											
White	56.6%	58.6%	57.2%	57.4%	62.7%	64.1%	65.5%	67.9%	71.1%	70.2%	70.9%
Black	9.4%	7.1%	8.7%	8.9%	8.5%	9.3%	12.4%	11.7%	11.3%	12.1%	12.1%
Hispanic	5.8%	5.3%	6.9%	5.6%	5.5%	6.6%	6.2%	7.2%	7.4%	7.7%	7.5%
Asian/Pacific Islander	1.5%	1.0%	1.7%	1.6%	1.8%	1.7%	2.3%	1.5%	2.3%	2.3%	2.1%
Native American	0.3%	0.2%	0.4%	0.5%	0.5%	0.5%	0.6%	0.4%	0.5%	0.4%	0.5%
Other	1.9%	2.3%	1.5%	1.8%	2.3%	3.0%	2.1%	2.1%	2.6%	2.2%	2.6%
Missing Race	24.5%	25.5%	23.6%	24.3%	18.6%	14.9%	10.8%	9.2%	4.7%	5.0%	4.3%
Weekend admission	26.6%	26.7%	26.0%	26.9%	27.2%	27.2%	27.3%	26.6%	26.5%	27.1%	26.9%
Primary expected payer, %											

Medicare	68.6%	71.5%	70.5%	70.7%	72.0%	71.9%	72.9%	74.6%	75.1%	74.8%	74.4%
Medicaid	6.0%	5.3%	5.2%	4.9%	5.5%	5.5%	5.8%	5.7%	6.1%	6.0%	7.5%
Private Insurance	19.4%	17.6%	18.2%	18.4%	17.1%	16.4%	15.1%	14.1%	13.0%	13.2%	13.3%
Self-pay	4.0%	3.7%	4.0%	3.6%	3.1%	4.0%	3.7%	3.3%	3.6%	3.4%	2.8%
No charge	0.3%	0.3%	0.3%	0.4%	0.2%	0.2%	0.4%	0.3%	0.3%	0.4%	0.3%
other	1.8%	1.6%	1.8%	1.8%	2.1%	2.0%	2.0%	2.0%	1.9%	2.2%	1.7%
Median Household Income (percentile											
0-25th	31.1%	29.5%	30.1%	29.9%	28.9%	30.3%	30.5%	31.1%	31.7%	30.0%	30.3%
26-50th	27.8%	26.2%	26.7%	26.5%	28.5%	26.9%	26.9%	25.7%	25.6%	27.4%	27.0%
51-75th	21.2%	23.5%	22.3%	23.4%	21.8%	23.1%	23.2%	23.6%	22.6%	22.7%	22.7%
76-100th	20.0%	20.7%	20.9%	20.3%	20.8%	19.7%	19.4%	19.6%	20.1%	19.8%	20.0%
Comorbidities, %											
Dyslipidaemia	28.6%	30.6%	32.3%	35.1%	35.5%	38.9%	40.4%	42.2%	44.9%	45.9%	46.8%
Smoking	15.3%	16.6%	17.9%	19.2%	19.3%	22.6%	24.1%	26.3%	27.9%	30.0%	33.9%
Previous AMI	7.3%	7.5%	7.8%	8.4%	8.4%	9.8%	10.6%	11.4%	11.7%	11.5%	11.9%
History of IHD	36.2%	37.8%	38.7%	40.4%	42.1%	44.1%	44.7%	46.7%	47.7%	47.8%	47.9%
Previous PCI	4.6%	4.9%	5.1%	6.3%	6.3%	7.8%	8.6%	10.1%	11.0%	11.3%	12.4%
Previous CABG	8.4%	8.4%	8.6%	8.6%	8.9%	10.6%	10.7%	12.1%	11.9%	11.9%	12.5%
Previous CVA	No data	No data	No data	0.6%	3.8%	5.6%	6.5%	7.0%	7.6%	8.0%	8.6%
Family history of CAD	2.6%	2.6%	2.8%	3.3%	2.9%	3.3%	3.7%	4.0%	3.9%	4.1%	4.5%
Valvular heart disease	0.3%	0.4%	0.4%	0.4%	0.4%	0.3%	0.5%	0.4%	0.5%	0.4%	0.3%

Peripheral vascular disease	8.4%	8.8%	9.4%	10.7%	11.3%	12.3%	12.5%	13.6%	13.8%	14.1%	14.6%
Use of assist devise or IABP	0.3%	0.4%	0.5%	0.4%	0.5%	0.5%	0.4%	0.6%	0.7%	0.8%	0.9%
Shock	1.6%	1.5%	1.7%	1.8%	1.7%	2.3%	2.2%	2.9%	2.9%	3.1%	3.4%
AIDS	0.14%	0.11%	0.08%	0.13%	0.12%	0.11%	0.15%	0.1%	0.11%	0.11%	0.15%
Alcohol abuse	2.0%	2.1%	2.2%	2.2%	2.4%	2.4%	2.4%	2.6%	2.7%	2.8%	2.9%
Deficiency anaemias	13.9%	14.7%	15.7%	18.3%	20.9%	22.1%	22.7%	24.6%	25.3%	25.2%	25.1%
Chronic Blood loss anaemia	1.9%	2.0%	2.0%	2.0%	1.6%	1.4%	1.4%	1.4%	1.3%	1.1%	1.1%
RA/collagen vascular diseases	1.8%	1.9%	2.0%	2.1%	2.3%	2.4%	2.7%	2.7%	2.8%	2.9%	2.9%
Congestive heart failure	1.3%	1.2%	1.0%	1.1%	1.3%	1.6%	1.6%	1.4%	1.2%	1.2%	1.2%
Chronic pulmonary disease	23.5%	24.8%	24.9%	25.2%	24.9%	24.9%	24.9%	26.5%	26.7%	26.7%	27.0%
Coagulopathy	2.8%	2.9%	3.2%	3.7%	3.7%	4.4%	4.6%	5.4%	6.1%	6.2%	6.7%
Depression	5.4%	5.7%	6.3%	7.3%	7.8%	8.0%	8.6%	9.4%	9.6%	9.8%	10.1%
Diabetes	27.2%	27.6%	28.4%	29.3%	29.7%	30.4%	31.1%	31.6%	32.7%	32.7%	33.2%
Diabetes with complications	5.9%	6.2%	6.4%	7.2%	7.3%	7.5%	7.6%	8.1%	8.5%	9.2%	9.7%
Drug abuse	1.3%	1.4%	1.6%	1.7%	1.5%	1.7%	1.8%	1.8%	2.0%	2.2%	2.6%
Hypertension	59.1%	61.3%	63.5%	65.3%	67.6%	70.4%	71.4%	72.6%	74.5%	76.1%	76.4%

Hypothyroidism	9.0%	9.8%	10.3%	11.4%	12.7%	13.0%	13.7%	14.8%	15.7%	15.8%	16.0%
Liver disease	1.1%	1.1%	1.2%	1.2%	1.2%	1.3%	1.5%	1.6%	1.8%	1.9%	2.2%
Lymphomas	0.5%	0.5%	0.5%	0.6%	0.7%	0.7%	0.7%	0.7%	0.8%	0.8%	0.8%
Fluid and electrolyte disturbances	19.3%	21.3%	21.5%	23.3%	25.1%	25.5%	26.1%	28.3%	29.1%	30.4%	30.8%
Other neurological disorders	7.0%	7.3%	7.9%	8.7%	9.6%	10.0%	10.0%	10.4%	10.4%	10.3%	10.2%
Obesity	6.1%	6.6%	6.8%	7.8%	8.5%	9.5%	9.2%	10.8%	11.7%	12.6%	13.6%
Paralysis	2.2%	2.1%	2.3%	2.4%	3.1%	2.7%	2.8%	2.7%	2.7%	2.6%	2.7%
Psychoses	1.9%	1.9%	2.1%	2.2%	2.7%	2.7%	3.1%	3.2%	3.3%	3.5%	3.5%
Pulmonary circulation disorder	0.06%	0.06%	0.06%	0.08%	0.2%	0.3%	0.2%	0.3%	0.2%	0.2%	0.2%
Renal failure (chronic)	10.8%	14.0%	21.1%	24.1%	24.5%	27.3%	29.1%	31.6%	32.4%	33.6%	34.0%
Peptic ulcer disease	0.07%	0.04%	0.05%	0.07%	0.04%	0.04%	0.06%	0.05%	0.02%	0.02%	0.03%
Weight loss	1.8%	1.7%	1.9%	2.4%	3.1%	3.6%	3.8%	4.4%	4.6%	4.7%	4.6%
Solid tumour without Mets	1.7%	1.8%	1.8%	2.1%	2.2%	2.0%	2.3%	2.2%	2.2%	2.3%	2.2%
Metastatic cancer	1.2%	1.4%	1.3%	1.5%	1.6%	1.8%	1.5%	1.7%	1.6%	1.7%	1.8%
Dementia	8.9%	9.9%	10.8%	11.3%	13.2%	13.9%	14.9%	15.5%	15.9%	15.7%	15.4%
Comorbidities - Charlson Comorbidity Index											
0	28.4%	26.6%	26.8%	25.4%	23.6%	22.3%	21.0%	20.2%	19.0%	18.0%	17.6%

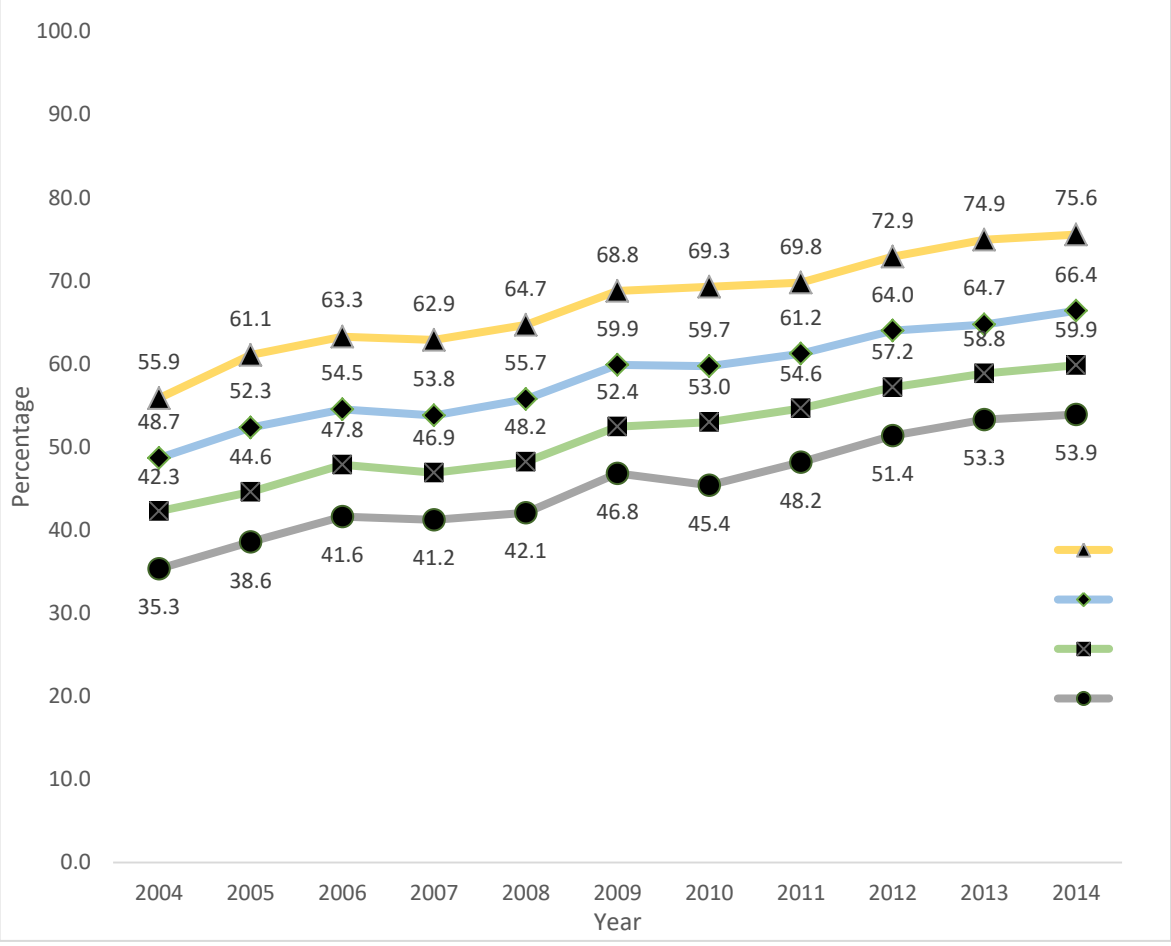
1	32.8%	33.2%	33.6%	32.8%	32.4%	31.2%	30.8%	29.7%	29.5%	29.8%	28.7%
2	23.2%	24.0%	23.9%	24.0%	24.8%	24.7%	25.3%	24.7%	25.5%	25.6%	25.6%
≥3	15.6%	16.2%	15.7%	17.8%	19.2%	21.8%	22.9%	25.3%	26.0%	26.6%	28.1%
Hospital bed size											
Small	15.9%	13.9%	16.7%	14.7%	16.0%	15.0%	13.7%	14.7%	16.4%	16.3%	22.3%
Medium	28.6%	28.1%	27.9%	27.4%	26.5%	27.0%	27.2%	28.2%	29.1%	29.1%	31.3%
Large	55.5%	58.0%	55.4%	57.9%	57.5%	59.0%	59.1%	57.1%	54.5%	54.6%	46.4%
Hospital Region											
Northeast	26.9%	29.7%	28.6%	26.8%	24.5%	25.0%	24.9%	26.4%	25.5%	24.6%	24.7%
Midwest	21.5%	19.1%	19.0%	20.6%	21.1%	20.9%	21.8%	20.6%	20.2%	19.9%	20.4%
South	38.1%	38.3%	38.3%	38.3%	39.5%	39.6%	38.5%	37.3%	37.6%	38.2%	37.9%
West	13.5%	12.9%	14.1%	14.3%	14.9%	14.5%	14.8%	15.7%	16.7%	17.3%	17.0%
Location/ Teaching status											
Rural	21.6%	21.0%	19.6%	18.3%	17.9%	18.5%	17.9%	17.8%	16.0%	15.6%	13.7%
Urban-non teaching	50.5%	50.1%	45.6%	50.0%	50.1%	47.5%	48.1%	47.3%	45.0%	44.0%	32.8%
Urban- teaching	27.9%	28.9%	34.8%	31.7%	32.0%	34.0%	34.0%	34.9%	39.0%	40.4%	53.5%
Length of stay, Median (IQR)	3(2-6)	3(2-6)	3 (2-6)	3 (1-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)	3 (2-6)
Total charge,$, Median (IQR)	13153 (7219-25739)	14264 (7699-27568)	15770 (8585-30362)	16699 (9301-31134)	18276 (10103-33945)	18043 (10019-34169)	18830 (10586-34652)	21354 (11981-39425)	21862 (12141-40742)	23005 (12994-43986)	24223 (13606-45146)
Bleeding complications	11.2%	11.8%	11.7%	12.7%	12.7%	12.5%	12.2%	11.9%	11.9%	11.8%	10.6%
Vascular	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.4%	0.4%	0.5%	0.5%

complications											
Cardiac complication	0.3%	0.4%	0.5%	0.4%	0.4%	0.6%	0.4%	0.4%	0.5%	0.6%	0.6%
In-hospital mortality	6.8%	6.9%	6.6%	6.3%	6.7%	6.4%	6.4%	6.5%	7.0%	6.7%	6.7%

IQR=interquartile range, AIDS= acquired immunodeficiency syndrome, AMI=acute myocardial infarction, CVA= cerebrovascular accident, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CAD= coronary artery disease, IABP= intra aortic balloon pump, RA= Rheumatoid arthritis.

Temporal trends in the comorbidity burden of patients receiving an invasive strategy as defined by the Charlson score are shown in Figure 4.4**.** An increase in the use of the invasive strategy was noted across all four categories of Charlson score, albeit with the lowest uptake in patients with the highest comorbidity burden. From 2004 to 2014, the use of an invasive strategy increased from 55.9% to 75.6% (P_{trend} <0.001) in patients with no comorbidity (CCI=0), from 48.7% to 66.4% (P_{trend} <0.001) in CCI=1 category, from 42.3% to 59.9% (P_{trend} <0.001) in CCI=2 and 35.3% to 53.9% (P_{trend} <0.001) in CCI≥3 category respectively. Very interestingly, the delta between all four curves seems to remain stable throughout the study periods showing persistent disparities.

Figure 4.4 Temporal trends in proportions of patients receiving invasive strategy according to their comorbidity burden as defined per the Charlson comorbidity index from 2004-2014.

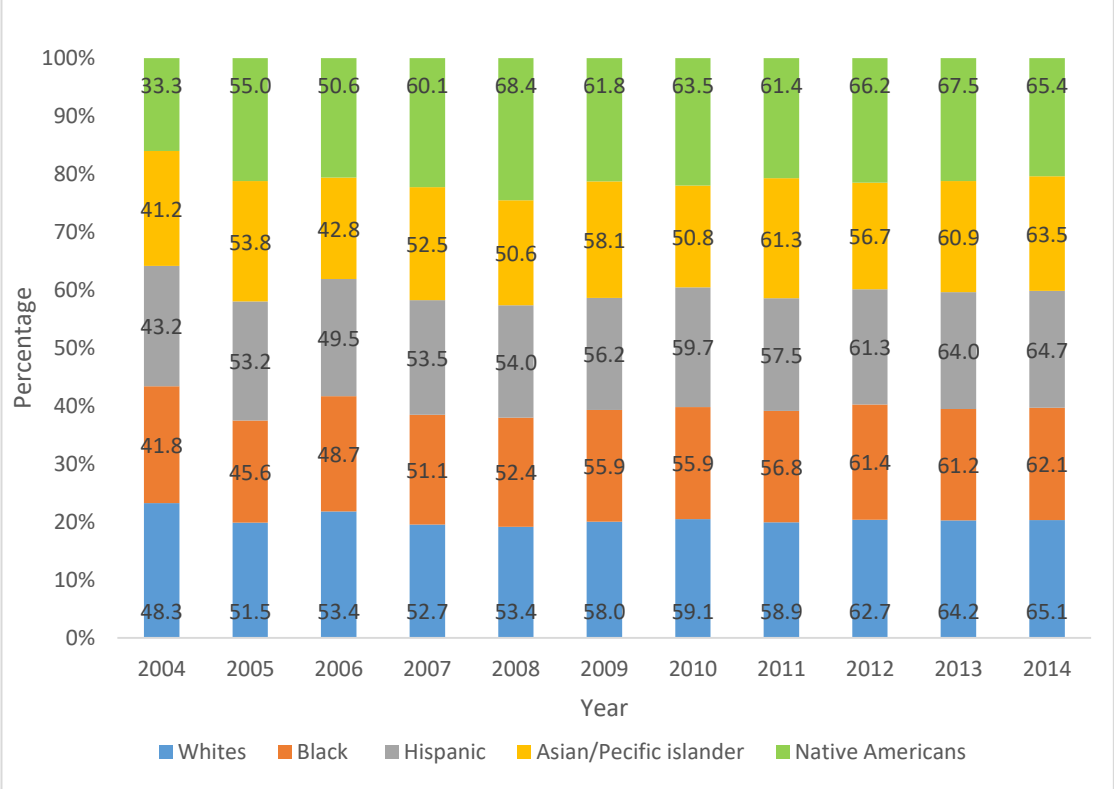


Similar disparities were observed in the use of an invasive strategy when patients were stratified according to age group, gender, ethnicity and hospital location/teaching status. For instance, patients age ≤60 years showed a higher proportional increase in the utilisation of an invasive strategy (59.0% to 77.9%, P_{trend} <0.001) compared to patients age≥81(27.2% to 37.9%, P_{trend} <0.001) between the study period. (Figure 4.5)

Figure 4.5 Temporal trends in proportions of patients receiving an invasive strategy according to their age category from 2004-2014

Similarly, a greater proportional increase in the use of an invasive strategy was observed in Native Americans (33.3% to 65.4%, P_{trend} <0.001) compared to the Whites (48.3% to 65.1%, P_{trend} <0.001). In contrast, the use of an invasive strategy remained lowest in the African American group throughout the study periods compared to all other ethnicities (41.8% to 62.1%, P_{trend} <0.001) (Figure 4.6)

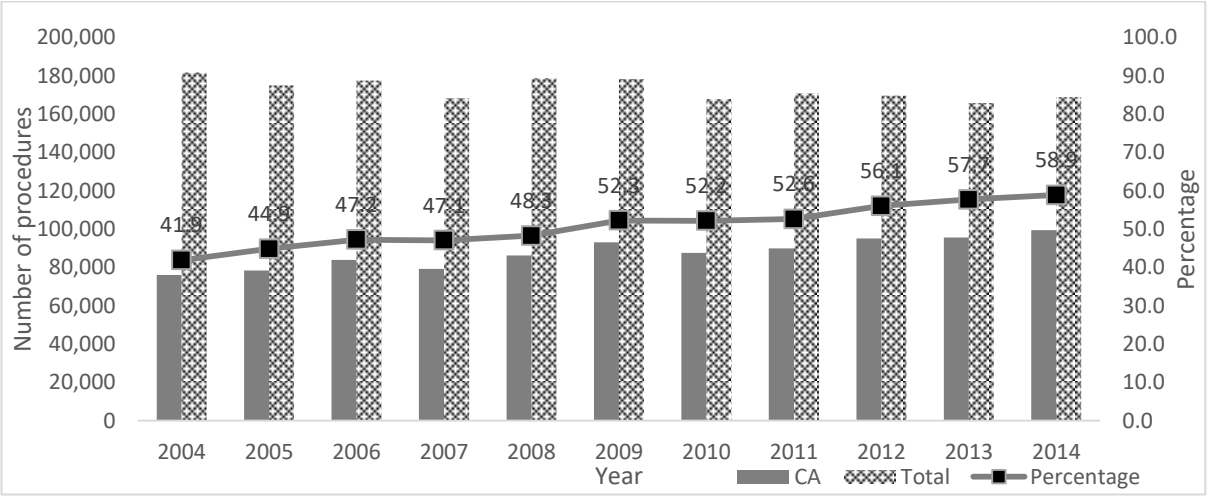
Figure 4.6 Temporal trends in proportions of patients receiving invasive strategy according to their Ethnicity from 2004-2014



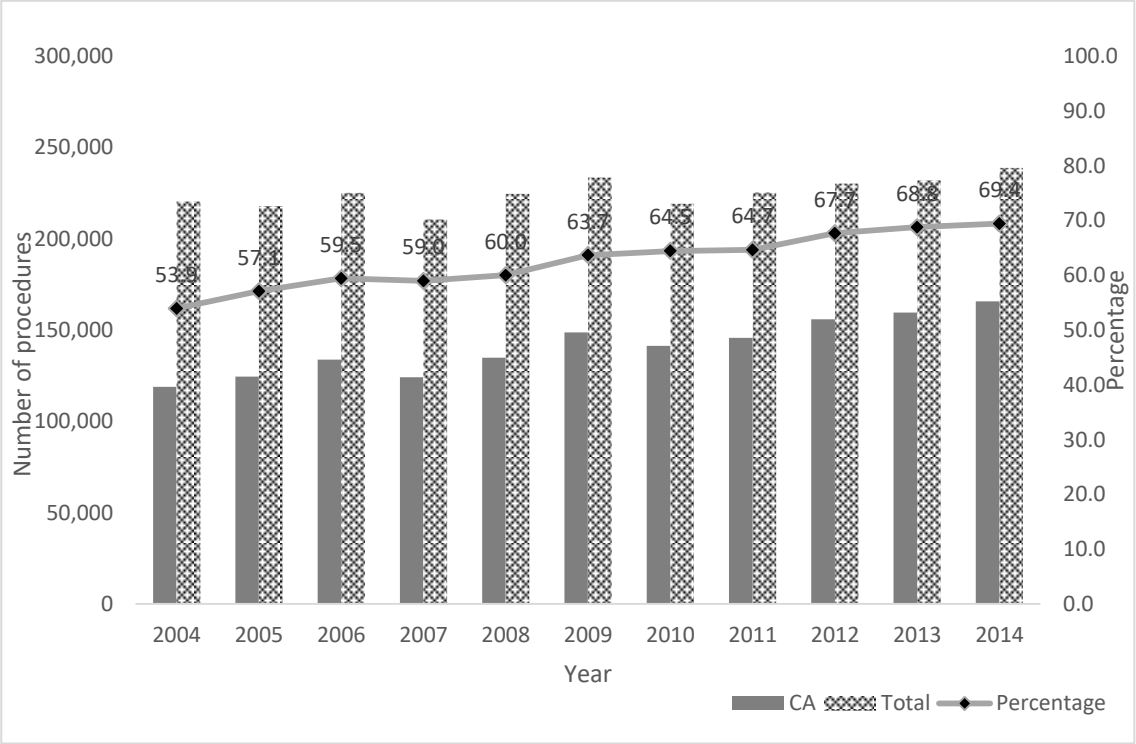
Although, there was an increase in the proportion of the women receiving an invasive strategy from 41.9% to 58.9%, P_{trend} <0.001 the overall adoption of the invasive strategy lagged behind in women compared to men (53.9% to 69.4%, P_{trend} <0.001). (Figure 4.7)

Figure 4.7 Temporal trends in proportions of patients receiving invasive strategy according to their gender from 2004-2014

a) Women

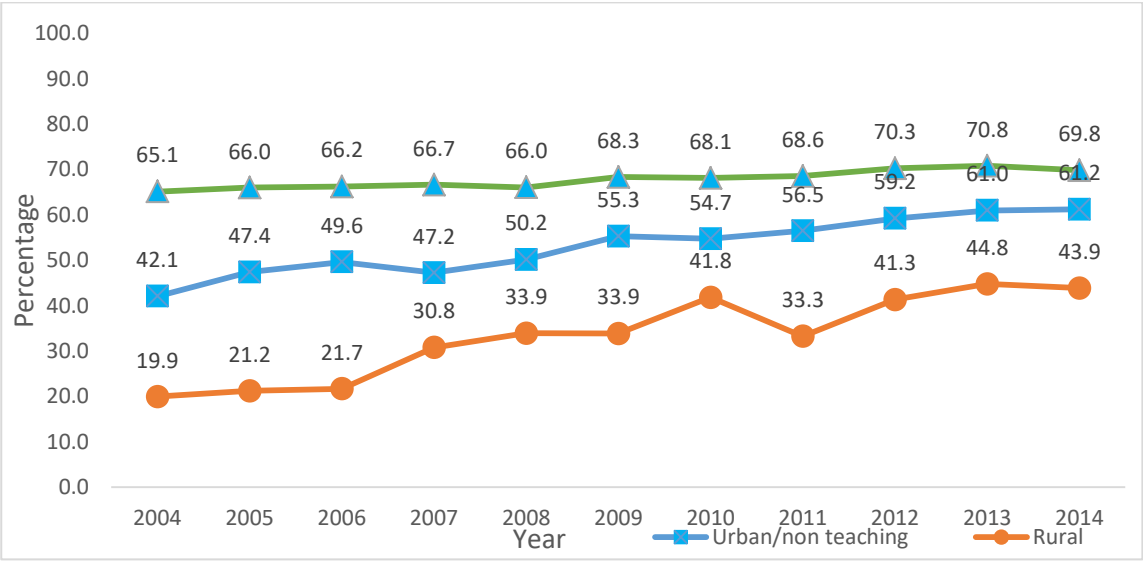


b) Men



Finally, whilst there has been a steady increase in use of an invasive strategy in teaching hospitals (65.1% to 69.8%, P_{trend} <0.001), a greater increase was noted in patients admitted to urban non-teaching (42.1% - 64.2%, P_{trend} <0.001) and rural hospitals (19.9% to 43.9%, P_{trend} <0.001) **(**Figure 4.8).

Figure 4.8 Temporal trends in proportions of patients receiving an invasive strategy according to the teaching status and location of the hospital from 2004-2014



4.4.3 *Independent predictors of receipt of an invasive strategy*

The predictors of receipt of an invasive strategy are shown in Table 4.7. The independent predictors of an invasive strategy receipt included the history of smoking (OR 1.17 95%CI 1.16-1.19), dyslipidemia (OR 1.39 95%CI 1.37-1.40), and history of IHD (OR 6.21 95%CI 6.13-6.29). Notably, patient characteristics which are known to be related to adverse outcomes in NSTEMI such as increasing age (OR 0.96 95%CI 0.960-0.961), prior history of CABG (OR 0.35 95%CI 0.35-0.36), prior PCI (OR 0.84 95%CI 0.83-0.86), history of diabetes (OR 0.88 95%CI 0.87-0.89), diabetes with complications (OR 0.85 95%CI 0.83-0.87) and previous history of AMI (OR 0.65 95%CI 0.64-0.67) had a strong inverse relationship with receipt of invasive strategy. Certain non-cardiac comorbidities which are also associated with poor outcomes such as metastatic cancer (OR 0.33 95%CI 0.31-035), dementia (OR 0.32 95%CI 0.31-0.33) and chronic renal failure (OR 0.66 95%CI 0.65-0.67) were also independently associated with lower odds of receipt of an invasive strategy. Finally, patients treated at large bed or teaching hospital had approximately 3 and a 5-fold increase in odds of receiving invasive strategy (large hospital bed size (OR 3.05 95%CI 2.99-3.11) and urban hospital teaching status (OR 5.51 95%CI 5.39-5.62)) respectively.

Table 4.7 Independent Variables associated with the invasive strategy after excluding for in-hospital mortality and association between the use of an invasive strategy and clinical outcomes.

Predictors	Odds Ratio	95% Confidence Interval	P Value
Age	0.96	0.960-0.961	<0.001
Weekend admission	0.92	0.91-93	<0.001
Female	0.91	0.90-0.92	<0.001
AIDS	0.79	0.67-0.93	<0.001
Alcohol abuse	0.88	0.85-0.91	<0.001
Deficiency anaemias	0.82	0.81-0.83	<0.001

Chronic Blood loss anaemia	0.72	0.68-0.76	<0.001
Congestive heart failure	0.53	0.49-0.57	<0.001
Chronic pulmonary disease	0.85	0.84-0.86	<0.001
Coagulopathy	1.12	1.08-1.15	<0.001
Depression	0.86	0.84-0.86	0.009
Diabetes	0.88	0.87-0.89	<0.001
Diabetes with complications	0.85	0.83-0.87	<0.001
Drug abuse	0.66	0.63-0.68	<0.001
Hypertension	1.02	1.00-1.03	0.001
Hypothyroidism	0.92	0.91-0.94	<0.001
Liver disease	0.76	0.72-0.80	<0.001
Fluid and electrolyte disturbances	0.85	0.83-0.86	<0.001
Other neurological disorders	0.79	0.76-0.81	<0.001
Obesity	1.09	1.07-1.11	<0.001
Paralysis	0.61	0.58-0.64	<0.001
Psychoses	0.67	0.64-0.70	<0.001
Renal failure (chronic)	0.66	0.65-0.67	<0.001
Weight loss	0.80	0.77-0.83	<0.001
Solid tumour without Mets	0.67	0.64-0.70	<0.001
Metastatic cancer	0.33	0.31-0.35	<0.001
Dementia	0.32	0.31-0.33	<0.001
Dyslipidaemia	1.39	1.37-1.40	<0.001
Smoking	1.17	1.16-1.19	<0.001
Previous AMI	0.65	0.64-0.67	<0.001
Previous PCI	0.84	0.83-0.86	<0.001
Previous CABG	0.35	0.35-0.36	<0.001
Previous CVA	0.82	0.79-0.84	<0.001
Family history of CAD	1.30	1.27-1.34	<0.001
Peripheral vascular disease	1.12	1.10-1.14	<0.001
Shock	2.16	2.06-2.26	<0.001
Hospital bed size(Ref small)			
Medium	1.56	1.52-1.59	<0.001
Large	3.05	2.99-3.11	<0.001

Location/ Teaching status (Ref Rural)			
Urban-non teaching	2.58	2.53-2.63	<0.001
Urban- teaching	5.51	5.39-5.62	<0.001

4.4.4 *Clinical outcomes*

Association between the use of an invasive strategy and in-hospital outcomes are reported in Table 4.8. In the multivariate adjusted analysis, the use of an invasive strategy was associated with a significantly decreased odds of in-hospital death (OR 0.38 95%CI 0.36-0.40). There was a significant increase in the incidence of major bleeding (OR 1.23 95%CI 1.16-1.31), vascular complications (OR 3.96 95%CI 3.09-5.07), cardiac complications (OR 4.77 95%CI 3.88-5.87) and MACCE (OR 0.76 95%CI 0.74-0.79) in patients receiving an invasive strategy.

Table 4.8 Association between the use of an invasive strategy and clinical outcomes

Clinical outcome	Odds Ratios	95% Confidence Interval	P value
In hospital mortality	0.38	0.36-0.40	<0.001
Cardiac Complications	4.77	3.88-5.87	<0.001
Major Bleeding	1.23	1.16-1.31	<0.001
Vascular Complications	3.96	3.09-5.07	<0.001
MACCE	0.76	0.74-0.79	<0.001

4.5 Discussion

In this analysis of over 4.3 million patients admitted with a diagnosis of an NSTEMI in the United States, there was a gradual increase in uptake of an invasive strategy for management of NSTEMI over an 11-year period. The results show that there is a paradigm shift in the demographics and risk profile of patients presenting with an NSTEMI resulting in a significant increase in case mix complexity, comorbidity burden in an increasingly older population. Consequently, treating physicians are required to make decisions about the adoption of an invasive strategy in an elderly and more comorbid cohort of patients who have a higher prevalence of both cardiac and non-cardiac comorbidities. There was marked heterogeneity in invasive strategy practices according to patient's baseline cardiovascular profile, comorbidities and hospital characteristics. The use of an invasive strategy remained relatively confined to patients with lower baseline risk such as young age, males, lesser comorbid burden and those admitted to large bed size or teaching hospitals during the study period. In addition, there was a strong inverse relationship between receipt of an invasive strategy and known risk factors of coronary artery disease such as the history of diabetes, hypertension, prior history of CABG, PCI, or AMI. Finally, the use of an invasive strategy was associated with a significant reduction in in-hospital mortality and increased odds of major bleeding, vascular and cardiac complications and trends remained consistent across all years during the study period.

This study demonstrates that clinical spectrum, baseline characteristics and comorbidity status of patients presenting with an NSTEMI has changed significantly over the past decade reflecting and ageing demographics in the United States. The utilisation of an invasive strategy in this cohort increased from 48.5% to 65.1% during the study period; however, there were significant disparities in invasive strategy

practices. Previous studies have reported that the use of an invasive strategy ranges from 79.6%, 84% and 95% in United states[133], United Kingdom[41], and France respectively[20]. This lower utilisation of invasive strategy in the United States may be attributed to inequalities in uniform health coverage by the insurance-based system and differences in the associated comorbid burden of the patients. More importantly, there was significant heterogeneity in the utilisation of an invasive strategy in different patient groups stratified according to gender, age, ethnicity and hospital characteristics. For instance, the higher proportional increase in the utilisation of an invasive strategy was noted in young patients aged ≤60 years compared to elderly patients (age ≥81) despite a progressive increase in the average age of this NSTEMI cohort. More importantly, there was significant heterogeneity in the utilisation of an invasive strategy in different patient groups stratified according to sex, age, ethnicity and hospital characteristics. A higher proportional increase in the utilisation of an invasive strategy was noted in young patients aged ≤60 years compared to elderly patients (aged ≥81) despite a progressive increase in the average age of NSTEMI population. The inequalities in the use of an invasive strategy were also evident in women and African Americans wherein adoption of an invasive strategy has been particularly slower in comparison to men and Native Americans respectively. African Americans and Asians were almost 30% less likely to receive an invasive strategy. Teaching hospital status was associated with higher use of an invasive strategy compared to rural hospitals despite the expansion of cardiac catheter laboratory services in rural hospitals[134].

The delay in uniform adoption of an invasive approach across the whole spectrum of NSTEMI patients may be related to a complex web of underlying factors including local practice, service availability and inequalities in uniform health coverage by the insurance-based system. It is important to note that the under-utilisation of both

invasive and medical therapies in women and the elderly have been widely described which in part has been related to the increased perception of adverse outcomes in women and older patients[97,135,136]. Increase knowledge and understanding of important factors which influence clinician's decision-making about the use of an invasive strategy is required to ensure a uniform and effective use of invasive management in this underserved group of patients.

This analysis also allowed to study the temporal changes in the clinical characteristics and associated comorbidities of the patients receiving an invasive strategy compared to those medically managed in much greater details. Previous studies have mainly reported on the cardiovascular comorbid burden of NSTEMI patients such as history of hypertension, dyslipidaemias, smoking, and diabetes[20,21,97,133,137]. However, the granularity of comorbidity data in NIS facilitates the study of both cardiac and non-cardiac comorbidities in decision making in much greater detail. The findings from this study illustrate that non-cardiac comorbid burden has increased considerably in patients with NSTEMI over the last decade. There was a significantly higher prevalence of non-cardiac comorbidities such as dementia, chronic obstructive airway disease, renal disease and cancer in patients not receiving an invasive strategy. For instance, the prevalence of dementia was significantly higher in patients not receiving an invasive strategy (12.9% vs 2.5% $p<0.001$) and it was a strong negative predictor of receiving an invasive strategy (OR 0.32 95%CI 0.31-0.33, $p<0.001$). Furthermore, there were significant disparities in selection for invasive strategy and global measures for the severity of comorbidity burden. The utilisation of an invasive strategy remained lower in patients with a higher Charlson score category (CCI≥3) compared to no comorbidity (CCI=0) group throughout the study time period. There is a paucity of data on the utilisation of invasive management in patients with multimorbidity as these patients are

often excluded from randomised control trials[9]. It is conceivable that treating physicians may adopt a more conservative approach in older, frailer and multimorbid patients due to the perceived increased risk of adverse events. However, previous studies have shown that impact on mortality with invasive therapies for ACS is not attenuated with age [136] and patients with higher comorbidities may have even greater gains from guidelines recommended treatment[23,138]. Therefore, age alone or the presence of comorbidities should not deter the physician from offering an invasive strategy to these patients. Women have often been denied an early invasive approach[139,140] but recent data from Ontario, Canada showed that women had worse outcomes after undergoing an early invasive strategy after an NSTEMI when compared to men[141]. Women had more bleeding complications after undergoing invasive strategy but it was also seen that women were less likely than men to undergo any revascularisation even after undergoing an invasive strategy. Younger women were less likely to undergo an invasive strategy in this population but there were no noted sex-differences in outcomes in those receiving medical management rather than an invasive approach. These observational data may bias the management of female patients, where an invasive strategy continues to be underutilised in women.

Current guidelines advocate a risk-based approach for offering an invasive strategy in the setting of an NSTEMI which includes several parameters such as age, history of renal insufficiency, prior history of CABG or PCI and presence of coronary disease risk factors such as diabetes[3,4]. This study shows that patient features which are known to be associated with increased risk of adverse events in NSTEMI such as age, diabetes with complications, prior history of CABG, PCI or AMI actually have a strong inverse relationship with receipt of an invasive strategy. In a previous analysis of the CRUSADE registry, Cohen et al reported that patients with the greatest probability of

having severe coronary artery disease were least likely to have invasive strategy[137]. Patients with prior CABG, severe comorbidities and advanced age were excluded from this analysis. This study adds new knowledge to this literature by using granular data from both cardiac and non-cardiac comorbidities, older age, racial and institutional factors thus representing a truly real-world population elucidating a persistent treatment-risk paradox. More importantly, this is the first national analysis spanning over a decade where there have been major changes in clinical practice with advancements in both diagnostic and therapeutic tools to diagnose and manage patient admitted with an NSTEMI. For example, the use of highly sensitive troponin assays has significantly increased the diagnostic accuracy of an NSTEMI and therefore increase utilisation of invasive strategy. More importantly, such disparities in the invasive strategy practices have not been described in the literature from the contemporary era and underline the importance to develop focused efforts for a homogenous and risk-assessment based utilisation of the invasive strategy.

One final finding worthy of discussion in this investigation was the association of an invasive strategy with in-hospital mortality, major bleeding, vascular and cardiac complications. the invasive strategy was associated with significantly decreased odds of in-hospital mortality (OR 0.38 95%CI 0.36-0.40) albeit at the expense of a slight increase in relative risk of major bleeding, vascular and cardiac complications. Procedure safety and risk profile have improved significantly over the past decade due to improvement in procedural skills, changes in access site practice from femoral to radial access, operator volume, and better equipment and as a result, the absolute risk of such procedure-related adverse events has declined[142-144]. Nevertheless, the main finding in the outcome analysis is a significant reduction in in-hospital mortality in patients receiving an invasive strategy which corroborates the results of previously

reported better outcomes of patients receiving routine invasive approach compared to conservative or selective invasive approach[11,57,104,145], thus providing reassurance about the accuracy of the overall findings.

4.6 Study strengths and limitations

The strengths of this study findings arise from the use of comprehensive, unselected, national records that are derived from an obligatory administrative database which are representative of true real-world practice. The granularity of comorbidity data, diversity in geographic, racial and hospital characteristic information within the NIS dataset allowed to study the disparities in the invasive strategy practices.

Nevertheless, this work must be interpreted within the context of certain limitations. First, this work is observational in nature and the possibility of unmeasured confounders cannot be ruled out. Secondly, important clinical information such as medication history, frailty, ECG and cardiac biomarker information is not captured within the NIS database. Cardiac biomarkers, ECG changes, and hemodynamic parameters are important for risk stratification and may influence a physician's decision on whether to adopt an invasive approach[146,147]. The information regarding onsite facility to perform angiography is not available in the database which may have limited the estimation of the utilisation of an invasive strategy. Finally, as with any administrative database, there is a potential for coding error for diagnoses or procedure codes

4.7 Conclusion

In summary, for the first time in literature, this study in over 4 million inpatient admissions of NSTEMI across the United States from 2004 – 2014 demonstrates a steady rise in the use of an invasive strategy. There was significant heterogeneity in the utilisation of an invasive strategy across different patient groups stratified according to age, gender, race, comorbidity burden and hospital characteristics wherein severe

comorbidity burden as defined by Charlson score (CCI>3), female, elderly and Native Americans were less likely to receive an invasive strategy. Although, utilisation of an invasive strategy was associated with decreased odds of in-hospital mortality, patients who are more likely to benefit such as elderly, diabetic and previous PCI or AMI were least likely to receive it. Future strategies need to focus on identification of factors associated with these disparities and developing pathways for a uniform uptake of invasive coronary approach particularly in patients in whom there is a greatest potential benefit

Chapter 5

Trends and outcomes in the timing of an invasive strategy in the management of non-ST elevation acute myocardial infarction

5.1 Introduction

In line with part 1 of this thesis to investigate patient level factors associated with the use of an invasive strategy, this study was designed to further understand how timing of an invasive strategy varies amongst different subgroup of patients, secular trends in the timing of an invasive strategy and association with clinical outcomes to further augment the findings presented in chapter 4. The findings from this chapter have been published in Coronary Artery Disease Journal (impact factor 1.7).

A routine invasive strategy has been shown to be associated with a reduced risk of re-infarction, repeat hospitalisation, and improved survival compared to a selective invasive or conservative approach, particularly in high-risk NSTEMI such as those who are troponin positive or high GRACE risk score >140[52,104,146]. An invasive strategy plays a pivotal role in the early diagnosis and management of patients admitted following an NSTEMI. Time to an invasive strategy for patients with NSTEMI varies greatly according to national and regional practices. In the UK, NICE recommends that the invasive strategy should be undertaken within 96 hours following admission with an NSTEMI in patients that are intermediate to high risk per GRACE risk score [8]. In contrast, the European Society of Cardiology advocates offering an invasive strategy within 72 hours to low-risk patients and within 24 hours to patients with high-risk features defined as GRACE score >140. However, patients presenting with haemodynamic instability, cardiac arrest, cardiogenic shock or acute heart failure are advised to undergo an immediate invasive strategy within 2 hours according to expert consensus[148]. Lastly, the AHA/ACC has recommended three different points for invasive strategy whilst acknowledging the fact that the optimal timing of an invasive strategy is not known[3]. An immediate invasive strategy (within 2 hours) is recommended in patients with hemodynamic instability, signs of new heart failure or

recurrent angina despite maximum medical therapy, an early approach (within 24h) for patients with changes in cardiac biomarker or ECG changes and a late invasive approach (>24 hours) for patients with low GRACE score (109-140). Although an invasive approach during the index admission is now routinely practised for management of NSTEMI, the optimal timing of the procedure remains contentious due to conflicting data derived from the previous studies[51,59,60]. The ISAR-COOL study was the first trial with a relatively smaller sample size of 410 patients which compared early (3h) with delayed (72h) invasive strategy in patients admitted with NSTEMI. Patients were randomly allocated to antithrombotic pre-treatment for 3 to 5 days or to early intervention after pre-treatment for less than 6 hours. At 30 days, the cumulative incidence of primary endpoints (large AMI or death) was significantly different between the two groups (early intervention 5.9% vs late intervention 11.6%, p=0.04) demonstrating that an early invasive approach resulted in a reduction in MI or death [149]. The authors concluded that late invasive strategy is associated with significant cardiac complications, costs related to a prolonged hospital stay and does not reduce the risk of subsequent revascularisation procedures. More recently, two other smaller RCTs tested the hypothesis if treating NSTEMI with an immediate invasive strategy like STEMI improves cardiovascular outcomes [51,105]. The LIPSIA-NSTEMI trial randomised the patients to immediate (<2h) versus early (10-48h) or delayed selective invasive approach (>48h) [51]. They concluded that immediate invasive approach did not offer any advantage over the early or delayed selective high invasive approach in reducing myocardial infarction as defined by peak CKMB activity level. More interestingly, a very recent study of 323 NSTEMI patients reported a greater benefit of immediate invasive approach in reducing death or new MI at short to medium term follow up, using approximately the same time points of an invasive strategy (2h vs 72h after

randomisation) as LIPSIA-NSTEMI[105]. Meta-analyses of RCTs and observational studies reveal that an early invasive strategy does not reduce mortality compared with a delayed invasive strategy in all patients with NSTEMI, but there may be a benefit in high-risk patients such as those with GRACE risk score >140 [60,149-151]. Moreover, the timing of an invasive strategy has changed significantly in the last decade due to expansion in services and changes in guideline recommendations around the cut off for an invasive approach[3,4]. There are limited data in contemporary practice and in national cohorts regarding temporal trends and changing characteristics of patients undergoing an invasive strategy following an NSTEMI diagnosis at different time points.

5.2 Objectives

The main objectives of this chapter were as follows

I. To investigate the temporal trends in timing to an invasive strategy stratified into early, intermediate and late.

II. To describe changes in the profile of patients undergoing early, intermediate and late invasive strategy following admission with NSTEMI over the past decade in the United States.

III. To study these trends stratified according to age, ethnicity, gender, weekday versus weekend admission and comorbidity burden.

IV. To investigate the independent predictors of an early invasive strategy.

V. To study the association of in-hospital mortality, Major Adverse Cardiovascular & Cerebrovascular Events(MACCE) and major bleeding with different time points of an invasive strategy.

5.3 Methods

Full details of NIS dataset and methods have already been described in chapter 3. However, a brief summary of methods is provided here.

5.3.1 *Study design*

This study was a retrospective analysis of prospectively collected data from NIS. The NIS is one of the largest publically available all-payer inpatient healthcare database sponsored by the Agency for Healthcare Research and Quality (AHRQ) as a part of Healthcare Cost and Utilisation Project (HCUP)[83]. NIS collects discharge level anonymised data encompassing more than 7 million yearly hospital records. Patient ethical approval was not required for this study as NIS is publically available anonymised data.

5.3.2 *Study population*

International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 4111and 4107 were used to identify patients admitted with a primary diagnosis of NSTEMI from 2004 to 2014. Data were restricted to urgent or emergency diagnoses thereby excluding elective admissions, as they do not represent a true diagnosis of NSTEMI. the invasive strategy was defined as ICD-9-CM procedure codes 8853, 8854, 8855, 8856 3722 and 3723, with or without PCI (ICD-9-CM procedure codes 0066, 3601, 3602, 3605, 3606 and 3607. Time to the invasive strategy was defined as the number of days from admission date to procedure date provided within the NIS dataset. It was then categorised into early (day 0, 1), intermediate (day 2) and late (day ≥3). Patients who did not undergo an invasive strategy comprise the conservative (comparison) group.

5.3.3 *Study covariates*

The information on patient demographics, including age, sex, race, median household income by zip code, primary expected payer, weekend admission and comorbidities using Elixhasuer comorbidities, as defined by AHRQ were also collected. The length of stay and total cost of hospitalisation for each admission were recorded. The cost of

hospitalisation was calculated using cost to conversion ratio to convert the reported charges into the actual cost for the primary payer. Additionally, hospital characteristics such as region, location, teaching status and bed size were also included. Finally, information around cardiovascular risk factors and other important relevant diagnoses such as the history of smoking, hyperlipidaemia, coronary artery disease, family history of ischemic heart disease, previous myocardial infarction or CABG, and dementia were also extracted using ICD-9-CM codes provided in the Appendix Table 1. The ICD-9-CM coded used for calculating the Charlson comorbidity index are given in the Appendix Table 2. The ICD-9-CM codes utilised in this study were based on a thorough literature search of previous studies using NIS dataset as described earlier in chapter 4[10,114,116,120-126].

5.3.4 *Study outcomes*

The in-hospital mortality is collected in the NIS database as DIED variable. Whereas, other in-hospital outcomes including major bleeding, acute ischemic stroke, adverse cardiac complications, and MACCE; a composite of acute ischemic stroke, in-hospital mortality and adverse cardiac complications were obtained using ICD-9-CM codes provided in the Appendix Table 3.

5.3.5 *Statistical analysis*

The differences in the baseline, hospital characteristics, and crude outcomes of interest across all four categories were made using descriptive statistics. Continuous variables were reported as the median and interquartile range to account for the skewness of the data whereas categorical variables were presented as a number and percentage. All the analyses were undertaken using the survey estimation command as recommended by AHRQ in order to account for the complex survey design of the NIS database as described before in chapter 3. The updated AHRQ trend weights for years 2004-2011

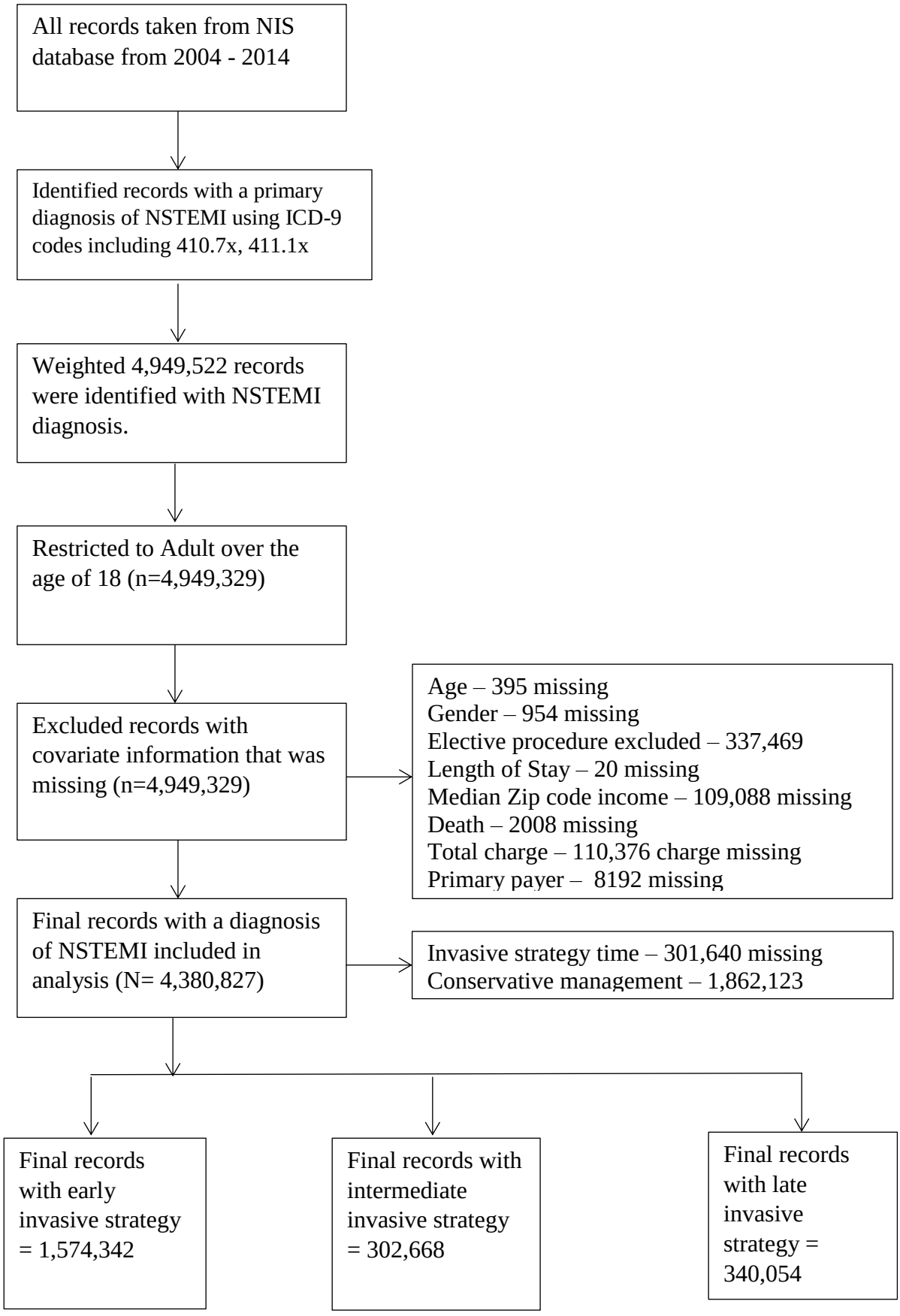
(TRENDWT) and existing discharge weights for years 2012-2014 (DISCHWT) were used to produce national discharge-level estimates for trends analysis. Multivariable logistic regression models were fitted to investigate the independent predictors of early invasive strategy (0,1 day) and determine the association between time to invasive strategy category with the aforementioned clinical outcomes. The following covariates were adjusted for in all analyses: age, sex, elective admission, weekend admission, primary expected payer, median household income, dyslipidaemia, smoking status, previous acute myocardial infarction, previous CABG, history of IHD, previous PCI, previous CVA, family history of CAD, use of assist device or IABP, shock during hospitalisation, dementia, bed size of hospital, region of hospital, location/teaching status of hospital and 29 AHRQ comorbidities. All odds ratios (ORs) are adjusted for the aforementioned covariates and presented with the corresponding 95% confidence intervals. This methodology has previously been used for analysing data from HCUP[114,116,152].

5.4 Results

5.4.1 *Patient and hospital characteristics*

A total of 4,380,827 records with a diagnosis of NSTEMI were identified between 2004 and 2014, of which 1,862,123 (42.5%) were managed medically and 2,518,704 (57.5%) received invasive strategy. After excluding the records with missing information on time to invasive strategy (12%), the patients that received an invasive strategy, 1,574,342 (62.5%), 302,668 (12.0%), 340,054 (13.5%) were categorised into early (day 0,1), intermediate (day 2) and late (day ≥3) groups respectively (Figure 5.1).

F*igure* 5.1: Flow diagram of included/excluded records



There were significant differences in the profile of the patient undergoing an invasive strategy at different time points. Patients receiving early invasive strategy were younger (median age 64 vs 70 years), more likely to be men (63.7% vs 55.3%) and of white ethnic background (68.7% vs 64.7%) compared to late invasive strategy group. Conversely, patient in the late invasive strategy group were more likely to be women (44.7% vs 26.3%), had higher proportions of co-existing comorbidities such as COPD (28.5% vs 18.2%), complicated diabetes (11.6% vs 4.8%), fluid and electrolyte disturbances (27.5% vs 13.2%), CCI score ≥3 (24.2% vs 10.4%), and were more likely to be admitted on weekend (25.1% vs 19.4%). Finally, patients with private insurance were more likely to have an early invasive strategy (33.5%) than late invasive strategy (16.7%), while patients on Medicare were more likely to have a late invasive strategy (66.4%) than early invasive strategy (49.5%). More than half of all patients treated conservatively (54.2%) were on Medicare, while only 30.8% had private insurance (Table 5.1).

Table 5.1: Baseline characteristics of patients receiving an invasive strategy at different time points compared to medically managed patients.

Timing of invasive strategy	**Early**	**Intermediate**	**Late**	**Conservative approach**
Number of Cases weighted (%age)	1,574,342 (38.6%)	302,668 (7.4%)	340,054 (8.3%)	1,862,123 (45.6%)
Age (year), Median IRQ	64 (54-74)	67 (57-77)	70 (60-78)	66 (56-75)
Men %	63.7%	58.6%	55.3%	49.7%
Ethnicity				
White	68.7%	66.8%	64.7%	63.3%
Black	8.9%	11.2%	12.7%	10.0%
Hispanic	6.4%	7.7%	8.3%	6.4%
Asian/Pacific Islander	1.7%	1.7%	2.0%	1.8%
Native American	0.5%	0.5%	0.4%	0.4%
Other	3.1%	2.7%	2.7%	2.2%

Missing Race	10.8%	9.4%	9.2%	16.0%
Weekend admission	19.4%	53.0%	25.1%	26.8%
Primary expected payer, %				
Medicare	49.5%	58.2%	66.4%	54.2%
Medicaid	6.6%	6.8%	7.2%	5.7%
Private Insurance	33.5%	25.9%	16.7%	30.8%
Self-pay	6.6%	5.7%	4.5%	5.8%
No charge	0.7%	0.7%	0.6%	0.5%
other	3.1%	2.7%	2.3%	1.9%
Median Household Income (percentile)				
0-25th	28.2%	30.5%	31.9%	30.3%
26-50th	27.5%	27.8%	26.7%	27.0%
51-75th	23.9%	23.5%	22.8%	22.7%
76-100th	20.4%	18.2%	18.6%	20.0%
Comorbidities, %				
Dyslipidaemia	60.1%	55.5%	45.0%	37.6%
Smoking	40.8%	35.8%	29.6%	22.4%
Previous AMI	9.5%	10.4%	9.3%	9.5%
History of IHD	83.9%	80.0%	73.7%	42.6%
Previous PCI	12.1%	12.4%	10.0%	7.7%
Previous CABG	5.5%	6.9%	7.0%	10.1%
Previous CVA	3.1%	3.7%	3.8%	4.0%
Family history of CAD	9.2%	6.7%	4.0%	3.4%
Valvular heart disease	0.1%	0.2%	0.3%	0.4%
Peripheral vascular disease	10.7%	13.4%	16.0%	11.5%
Multivessel PCI	10.8%	8.3%	7.6%	0%
Use of assist devise or IABP	4.4%	2.4%	2.8%	0.5%
Shock	2.7%	1.6%	2.7%	2.2%
AIDS	0.13%	0.14%	0.18%	0.12%
Alcohol abuse	2.9%	3.0%	3.4%	2.4%
Deficiency anaemias	10.8%	15.6%	23.2%	20.3%
Chronic Blood loss anaemia	0.6%	0.8%	1.8%	1.6%
RA/collagen vascular diseases	2.1%	2.4%	2.5%	2.4%
Congestive heart failure	0.3%	0.4%	0.9%	1.3%
Chronic pulmonary disease	18.2%	22.6%	28.5%	25.4%

Coagulopathy	3.8%	4.2%	6.0%	4.4%
Depression	6.6%	7.4%	7.4%	7.8%
Diabetes	29.6%	32.4%	33.6%	30.1%
Diabetes with complications	4.8%	7.3%	11.6%	7.4%
Drug abuse	2.2%	2.3%	2.3%	1.8%
Hypertension	71.0%	73.5%	71.8%	68.3%
Hypothyroidism	9.1%	10.4%	11.2%	12.7%
Liver disease	1.1%	1.3%	1.8%	1.4%
Lymphomas	0.4%	0.5%	0.6%	0.6%
Fluid and electrolyte disturbances	13.2%	17.9%	27.5%	25.1%
Other neurological disorders	3.6%	4.7%	5.8%	9.1%
Obesity	14.9%	15.1%	14.3%	9.1%
Paralysis	1.0%	1.3%	2.0%	2.5%
Psychoses	1.7%	2.1%	2.6%	2.7%
Pulmonary circulation disorder	0.05%	0.07%	0.1%	0.2%
Renal failure (chronic)	11.8%	18.3%	28.6%	24.8%
Peptic ulcer disease	0.03%	0.05%	0.05%	0.05%
Weight loss	1.2%	1.6%	3.0%	3.2%
Solid tumour without mets	1.0%	1.2%	1.7%	2.0%
Metastatic cancer	0.4%	0.5%	0.7%	1.5%
Dementia	2.1%	3.1%	4.4%	13.0%
Charlson Comorbidity Index				
0	38.9%	29.3%	18.8%	23.0%
1	33.3%	32.8%	30.2%	31.5%
2	17.4%	22.0%	26.8%	24.6%
≥3	10.4%	15.9%	24.2%	20.9%
Hospital bed size				
Small	7.7%	7.2%	7.7%	15.9%
Medium	22.3%	23.3%	23.1%	28.1%
Large	70.0%	69.5%	69.8%	56.0%
Hospital Region				
Northeast	20.3%	20.1%	23.6%	26.3%
Midwest	21.3%	19.5%	17.7%	20.5%
South	42.1%	46.2%	46.2%	38.4%
West	16.3%	14.2%	12.4%	14.9%
Location/ Teaching status				

Rural	6.3%	6.5%	5.7%	18.2%
Urban-non teaching	38.3%	40.9%	40.0%	46.9%
Urban- teaching	55.4%	52.6%	54.3%	34.9%
Length of stay, Median (IQR)	2 (2-4)	4 (3-6)	6 (4-10)	3 (2-6)
Total charge,$, Median (IQR)	49757 (30830-81841)	51034 (31227-84244)	63602 (39026-108596)	18078 (9841-34417)

AMI= acute myocardial infarction, IHD, ischemic heart disease, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CVA= cerebrovascular accident, CAD= coronary artery disease, IABP= intra-aortic balloon pump, AIDS= acquired immunodeficiency syndromes, RA= Rheumatoid arthritis, IQR= interquartile range.

The prevalence of risk factors for coronary artery disease including smoking (31.5%, 47.5% vs 35.4% in 2004 to 47.1%, 42.8% vs 39.6% in 2014), dyslipidaemia (51.6%, 47.5% vs 35.4% in 2004 to 64.0%, 60.1% vs 53.1% in 2014), previous AMI (8.0%, 8.5% vs 7.6% in 2004 to 11.0%, 12.4% vs 11.1%), hypertension (61.9%, 65.5% vs 62.5% in 2004 to 76.1%, 79.4% vs 78.0% in 2014), and peripheral vascular disease (8.5%, 10.8% vs 12.2% in 2004 to 11.3%, 14.0% vs 18.5% in 2014) has increased in both early and intermediate groups, but with a greater proportional increase observed in the early invasive strategy group. In contrast, patients undergoing late invasive strategy had a greater proportional increase in the non-cardiac comorbidities such as COPD (26.1% vs 15.5% in 2004 to 30.2% vs 19.4% in 2014), hypothyroidism (7.9% vs 6.5% in 2004 to 13.5% vs 10.8% in 2014) and chronic renal failure (13.2% vs 4.0% in 2004 to 35.3% vs 14.7% in 2014) compared to the early invasive strategy group throughout the study period. (Table 5.2).

Table 5.2: Temporal trends in baseline and hospital characteristics of patients stratified according to different cut off of time to an invasive strategy

Year		**2004**			**2005-2006**			**2007-2008**	
Timing of invasive strategy	Early	Interm.	Late	Early	Interm.	Late	Early	Interm.	late
Number of Cases weighted (%age)	102,568 (65.6%)	23,208 (14.8%)	30,634 (19.6%)	236,276 (68.4%)	48,367 (14.0%	60,675 (17.6%)	245,239 (70.7%)	46,976 (13.5%)	54,470 (51.7%)
Age (year), Median IRQ	64 (54-74)	67 (57-77)	71 (61-78)	64 (54-74)	57 (57-77)	70 (60-79)	64 (54-74)	67 (57-77)	70 (60-79)
Men %	63.8%	58.2%	55.7%	63.7%	58.5%	54.6%	63.2%	58.2%	54.2%
Ethnicity									
White	64.6%	62.0%	60.2%	63.9%	63.9%	62.2%	66.2%	64.0%	62.7%
Black	7.1%	9.6%	11.3%	6.2%	8.3%	9.6%	8.5%	10.1%	11.4%
Hispanic	4.7%	6.4%	7.4%	5.8%	7.1%	8.5%	5.9%	7.8%	7.8%
Asian/Pacific Islander	1.2%	1.2%	1.5%	1.2%	1.4%	1.6%	1.7%	1.8%	2.1%
Native American	0.2%	0.3%	0.2%	0.2%	0.2%	0.2%	0.8%	0.9%	0.8%
Other	2.3%	2.1%	2.2%	3.7%	1.7%	1.9%	3.3%	2.8%	2.9%
Missing Race	19.8%	18.3%	17.3%	18.9%	17.3%	16.0%	13.6%	12.6%	12.3%
Weekend admission	17.1%	50.2%	25.8%	17.8%	51.5%	26.0%	18.7%	53.7%	24.8%
Primary expected payer, %									
Medicare	48.0%	55.8%	66.8%	48.6%	58.0%	66.4%	47.7%	56.5%	65.4%
Medicaid	5.8%	5.8%	6.1%	5.7%	6.2%	6.5%	5.7%	6.3%	6.9%
Private Insurance	37.7%	30.3%	21.0%	36.5%	27.5%	19.7%	35.7%	27.8%	19.8%
Self-pay	5.4%	5.0%	3.8%	5.7%	5.0%	4.2%	6.4%	5.6%	4.4%
No charge	0.5%	0.7%	0.6%	0.7%	0.8%	0.8%	0.8%	0.8%	0.8%

other	2.6%	2.2%	1.6%	2.9%	2.5%	2.3%	3.7%	3.0%	2.7%
Median Household Income (percentile)									
0-25th	25.9%	28.3%	30.4%	26.0%	28.8%	31.4%	26.4%	30.5%	31.6%
26-50th	28.0%	28.3%	26.6%	26.5%	27.1%	26.0%	28.3%	28.3%	26.9%
51-75th	21.9%	22.6%	21.4%	25.0%	24.5%	23.1%	23.2%	23.1%	22.9%
76-100th	24.2%	20.8%	21.6%	22.4%	19.6%	19.5%	22.1%	18.1%	18.6%
Comorbidities, %									
Dyslipidaemia	51.6%%	47.5%%	35.4%	54.1%	49.5%	37.2%	57.9%	53.0%	40.3%
Smoking	31.5%	26.4%	19.7%	34.0%	29.9%	21.7%	37.7%	32.0%	24.4%
Previous AMI	8.0%	8.5%	7.6%	7.7%	9.0%	7.7%	8.6%	8.7%	7.9%
History of IHD	84.4%	80.1%	72.0%	84.1%	79.1%	71.0%	84.0%	79.4%	72.4%
Previous PCI	7.8%	7.7%	6.0%	9.0%	9.1%	6.6%	10.3%	10.2%	7.6%
Previous CABG	5.5%	6.2%	6.4%	5.3%	6.3%	6.0%	5.2%	6.4%	6.0%
Previous CVA	NA	NA	NA	NA	NA	NA	1.7%	2.1%	2.1%
Family history of CAD	6.3%	4.3%	2.6%	7.2%	5.3%	2.8%	7.9%	5.1%	2.4%
Valvular heart disease	0.1%	0.2%	0.4%	0.1%	0.1%	0.3%	0.1%	0.2%	0.3%
Peripheral vascular disease	8.5%	10.8%	12.2%	9.2%	11.5%	12.3%	10.9%	14.0%	16.1%
Multivessel PCI	10.6%	8.0%	6.9%	12.0%	9.1%	7.8%	10.4%	7.2%	6.5%
Use of assist devise or IABP	3.8%	2.0%	2.0%	4.2%	2.0%	2.0%	4.4%	2.6%	2.7%
Shock	1.8%	0.6%	1.4%	2.1%	1.1%	1.6%	2.3%	1.4%	2.6%
AIDS	0.11%	0.17%	0.15%	0.1%	0.13%	0.16%	0.1%	0.17%	0.14%
Alcohol abuse	2.1%	2.6%	2.7%	2.4%	2.4%	2.8%	2.8%	2.7%	3.0%
Deficiency anaemias	6.8%	10.3%	13.8%	7.7%	10.6%	15.0%	10.9%	15.3%	22.0%
Chronic Blood loss anaemia	0.5%	1.0%	2.3%	0.7%	1.1%	2.4%	0.8%	1.0%	2.2%

RA/collagen vascular diseases	1.7%	1.4%	1.9%	1.7%	2.4%	1.9%	2.0%	2.4%	2.4%
Congestive heart failure	0.4%	0.3%	1.0%	0.3%	0.3%	0.8%	0.3%	0.6%	0.9%
Chronic pulmonary disease	15.5%	20.0%	26.1%	17.2%	21.2%	27.7%	18.1%	22.1%	28.4%
Coagulopathy	2.1%	2.9%	4.3%	2.6%	2.8%	4.1%	3.1%	3.5%	5.1%
Depression	4.0%	4.4%	4.0%	4.7%	5.3%	5.0%	5.8%	6.4%	6.8%
Diabetes	25.7%	28.6%	30.6%	26.4%	28.8%	29.7%	28.2%	31.8%	32.7%
Diabetes with complications	3.3%	5.1%	8.2%	3.5%	6.0%	9.2%	4.3%	6.6%	11.0%
Drug abuse	1.3%	1.7%	1.4%	1.7%	1.9%	1.9%	2.0%	2.1%	1.9%
Hypertension	61.9%	65.5%	62.5%	64.6%	66.5%	64.5%	68.8%	71.1%	70.3%
Hypothyroidism	6.5%	7.2%	7.9%	7.0%	7.9%	8.6%	8.3%	9.7%	11.1%
Liver disease	0.6%	0.9%	1.0%	0.7%	0.8%	1.2%	0.9%	1.1%	1.6%
Lymphomas	0.3%	0.5%	0.6%	0.4%	0.4%	0.5%	0.4%	0.4%	0.6%
Fluid and electrolyte disturbances	7.6%	10.8%	17.5%	9.3%	13.2%	21.3%	11.8%	16.6%	25.3%
Other neurological disorders	2.5%	2.9%	3.7%	2.7%	3.7%	4.5%	3.3%	4.4%	6.0%
Obesity	8.7%	9.3%	7.8%	10.3%	10.3%	8.3%	12.9%	13.0%	12.4%
Paralysis	0.7%	0.9%	1.4%	0.8%	1.0%	1.6%	1.0%	1.4%	2.3%
Psychoses	1.1%	1.2%	1.4%	1.1%	1.2%	1.7%	1.5%	1.6%	2.3%
Pulmonary circulation disorder	0.01%	0.02%	0.05%	0.03%	0.00%	0.04%	0.05%	0.09%	0.1%
Renal failure (chronic)	4.0%	6.8%	13.2%	7.4%	11.9%	20.9%	11.2%	17.4%	28.2%
Peptic ulcer disease	0.06%	0.15%	0.1%	0.04%	0.07%	0.05%	0.02%	0.07%	0.07%
Weight loss	0.4%	0.5%	1.0%	0.6%	0.7%	1.6%	0.9%	1.1%	2.5%
Solid tumor without mets	0.9%	1.0%	1.4%	0.8%	1.1%	1.7%	0.9%	1.4%	1.6%
Metastatic cancer	0.3%	0.4%	0.5%	0.3%	0.4%	0.6%	0.4%	0.4%	0.7%

Dementia	1.4%	2.0%	2.4%	1.5%	2.3%	3.2%	1.9%	2.5%	3.8%
Charlson Comorbidity Index									
0	45.0%	35.6%	23.3%	43.9%	34.4%	22.9%	41.1%	31.1%	20.9%
1	33.7%	35.1%	33.8%	33.8%	34.9%	33.0%	33.8%	34.5%	32.1%
2	14.9%	19.3%	26.4%	15.5%	19.8%	26.8%	16.5%	21.1%	26.6%
≥3	6.4%	10.0%	16.5%	6.8%	10.9%	17.3%	8.6%	13.3%	20.4%
Hospital bed size									
Small	8.6%	5.7%	6.0%	5.6%	5.8%	5.9%	6.3%	6.0%	6.0%
Medium	17.1%	20.0%	19.6%	21.6%	22.8%	23.3%	20.7%	21.3%	21.9%
Large	74.3%	74.3%	74.3%	72.9%	71.4%	70.8%	73.0%	72.7%	72.1%
Hospital Region									
Northeast	28.6%	23.0%	28.6%	25.3%	24.1%	27.8%	22.8%	20.8%	24.6%
Midwest	17.5%	17.5%	15.3%	17.3%	15.9%	12.7%	17.7%	17.3%	16.1%
South	41.5%	46.6%	44.4%	42.9%	47.6%	47.9%	44.1%	47.3%	47.0%
West	12.4%	12.9%	11.7%	14.5%	12.4%	12.0%	15.4%	14.7%	12.3%
Location/ Teaching status									
Rural	6.0%	6.4%	5.1%	5.0%	6.5%	5.1%	6.5%	7.6%	7.2%
Urban-non teaching	35.5%	41.8%	41.5%	39.4%	42.2%	40.3%	39.3%	43.8%	43.4%
Urban- teaching	58.5%	51.8%	53.4%	55.6%	51.3%	54.6%	54.2%	48.5%	49.4%
Length of stay, Median (IQR)	3 (2-5)	4 (3-6)	6 (5-10)	3 (2-5)	4 (3-6)	7 (5-10)	4 (2-5)	4 (3-6)	6 (5-10)
Total charge,$, Median (IQR)	36276 (23074-56989)	36606 (22263-58425)	46759 (29189-77712)	40655 (25028-64583)	41498 (25563-66726)	52479 (32576-86384)	44303 (27789-73340)	46311 (29130-76450)	56737 (36702-98776)

Table 5.2 continued.

Year	2009-2010			2011-2012			2013-2014		
Timing of invasive strategy	Early	Interm.	Late	Early	Interm.	Late	Early	Interm.	Late
Number of Cases weighted (%age)	303,976 (71.9%)	56,837 (13.4%)	62,220 (14.7%)	328,890 (72.5%)	60,273 (13.3%)	64,664 (14.3%)	357,390 (72.7%)	67,005 (13.6%)	67,390 (13.7%)
Age (year), Median IRQ	64 (54-74)	67 (57-77)	69 (60-78)	64 (55-74)	67 (58-77)	70 (60-79)	65 (55-67)	67 (58-77)	70 (60-78)
Men %	63.5%	58.5%	44.7%	64.0%	58.6%	55.0%	64.0%	59.4%	57.5%
Ethnicity									
White	68.4%	66.6%	64.0%	71.8%	69.3%	67.7%	72.0%	70.3%	68.2%
Black	9.3%	11.7%	14.0%	10.0%	13.2%	14.9%	9.9%	12.2%	13.8%
Hispanic	6.3%	7.5%	8.0%	6.8%	7.7%	8.3%	7.3%	8.8%	9.0%
Asian/Pacific Islander	1.7%	1.5%	2.2%	1.8%	1.9%	2.1%	2.0%	2.1%	2.4%
Native American	0.6%	0.6%	0.6%	0.5%	0.5%	0.4%	0.4%	0.4%	0.4%
Other	2.7%	2.8%	2.9%	3.4%	3.3%	3.2%	3.0%	2.7%	2.9%
Missing Race	11.0%	9.3%	8.1%	5.8%	4.1%	3.3%	5.4%	3.6%	3.4%
Weekend admission	19.8%	53.4%	24.4%	20.0%	53.7%	26.0%	20.8%	53.3%	24.3%
Primary expected payer, %									
Medicare	48.4%	56.7%	64.9%	50.8%	60.1%	67.9%	51.3%	60.1%	67.6%
Medicaid	6.5%	6.7%	7.5%	6.8%	7.0%	7.2%	7.8%	8.0%	8.4%
Private Insurance	34.3%	26.6%	19.4%	31.1%	23.6%	16.9%	30.6%	23.5%	17.0%
Self-pay	7.1%	6.6%	5.2%	7.2%	6.2%	4.9%	6.5%	5.3%	4.4%
No charge	0.6%	0.6%	0.4%	0.8%	0.5%	0.5%	0.7%	0.7%	0.4%
other	3.1%	2.8%	2.6%	3.2%	2.7%	2.4%	3.0%	2.4%	2.1%

Median Household Income (percentile)									
0-25th	28.9%	31.0%	31.9%	29.6%	31.3%	32.9%	29.5%	31.3%	32.6%
26-50th	27.5%	28.3%	27.6%	26.3%	26.1%	25.0%	28.3%	28.8%	28.3%
51-75th	24.0%	23.1%	22.7%	24.6%	24.0%	23.6%	23.4%	23.0%	22.1%
76-100th	19.3%	17.6%	18.1%	19.5%	18.6%	18.5%	18.8%	16.8%	17.0%
Comorbidities, %									
Dyslipidaemia	60.8%	56.1%	45.9%	63.4%	59.5%	51.2%	64.0%	60.1%	53.1%
Smoking	41.0%	35.6%	30.4%	43.7%	39.3%	34.9%	47.1%	42.8%	39.6%
Previous AMI	9.4%	9.9%	9.6%	10.4%	11.7%	10.8%	11.0%	12.4%	11.1%
History of IHD	84.7%	80.6%	74.9%	84.1%	81.1%	76.0%	82.7%	79.3%	74.9%
Previous PCI	12.0%	12.0%	10.2%	13.9%	15.4%	12.7%	15.0%	15.8%	14.0%
Previous CABG	5.1%	6.6%	7.2%	5.7%	7.3%	7.7%	5.9%	7.5%	8.1%
Previous CVA	3.7%	4.6%	5.2%	4.5%	5.6%	6.3%	5.0%	6.3%	6.7%
Family history of CAD	10.1%	6.7%	4.4%	10.2%	7.8%	5.0%	10.9%	8.4%	5.9%
Valvular heart disease	0.1%	0.2%	0.3%	0.1%	0.2%	0.3%	0.07%	0.1%	0.2%
Peripheral vascular disease	10.8%	13.5%	16.5%	11.4%	14.7%	18.1%	11.5%	14.0%	18.5%
Multivessel PCI	9.7%	7.2%	6.5%	10.8%	8.6%	8.3%	11.3%	9.0%	8.9%
Use of assist devise or IABP	4.6%	2.5%	2.8%	4.6%	2.4%	3.5%	4.2%	2.5%	3.2%
Shock	2.8%	1.7%	2.7%	3.1%	1.8%	3.3%	3.1%	2.0%	3.7%
AIDS	0.15%	0.11%	0.22%	0.14%	0.13%	0.16%	0.13%	0.16%	0.21%
Alcohol abuse	2.9%	3.1%	3.4%	3.1%	3.3%	3.8%	3.3%	3.4%	3.9%
Deficiency anaemias	11.4%	16.5%	25.2%	12.3%	18.7%	28.7%	11.9%	17.8%	28.5%
Chronic Blood loss anaemia	0.6%	0.8%	1.8%	0.5%	0.8%	1.5%	0.5%	0.5%	1.2%
RA/collagen vascular	2.1%	2.3%	2.4%	2.3%	2.7%	3.0%	2.5%	2.6%	2.9%

diseases									
Congestive heart failure	0.4%	0.5%	1.3%	0.3%	0.4%	1.0%	0.2%	0.4%	0.9%
Chronic pulmonary disease	17.9%	22.2%	27.4%	18.9%	23.5%	29.8%	19.4%	24.3%	30.2%
Coagulopathy	3.9%	4.1%	6.2%	4.4%	5.1%	7.5%	4.7%	5.3%	7.5%
Depression	6.7%	7.4%	7.6%	7.6%	8.5%	9.6%	8.3%	9.4%	9.6%
Diabetes	29.4%	32.2%	33.3%	31.5%	34.8%	36.0%	32.1%	34.7%	37.3%
Diabetes with complications	4.5%	6.9%	11.3%	5.4%	8.6%	13.3%	6.0%	8.7%	14.4%
Drug abuse	2.1%	2.1%	2.3%	2.4%	2.5%	2.7%	2.7%	2.8%	2.8%
Hypertension	71.3%	73.4%	72.5%	74.3%	77.6%	77.0%	76.1%	79.4%	78.0%
Hypothyroidism	9.0%	10.8%	11.0%	10.1%	12.3%	13.0%	10.8%	11.8%	13.5%
Liver disease	1.0%	1.2%	1.8%	1.2%	1.5%	2.1%	1.4%	1.9%	2.6%
Lymphomas	0.3%	0.6%	0.7%	0.4%	0.5%	0.6%	0.4%	0.6%	0.7%
Fluid and electrolyte disturbances	13.4%	17.3%	28.5%	15.2%	20.8%	32.0%	16.4%	22.4%	34.2%
Other neurological disorders	3.5%	4.7%	6.2%	3.9%	5.4%	6.8%	4.3%	5.7%	6.8%
Obesity	14.8%	14.7%	14.2%	17.2%	18.1%	18.0%	19.1%	19.9%	21.0%
Paralysis	1.0%	1.3%	2.2%	1.1%	1.3%	2.2%	1.0%	1.5%	2.3%
Psychoses	1.8%	2.3%	2.6%	2.0%	2.5%	3.3%	2.2%	2.8%	3.4%
Pulmonary circulation disorder	0.07%	0.1%	0.2%	0.05%	0.1%	0.1%	0.04%	0.08%	0.1%
Renal failure (chronic)	12.5%	19.5%	31.0%	14.0%	22.9%	34.0%	14.7%	22.5%	35.3%
Peptic ulcer disease	0.02%	0.02%	0.04%	0.03%	0.05%	0.05%	0.02%	0.02%	0.04%
Weight loss	1.4%	1.5%	3.0%	1.5%	2.3%	4.3%	1.6%	2.2%	4.3%
Solid tumor without mets	1.0%	1.2%	1.6%	1.0%	1.1%	1.8%	1.0%	1.3%	1.8%
Metastatic cancer	0.4%	0.5%	0.7%	0.4%	0.5%	0.8%	0.4%	0.5%	0.7%
Dementia	2.3%	3.2%	4.6%	2.5%	3.6%	5.6%	2.4%	3.6%	5.2%

Charlson Comorbidity Index									
0	38.8%	29.9%	18.7%	36.2%	25.8%	15.8%	34.8%	25.1%	14.4%
1	33.3%	32.8%	30.3%	33.0%	31.1%	27.7%	32.5%	30.8%	26.6%
2	17.6%	21.9%	26.1%	18.3%	23.6%	26.9%	19.1%	23.5%	27.8%
≥3	10.2%	15.4%	24.9%	12.4%	19.5%	29.6%	13.6%	20.5%	21.1%
Hospital bed size									
Small	7.3%	6.6%	6.6%	7.6%	7.5%	7.5%	10.3%	9.8%	9.6%
Medium	19.4%	20.7%	21.4%	23.8%	24.8%	23.3%	26.4%	27.1%	26.7%
Large	73.3%	72.6%	72.0%	68.6%	67.7%	69.2%	63.2%	63.1%	63.7%
Hospital Region									
Northeast	19.1%	19.2%	21.9%	17.6%	18.2%	20.9%	17.0%	18.3%	21.1%
Midwest	21.9%	18.5%	17.6%	23.4%	20.9%	19.8%	24.9%	23.7%	22.6%
South	41.8%	47.5%	47.1%	41.6%	45.6%	46.7%	40.7%	43.6%	43.7%
West	17.2%	14.7%	13.4%	17.4%	15.3%	12.6%	17.4%	14.4%	12.6%
Location/ Teaching status									
Rural	7.3%	6.7%	5.9%	6.2%	5.6%	5.3%	6.4%	6.3%	5.2%
Urban-non teaching	41.4%	44.4%	42.4%	40.4%	42.3%	41.3%	33.0%	33.3%	33.2%
Urban- teaching	51.3%	48.9%	51.7%	53.4%	52.0%	53.4%	60.6%	60.4%	61.6%
Length of stay, Median (IQR)	3 (2-5)	4 (3-6)	6 (5-10)	2 (2-4)	3 (3-6)	6 (4-10)	2 (2-4)	3 (3-6)	6 (4-10)
Total charge,$, Median (IQR)	49564 (31416-81416)	52157 (31902-86213)	66233 (40732-112689)	54826 (35027-89429)	56866 (36117-92808)	74067 (45924-125048)	61279 (38541-99171)	63391 (39589-102309)	78990 (49389-132442

AMI= acute myocardial infarction, IHD, ischemic heart disease, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CVA= cerebrovascular accident, CAD= coronary artery disease, IABP= intra-aortic balloon pump, AIDS= acquired immunodeficiency syndromes, RA= Rheumatoid arthritis, IQR= interquartile range.

5.4.2 *Temporal trends*

The use of an invasive strategy in the early group increased from 65.6% to 72.6% and late invasive strategy declined commensurately from 19.6% to 13.5% from 2004 to 2014 (Figure 5.2). There were significant disparities in the secular trends of an invasive strategy in patients stratified according to gender, comorbidity burden, admission day, age and ethnicity. Temporal trends in the timing of an invasive strategy stratified according to gender reveal that early invasive strategy was comparatively higher in men (68.6% to 74.2%) during the study period, although there was a greater proportional increase in the use of early invasive strategy from 60.9% to 70.0% in women (Figure 5.3). There were significant disparities in the timing of invasive strategy use in patients with different comorbidity burden as defined by the Charlson comorbidity index (Figure 5.4). During the 11-year study period, the use of early invasive strategy increased from 75.0% to 82.1% in patients with no comorbidity (CCI=0) compared to 47.2% to 58.3% in the CCI≥3 category. For weekend admissions (Figure 5.5), the use of early invasive strategy has increased from 47.4% to 58.5% in patients admitted on a weekend, the intermediate invasive strategy group remained relatively unchanged (31.4% to 29.0%). Similar inequalities in use of early versus late invasive strategy were noted in patients from different ethnic backgrounds and age groups. Young patients aged <65 years were more likely to be managed with early invasive strategy (76.1%) compared to older patients aged >75 (63.1%) (Figure 5.6). Similarly, overall, higher proportions of African American received late invasive strategy compared to early invasive strategy (12.7% vs 8.9%) and this trend remained unchanged over the study period. (Figure 5.7).

Figure 5.2: Temporal trends in time to invasive strategy stratified according to the early, intermediate and late groups.

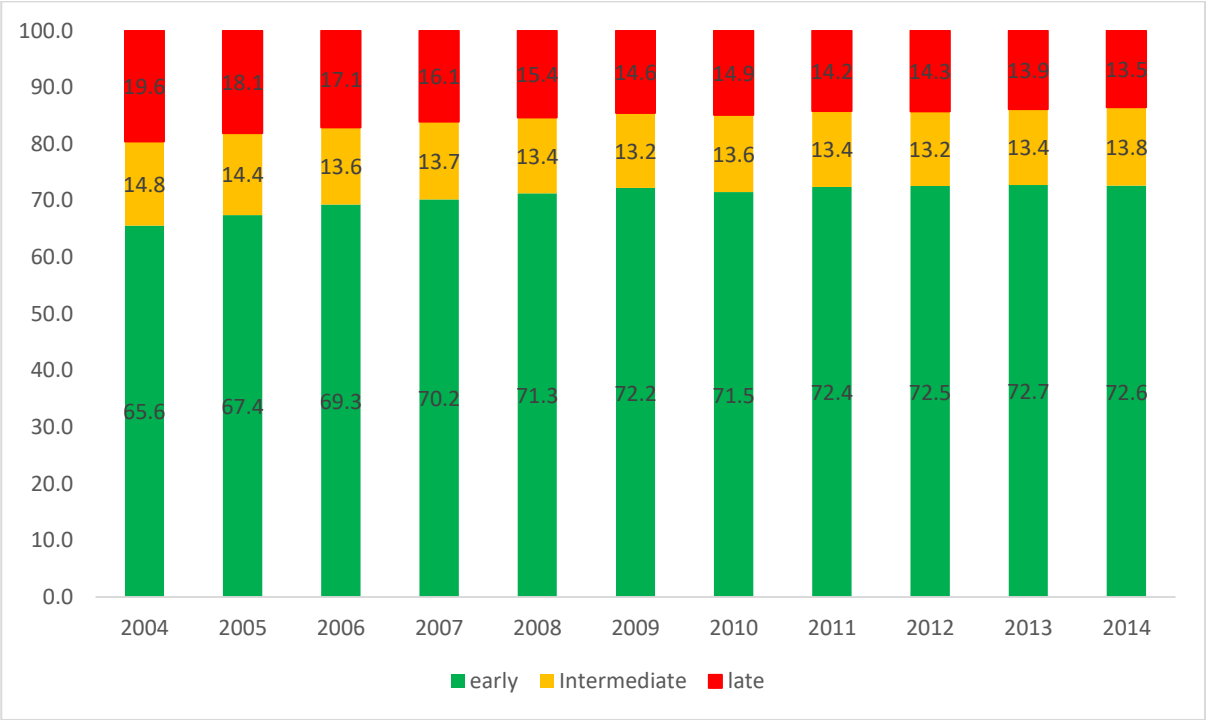
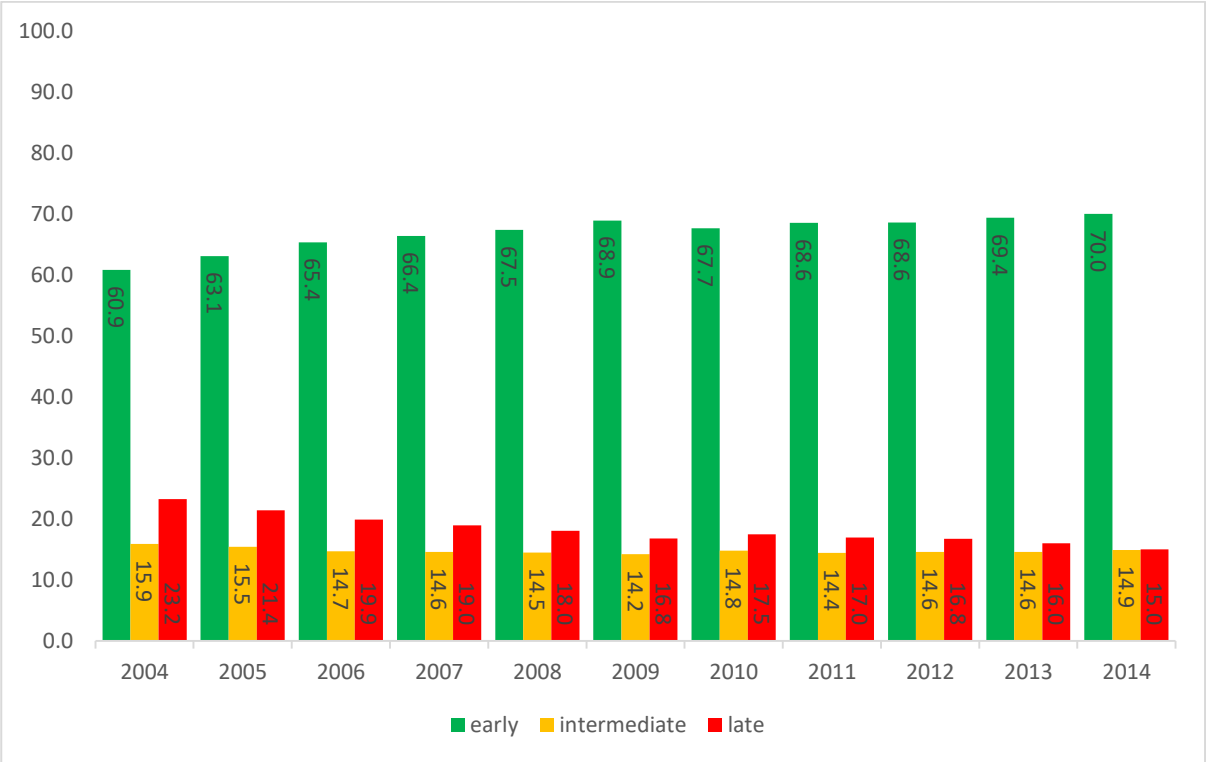


Figure 5.3: Trends in the timing of an invasive strategy stratified according to gender

a) Women



b) Men

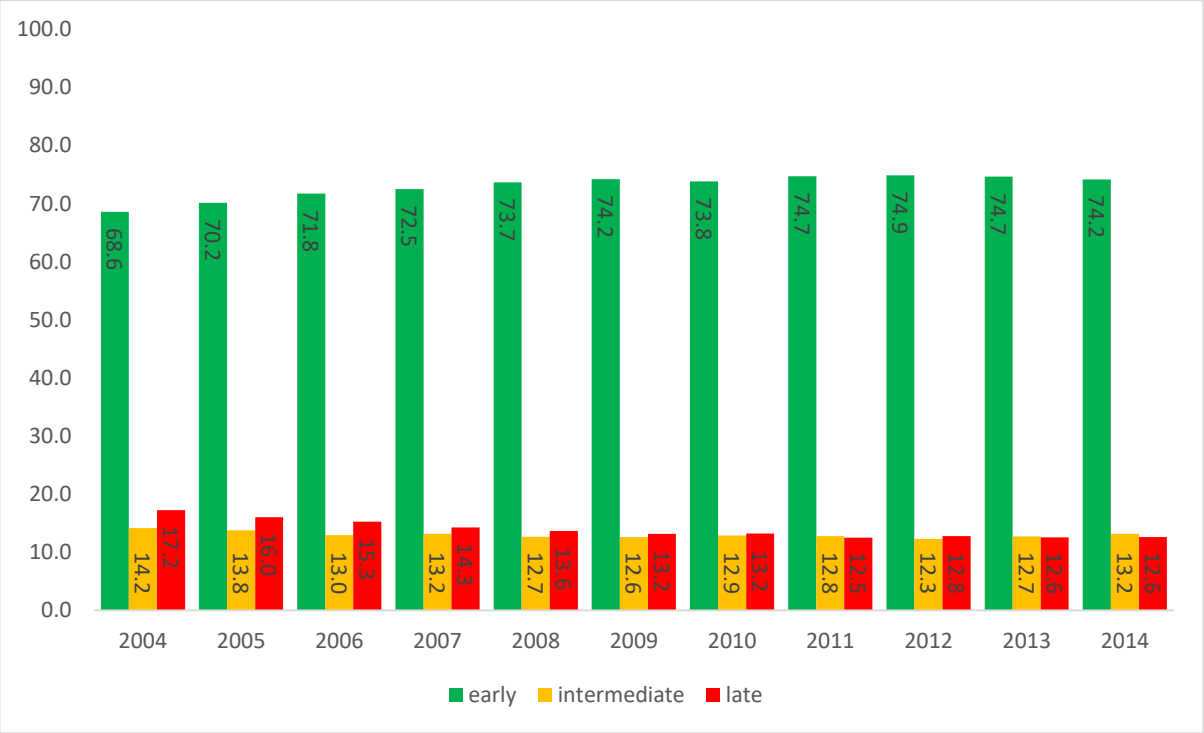
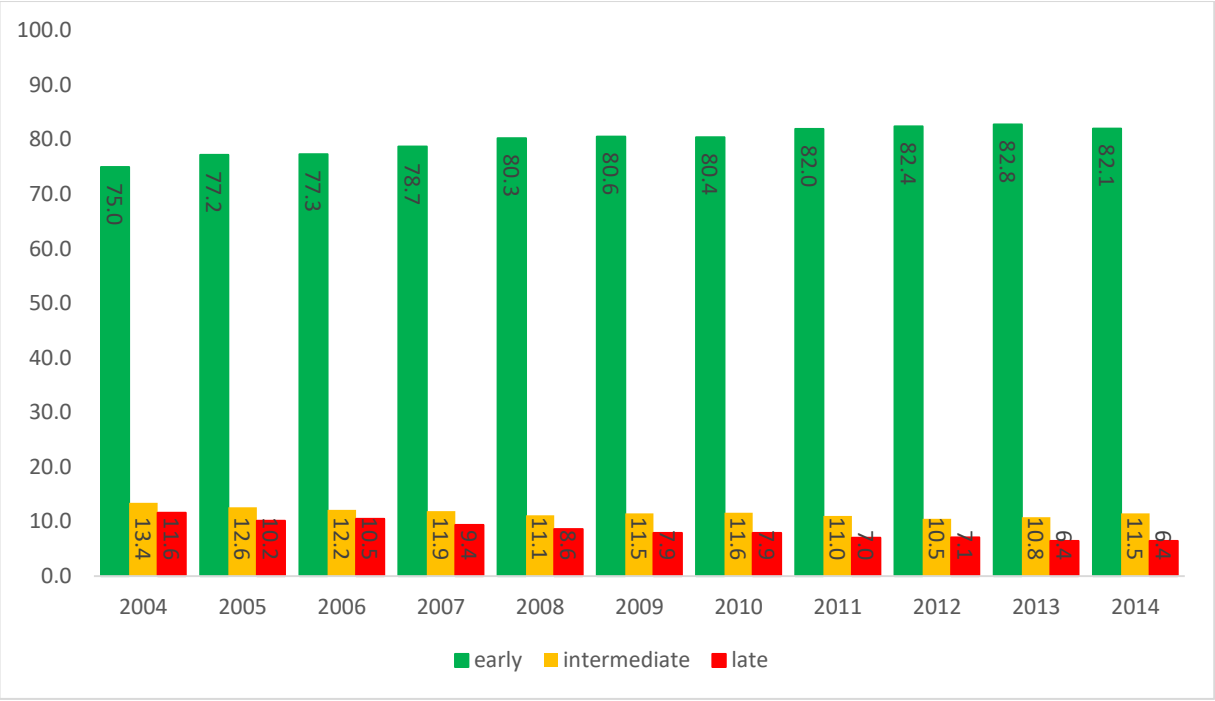


Figure 5.4: Temporal trends in time to invasive strategy and comorbidity burden as defined by Charlson comorbidity index

a) CCI=0



b) CCI>3

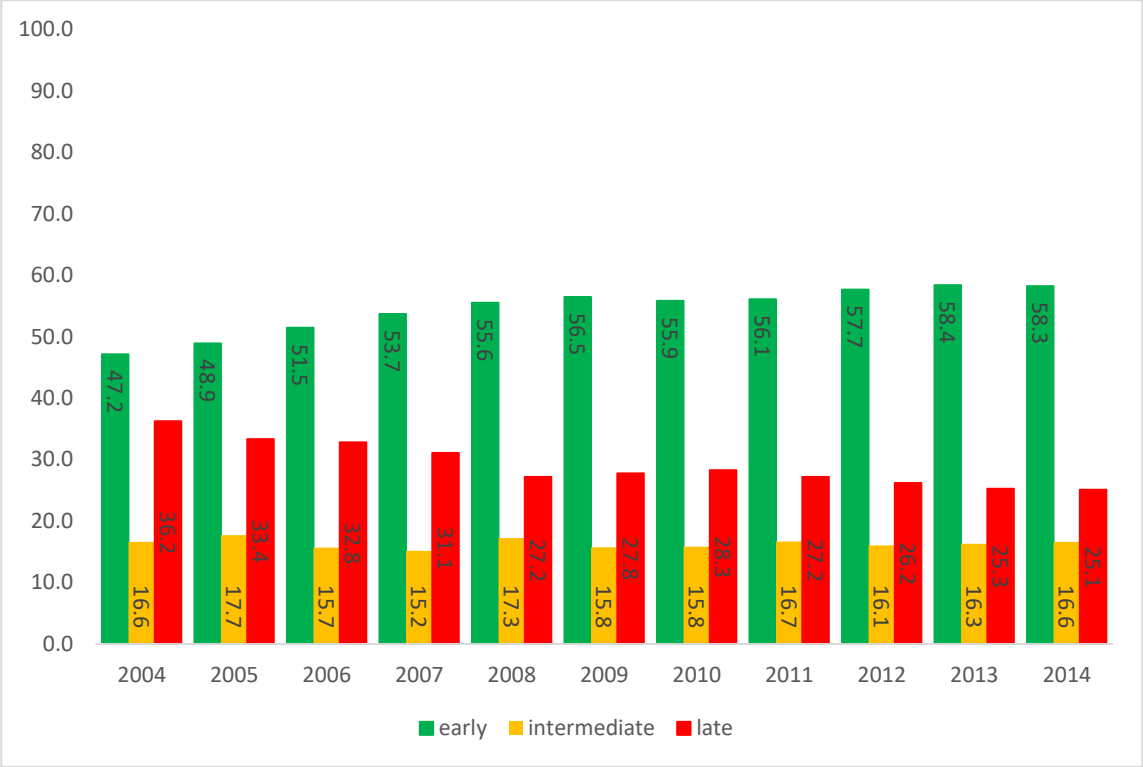
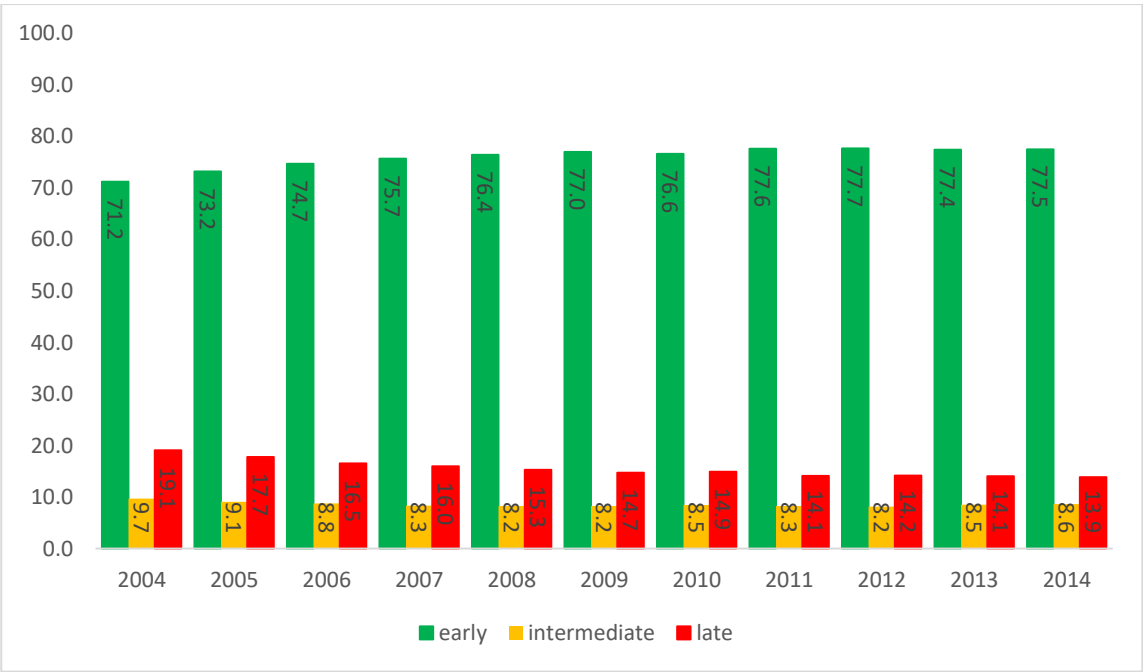


Figure 5.5: Trends in timing of invasive strategy stratified according to weekday versus weekend admission

a) Weekday admission



b: Weekend admissions

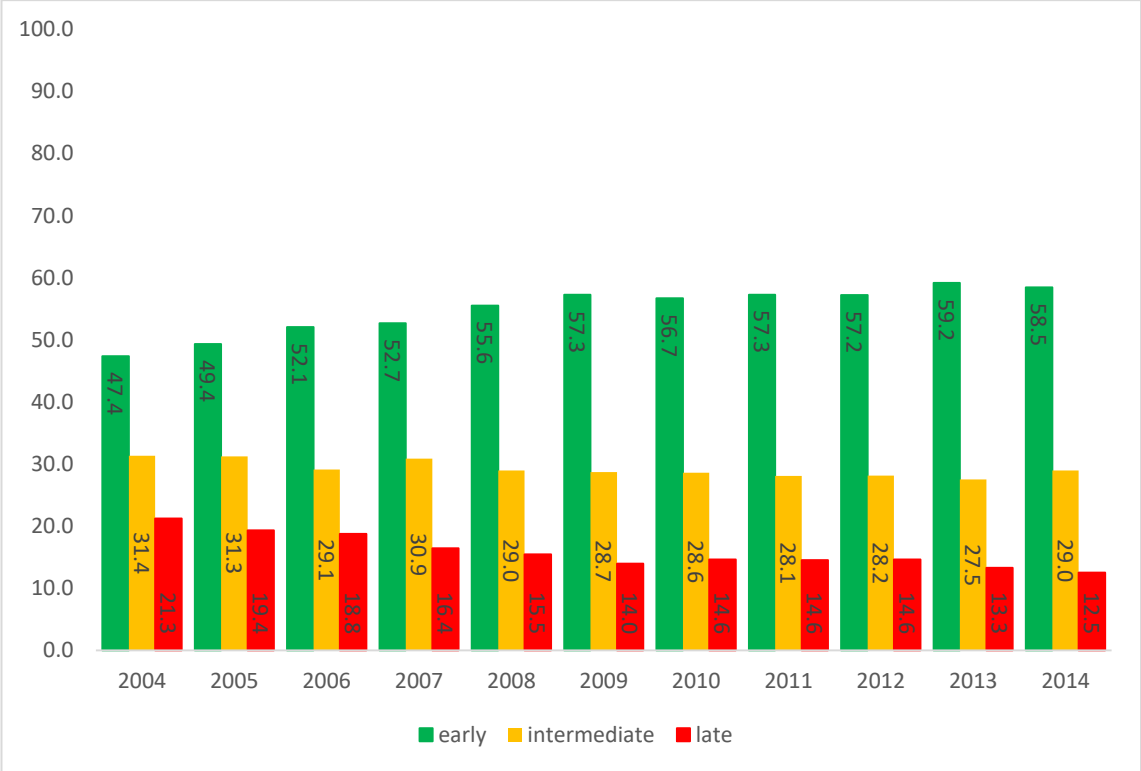


Figure 5.6: Relationship between age and time to an invasive strategy

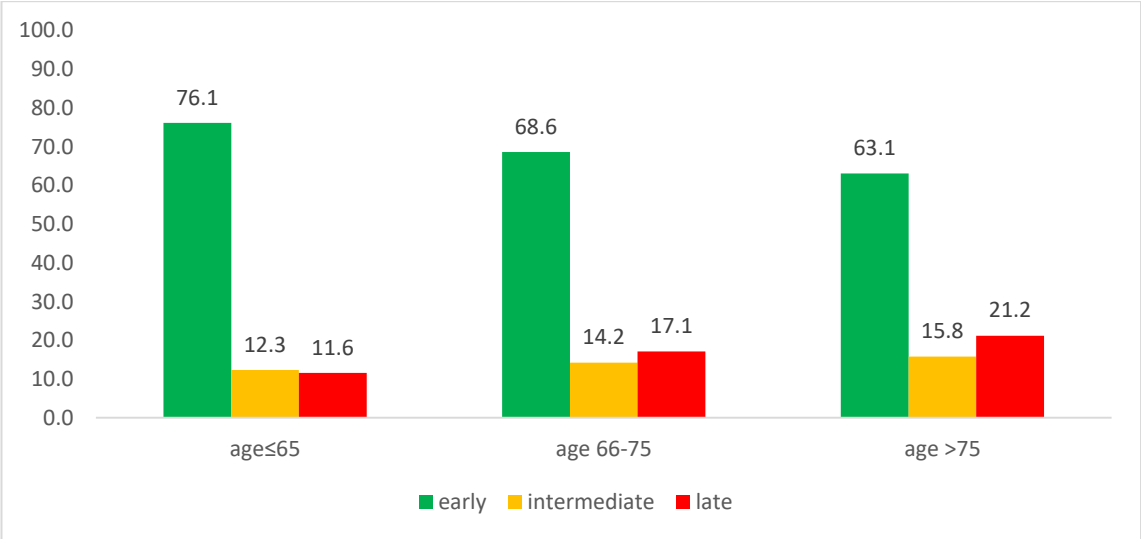
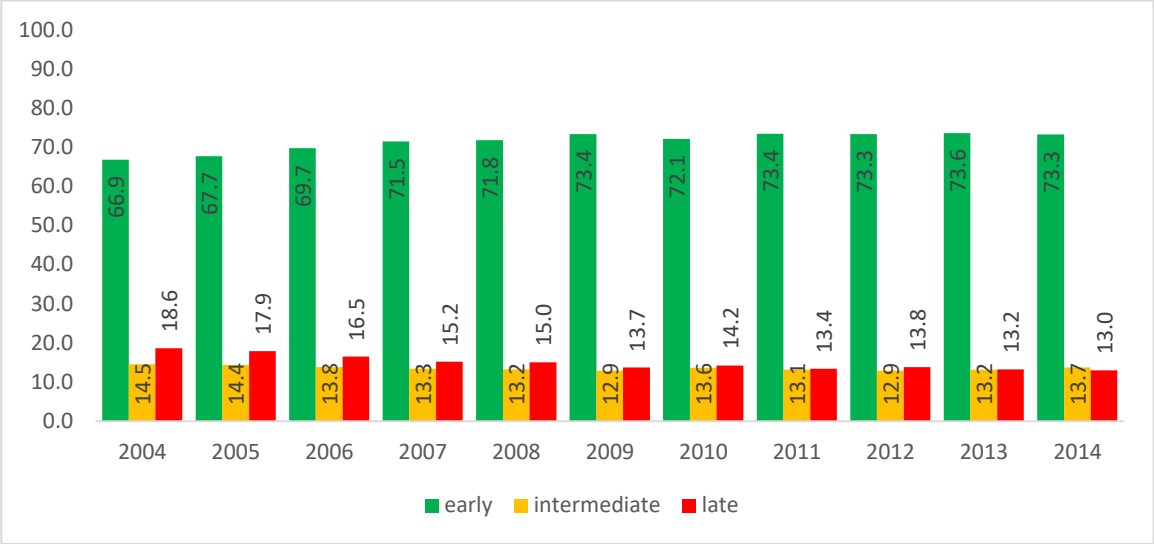
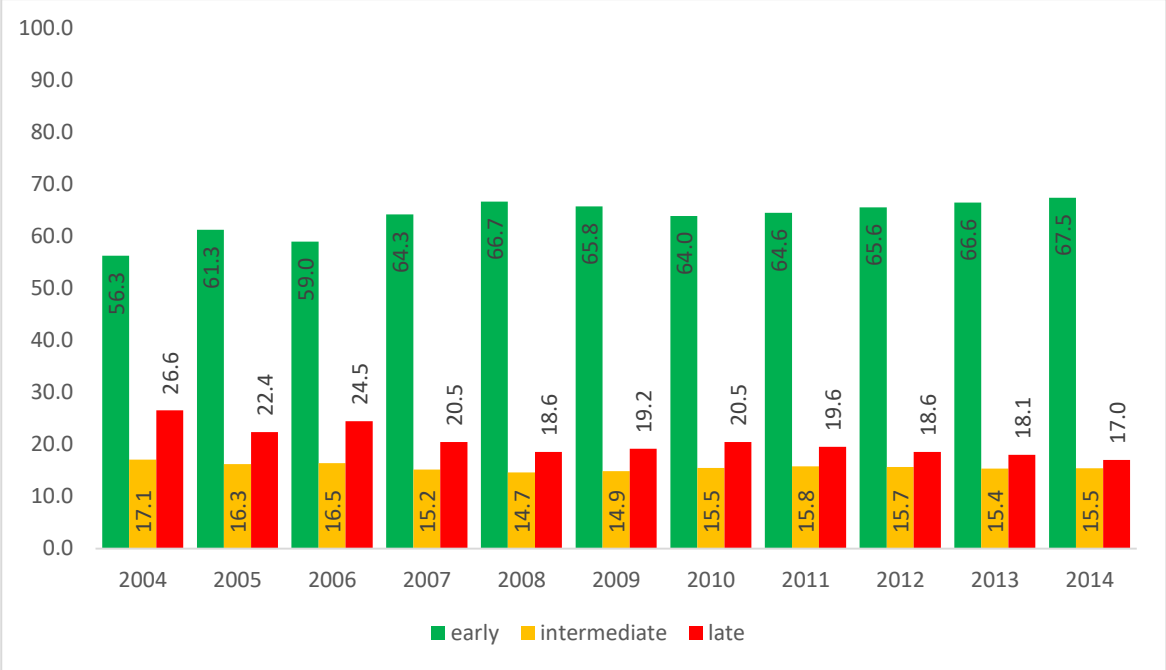


Figure 5.7: Trends in the timing of an invasive strategy stratified according to Ethnicity

a) white ethnicity



b) African American ethnicity



5.4.3 *Independent predictors*

Independent clinical and institutional predictors of early invasive strategy as shown in Table 5.3. The presence of haemodynamic compromises such as cardiogenic shock (OR 1.45, 95%CI 1.37-1.54) and use of intra-aortic balloon pump (OR 2.09, 95%CI 2.00-2.19) was associated with early use of invasive strategy. Conversely, Female sex (OR 0.92 95%CI 0.91-0.94), weekend admission (OR 0.35 95%CI 0.34-0.36), African

American (OR 0.77, 95%CI 0.74-0.81), complicated diabetes (OR 0.64, 95%CI 0.62-0.66) and chronic renal failure (OR 0.61, 95%CI 0.60-0.63) were strong negative predictors of early invasive strategy.

Table 5.3: Independent predictors of an early invasive strategy

Variable	Odds Ratio	95% confidence interval	
Age	0.98	0.98	0.98
Weekend admission	0.35	0.34	0.36
Female	0.92	0.91	0.94
African American (Ref White)	0.77	0.74	0.81
Alcohol abuse	0.81	0.77	0.85
Chronic deficiency anaemia	0.74	0.72	0.76
Chronic blood loss	0.61	0.56	0.66
Congestive heart failure	0.81	0.72	0.92
Depression	0.92	0.89	0.95
Diabetes mellitus	0.86	0.84	0.87
Diabetes mellitus with complications	0.64	0.62	0.66
Liver disease	0.76	0.71	0.81
Lymphoma	0.79	0.71	0.88
Metastatic cancer	0.82	0.73	0.91
Obesity	0.94	0.91	0.96
Paralysis	0.78	0.73	0.84
Peripheral vascular disease	0.90	0.88	0.92
Renal failure	0.61	0.60	0.63
Cancer	0.78	0.73	0.83
Weight loss	0.82	0.77	0.88
Smoking	1.15	1.12	1.17
Dyslipidemia	1.21	1.19	1.24
Ischemic heart disease	1.32	1.29	1.36
Family history of coronary artery disease	1.28	1.23	1.34
Previous myocardial infarction	0.92	0.90	0.95
Previous Cerebrovascular accident	0.92	0.88	0.96
Previous coronary artery bypass graft	0.84	0.81	0.87

Cardiogenic Shock	1.45	1.37	1.54
Intra-aortic balloon pump	2.09	2.00	2.19
Dementia	0.84	0.80	0.87

5.4.4 *Clinical outcomes*

Crude outcomes stratified according to the three different timings of an invasive strategy are shown in Figure 5.8. In-hospital mortality in the early, intermediate and late were 1.8%, 1.5% and 2.3%, ($p<0.0001$) respectively. Lower rates for crude MACCE and bleeding was observed in the early and intermediate category compared to late invasive strategy category as depicted in Figure 5.8. Multivariable logistic regression analysis after adjusting for all the potential confounders revealed that early invasive strategy was associated with reduced in-hospital mortality (OR 0.39 95%CI 0.37-0.41), in-hospital stroke (OR 0.86 95%CI 0.80-0.92) and MACCE (OR 0.80 95%CI 0.77-0.83); however, the lowest risk was observed in the intermediate category (Table 5.4). The comparison group in this analysis was patients receiving conservative management.

Figure 5.8: Crude outcomes stratified according to the timing of An invasive strategy

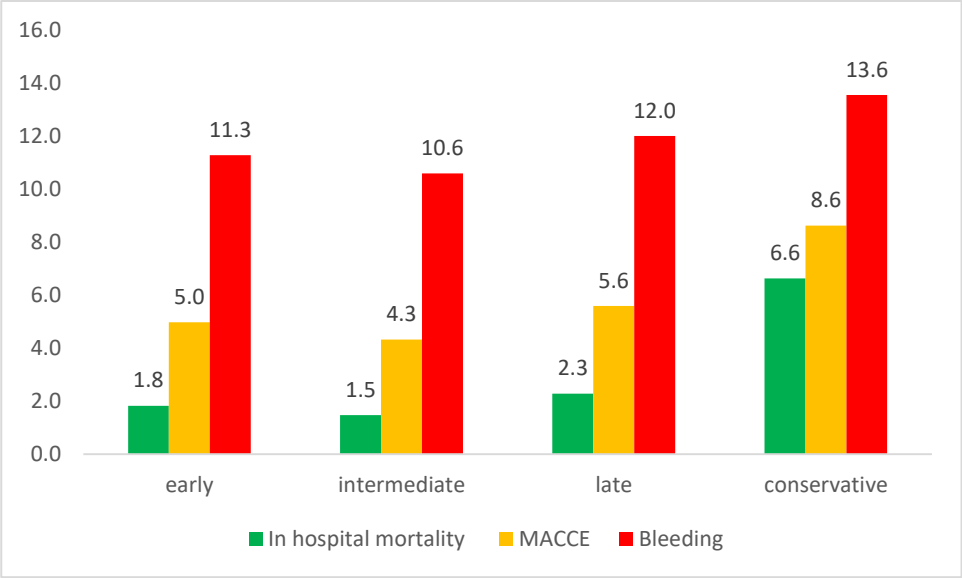


Table 5.4: Association between the timing of an invasive strategy and clinical outcomes

Clinical outcome	Reference No Cath	Early Day=0,1	Intermediate Day=2	Late Day≥3
MACCE	1.00	0.80 (0.77-0.83), p<0.001	0.66 (0.63-0.70), p<0.001	0.65 (0.62-0.78), p<0.001
In hospital mortality	1.00	0.39 (0.37-0.41), p<0.001	0.30 (0.28-0.33), p<0.001	0.33 (0.31-0.35), p<0.001
In-hospital stroke	1.00	0.86 (0.80-0.92), p<0.001	0.97 (0.93-1.02), p=0.8	1.19 (1.10-1.28), p<0.001
Cardiac Complications	1.00	4.71 (4.09-5.41),p<0.001	4.00 (3.47-4.61),p<0.001	3.49 (3.03-4.02), p<0.001
Bleeding complications	1.00	1.16 (1.11-1.22), p<0.001	1.15 (1.10-1.21), p<0.001	1.43 (1.37-1.49), p<0.001

5.5 Discussion

In this large, contemporary cohort of patients admitted with a diagnosis of an NSTEMI in the US, there are several important observations. First, there is an increasing trend in the use of early invasive strategy compared to intermediate and late invasive strategy over an 11-year period. Second, there were significant changes in clinical characteristics and baseline risk profile of patients treated with early invasive strategy compared to intermediate and late invasive strategy, so that use of an early invasive strategy remains attenuated in elderly, complex and multi-morbid patients despite an overall increase in adoption of an early invasive strategy in NSTEMI. Third, there remain significant disparities in use of early invasive strategy across different groups of patients particularly women, high comorbidity burden, weekend admission and African Americans, who were less likely to receive early invasive strategy compared to men, lower comorbidity burden, weekday admission and Caucasians. Fourth, the presence of

non-cardiac comorbidities such as liver disease, peripheral vascular disease, chronic renal failure, dementia and history of alcohol disease was inversely associated with receipt of an early invasive strategy. Finally, the use of invasive strategy on day 2 from admission appears to be safe and feasible in the majority of the patients admitted following NSTEMI.

This study demonstrates that women, African Americans and those without private insurance were less likely to undergo early invasive strategy. Women admitted with NSTEMI are older, burdened with more comorbidities and are known to have a higher risk of peri-procedural bleeding when compared to men[38]. However, women also have a higher risk of ischemic complications following NSTEMI admission such as re-infarction and repeat admissions and therefore are more likely to benefit from an early invasive approach[153-155]. This is in keeping with the current AHA/ACC NSTEMI guidelines recommending an early invasive approach be adopted particularly in those with high-risk features to improve outcomes[3]. Lower utilization of invasive cardiac procedures has been reported in patients without private health insurance[156]. Consistent with the literature, patients with private insurance were more likely to have an early invasive strategy (33.5%) than late invasive strategy (16.7%), while patients on Medicare were more likely to have a late invasive strategy (66.4%) than early invasive strategy (49.5%). More than half of all patients treated conservatively (54.2%) were on Medicare, while only 30.8% had private insurance. Socioeconomic status, varying practices amongst treating physician and hospitals, lack of access to appropriate health care resources, and regional factors may be responsible for these biases in management in different patient groups when partitioned into payer categories[139,157-160]. This study shows that there remain significant disparities in early aggressive treatment of these

undertreated subgroups of patients and the need for the development of uniform pathways to improve the outcomes in this underserved population.

Another important finding is the significantly lower adoption of an early invasive strategy in patients admitted on the weekend. Previous studies reporting on "weekend effect" in acute myocardial infarction setting have mainly studied the association of clinical outcomes with a weekend admission[161]. In this large contemporary analysis over the past decade, the results illustrate that almost 30% of the patients admitted on weekends receive invasive strategy after 2 days compared to only 8.6% on a weekday. More importantly, this trend has remained stable over the study period with very little change in the use of an invasive strategy in patients admitted on the weekend. The most likely explanation for this findings is that patients admitted on a weekend are less likely to be reviewed by a cardiologist and may wait till the weekday to receive a specialist input where the decision is taken around further invasive management.

It also appears that there exists a treatment paradox where younger and less comorbid patients selectively receive early invasive strategy in contrast to older, multimorbid patients who may have more to gain from the early invasive strategy. The presence of non-cardiac comorbidities such as liver disease, chronic kidney disease, previous CVA, dementia, and peripheral vascular disease were strong negative predictors of early invasive strategy. Current guidelines recommend the use of early invasive strategy in patients presenting with high-risk features including ischemic electrocardiographic changes, elevated troponin levels, new CHF symptoms, left ventricular dysfunction, or haemodynamic instability[3,4]. Presence of cardiogenic shock or use of intra-aortic balloon pump, cardiovascular risk factors such as smoking, dyslipidaemia was strongly associated with early use of invasive strategy in our study.

Finally, there was an overall decreasing trend in in-hospital mortality, MACCE and in-hospital stroke in patients managed invasively compared to a conservative approach consistent with the findings in chapter 4. Interestingly, there appears to be a U shaped relationship were patients in the intermediate category receiving an invasive strategy on day 2 appear to have the lowest in-hospital mortality and MACCE, both in the unadjusted and adjusted analysis. Although it is widely believed that an invasive strategy improves outcomes by reducing ischemic complications following NSTEMI, the studies have shown inconsistent results regarding the timing of an invasive strategy[58,60,105,150]. It is important to note that the majority of these studies are conducted in the pre-P2Y12 inhibitor era with far less aggressive pharmacotherapy compared to current practices. The main benefit of early invasive approach in NSTEMI in driven by the reduction in ischemic complications such as re-infarction and future events[16,18,162,163]. It is plausible that with newer potent antiplatelet and anticoagulant use, risk of ischemic complications has reduced and an early invasive strategy can be deferred safely. Lindholm et al used data from SWEADHEART registry to study the optimal timing of invasive strategy in NSTEMI patients demonstrating a 16% relative risk reduction (HR 0.86(95%CI 0.77-0.97) in patients undergoing an invasive treatment on day 2 or day 3 whereas no difference in death or MI was found on day 1[164]. National guidelines advocate a risk based approach in offering early invasive approach using validated risk scores such as Global Registry of Acute Coronary Events (GRACE) ACS score[3,4]. It is important to highlight that NIS data doesn't capture information around haemodynamic status, ECG findings, cardiac biomarker, the severity of coronary disease and GRACE ACS score, therefore a true casual inference between optimal timing of invasive strategy and in-hospital outcomes cannot be inferred from this study. The patient in the early invasive angiography had increased comorbidity burden and

likely to have other high-risk features such as ongoing pain, ECG changes, haemodynamic instability for each they undergo early invasive strategy. As such NIS lacks this information and therefore, the favourable outcomes in patients in the intermediate group may just reflect residual confounding.

5.6 Study strengths and limitations

These findings must be interpreted in the context of certain limitations. First, the time from admission to an invasive strategy is calculated from admission to procedure day which may be confounded by inter-hospital transfers and unavailability of onsite coronary angiography facilities. The NIS doesn't collect information around the haemodynamic status, ECG changes and biomarker positivity, hence risk stratification scores such as the GRACE score cannot be calculated or adjusted. This may be particularly relevant in the early invasive group, where high-risk features such as dynamic ECG changes, biomarker positivity, on-going symptoms or adverse haemodynamic profiles may be over-represented in the early invasive group and are unable to adjust for these features. Consequently, this may have confounded the influence of earlier angiography on mortality in these patients. Previous work has suggested that the benefit of an early invasive approach was seen predominantly in those patients with a high GRACE risk score (GRACE >140)[145], hence it was not possible to further study the timing of invasive strategy as well as clinical outcomes stratified by the GRACE score. Furthermore, the NIS does not capture the severity of coronary artery disease or antiplatelet therapy that are important determinants of clinical outcomes. Finally, it is important to note that NIS is an administrative database which is subject to coding errors in both diagnoses and procedure codes.

5.7 Conclusion

In this large contemporary national analysis of patients admitted with NSTEMI in the US, there was an increasing trend in the use of early invasive strategy associated with significant changes in baseline characteristics and risk profile of these patients compared to those receiving late invasive strategy. Although younger, healthier patients are more likely to receive early invasive strategy there remains important gender, ethnic, admission day and payment status inequalities in receipt of early invasive strategy. Women, African American, weekend admission and lack of private insurance were less likely to receive early invasive strategy. There was a U shape relationship in the time to invasive strategy and in-hospital clinical outcomes where patients receiving invasive strategy at day 2 had better outcomes compared to those receiving early or late invasive strategy. Future efforts should be focused around implementing a uniform risk guided approach in clinical practice and development of pathways to improve access to the invasive strategy in high-risk NSTEMI patients.

Chapter 6

Guidelines recommended risk stratification and receipt of an invasive strategy in the management of the NSTEMI

6.1 Introduction

In line with the second part of the thesis, this chapter was aimed to investigate the utilisation of an invasive strategy based on the risk criteria recommended by two major international guidelines namely ESC and AHA/ACC. The manuscript from this chapter is currently under review in peer review cardiology journal.

An invasive strategy followed by revascularisation where appropriate compared to conservative medical management is associated with reduced ischemic complications and improved survival in patients presenting with an NSTEMI and is recommended by international guidelines[3,4,52,57,58,104,165]. However, the results from individual studies evaluating the optimal timing of an invasive strategy in patients with different baseline risk profiles are inconsistent[60,105,150,164]. For instance, in the most comprehensive and up to date individual patient level meta-analysis of eight randomised control trial including 5324 patients, early intervention was not associated with mortality benefit at 180 days (HR 0.81, 95%CI 0.64-1.03, p=0.08). However, in pre-specified analyses of high-risk groups such as elevated cardiac biomarkers (HR 0.76 95%CI 0.58-0.99), high GRACE risk score more than 140 (HR 0.67 95%CI 0.45-0.99), early intervention was associated with lower mortality. As the debate around the optimal timing of an invasive strategy in NSTEMI continues, international guidelines have adopted a time sensitive approach that is risk profile dependent. Consequently, guidelines recommend that the timing of interventional management should be determined by baseline risk [3,4], with both the European Society of Cardiology (ESC) and American Heart Association / American College of Cardiology (AHA/ACC) guidelines advising early intervention (<24 hours) in patients meeting the high-risk criteria, whereas a period of medical management followed by an invasive strategy within 72 hours is advised in patients with an intermediate-risk profile. Finally, a selective invasive strategy is recommended in low-

risk patients who do not have any of the features present in the intermediate or high-risk criteria. The ESC and AHA/ACC risk criteria are presented in Table 6.1 & 6.2 below.

Table 6.1: ESC risk criteria for the use of an invasive strategy

Very- high-risk criteria (within 2 hours)
Haemodynamic instability or cardiogenic shock
Recurrent or ongoing chest pain refractory to medical management
Life-threatening arrhythmias or cardiac arrest
Mechanical complications of myocardial infarction
Acute heart failure
Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation
High-risk criteria (within 24 hours)
Rise of fall in cardiac troponin compatible with myocardial infarction
Dynamic ST or T-wave changes (symptomatic or silent)
GRACE risk score >140
Intermediate risk-criteria (within 72 hours)
Diabetes mellitus
Renal insufficiency (eGFR<60mL/min/1.73m2)
Left ventricular ejection fraction <40% or congestive cardiac failure
Early post-infarction angina
Prior percutaneous coronary intervention
Prior coronary artery bypass graft surgery
GRACE risk score >109 and <140
Low-risk criteria
Any characteristics not mentioned above

Adopted from Roffi M et al 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC), *European Heart Journal*, Volume 37, Issue 3, 14 January 2016, Pages 267–315.

Table 6.2: AHA/ACC risk criteria for the use of invasive strategy

Very- high-risk criteria (within 2 hours)
Haemodynamic instability
Recurrent angina
Sustained ventricular tachycardia or fibrillation
Acute heart failure
Recurrent angina or ischemia at rest or with low level activities despite intensive medical therapy
High-risk criteria (within 24 hours)
Temporal changes in troponin
New or presumable ST depression
GRACE risk score >140
Intermediate risk-criteria (within 72 hours)
Diabetes mellitus
Renal insufficiency (eGFR<60mL/min/1.73m2)
Left ventricular ejection fraction <40% or congestive cardiac failure
Early post-infarction angina
Prior percutaneous coronary intervention within 6 months
Prior coronary artery bypass graft surgery
GRACE risk score >109 and <140
Low-risk criteria
Any characteristics not mentioned above
Low-risk troponin negative female patients
Patient or clinician preference in the absence of high-risk features.

Adopted from Amsterdam EA et al 2014 AHA/ACC Guideline for the Management of Patients with Non–ST-Elevation Acute Coronary Syndromes

Despite these guidelines, provision of an invasive strategy in real world clinical practice is variable and often discrepant due to a variety of potential barriers such as treating physician's bias, local network guidelines and financial restraints[44-46]. In this thesis, chapters 4 & 5 results demonstrate that there is significant heterogeneity in the use of an invasive strategy and its timing in patients admitted with NSTEMI. The

patients who are most likely to benefit from an invasive strategy were least likely to receive it.

Sex differences in clinical outcomes of patients presenting with ACS are widely reported in the literature[26-31]. The unfavourable outcomes in women have often been attributed to the delayed or atypical presentation, older age, less aggressive management and higher comorbidity burden [9,32-35]. However, more contemporary data suggest that differences in clinical characteristics and presentation only partially contribute towards the higher mortality amongst women[36,37]. A recent analysis of the MINAP registry showed that women in England and Wales were less likely to receive guidelines indicated care and had significantly higher mortality than men following ACS[25]. These data highlight the need for greater understanding of factors driving these differences in outcomes and optimising the therapeutic strategies in women to improve survival [38].

Given this variable practice and the perception that use of invasive strategy in clinical practice is often discrepant with guidelines, it is important to understand the relationship between baseline risk and timing of access to the invasive strategy in contemporary practice. Therefore, this chapter aimed to meet the following objectives.

6.2 Objectives

I. To study the relationship between baseline risk as defined by two major international guidelines and timing of access to the invasive strategy in a large national population admitted with a diagnosis of NSTEMI in England and Wales.

II. To examine whether the timing of an invasive strategy is related to this baseline risk and how this varies in different components of each risk criteria.

III. To examine any inequalities in the utilization of guidelines based on an invasive strategy in women compared to men.

IV. To study the independent predictors of receiving an invasive strategy within the recommended time across all three risk groups.

V. Finally, to study whether the utility of an invasive strategy varies across healthcare regions in England and Wales.

6.3 Methods

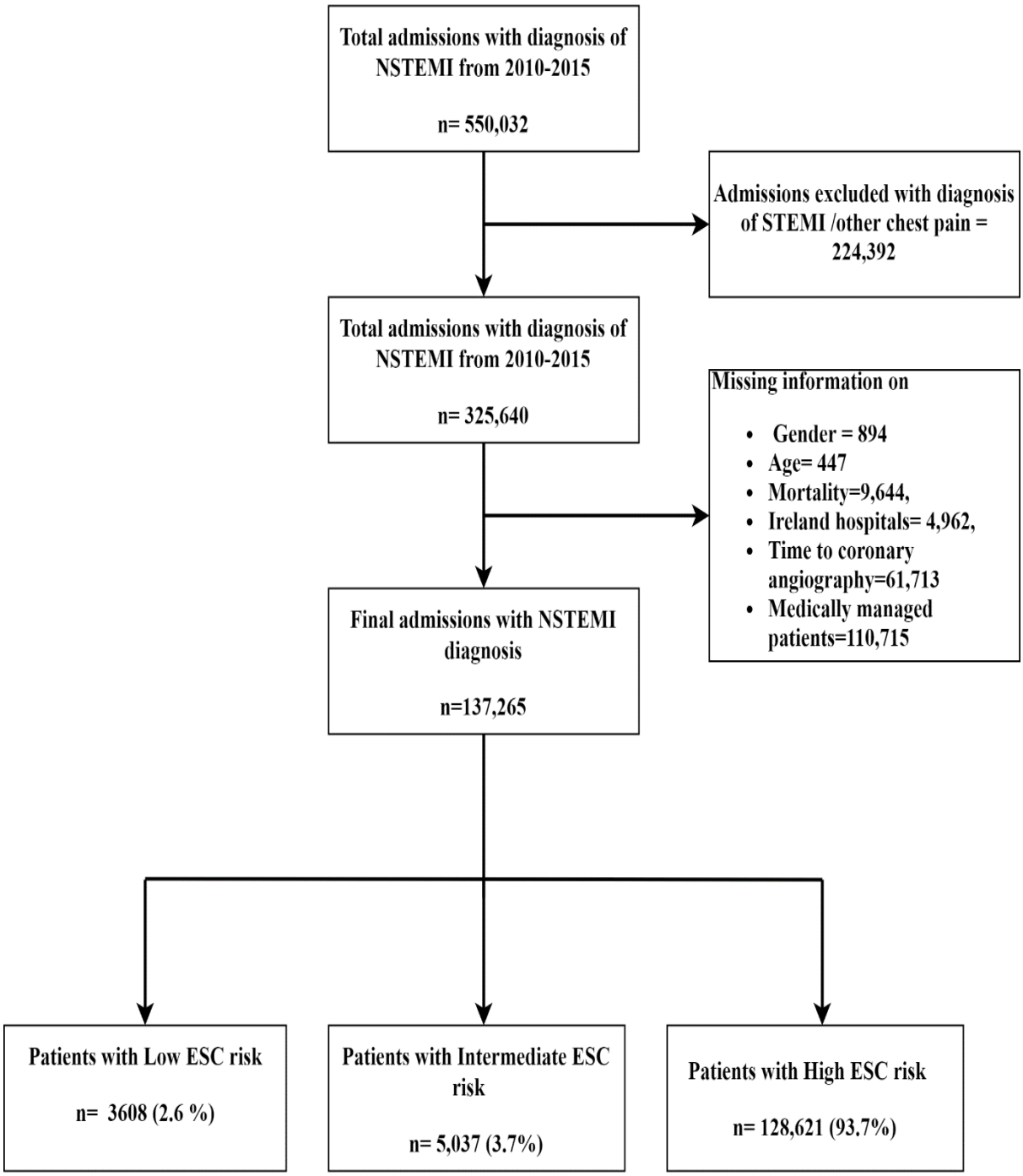
6.3.1 *Study design*

Data for this study were obtained from MINAP, a comprehensive, national registry of patients hospitalised with a diagnosis of ACS in England and Wales. The design, data variables, strengths and limitations of MINAP registry have been described in full details in chapter 3 of this thesis. Briefly, there are over 120 data fields in MINAP, encompassing baseline characteristics, comorbidities, the timing of presentation and invasive intervention, peri-admission pharmacology, in-hospital outcome, diagnosis on discharge and receipt of secondary prevention treatment[21,101,166]. Data collection is mandated by the Department of Health across 235 acute hospitals in the National Health Service (NHS) and its management have previously been described in chapter 3. Secondary use of anonymised MINAP dataset for research purposes is authorised under NHS research governance arrangements and further supported under section 251 of the NHS act 2006 (NIGB: ECC1-06(d)/2011), which allows researchers to use patient information collected within the dataset for medical research without patient consent. Therefore, formal ethical approval was not sought for this study, however, the data application was reviewed by the MINAP and HQIP data monitoring and research committee (appendix 10.3).

6.3.2 *Study population*

Consecutive patients admitted with a diagnosis of an NSTEMI in one of the 235 hospitals between 1st January 2010 to 31st December 2015 were included in this study. The discharge diagnosis of NSTEMI in the MINAP registry is determined by local clinicians according to the presenting history, clinical examination, and the results of inpatient investigations in keeping with the consensus document of the Joint European Society of Cardiology and American College of Cardiology[167]. Patients with missing information on age, gender, in-hospital mortality, the timing of invasive strategy and those managed conservatively were excluded from the analysis to allow a complete case analysis (Figure 6.1). This constituted a final cohort of 137,265 patients, which were then categorised into low, intermediate and high-risk groups as per ESC and AHA/ACC guidelines[3,4].

Figure 6.1: Flow diagram of the study selection


Total admissions with diagnosis of NSTEMI from 2010-2015
n= 550,032
Admissions excluded with diagnosis of STEMI /other chest pain = 224,392
Total admissions with diagnosis of NSTEMI from 2010-2015
n= 325,640
Missing information on
Gender = 894
Age= 447
Mortality=9,644,
Ireland hospitals= 4,962,
Time to coronary angiography=61,713
Medically managed patients=110,715
Final admissions with NSTEMI diagnosis
n=137,265
Patients with Low ESC risk
n= 3608 (2.6 %)
Patients with Intermediate ESC risk
n= 5,037 (3.7%)
Patients with High ESC risk
n= 128,621 (93.7%)

MINAP variables which were mapped against each guideline risk stratification criterion are shown in Table 6.3.

Table 6.3 Risk criteria mandating an invasive strategy in NSTEMI according to ESC, AHA/ACC guidelines and variables used from MINAP registry for risk-stratification

2015 ESC guidelines for the management of NSTEMI	**2014 AHA/ACC guidelines for the management of NSTEMI**	**Defined as or surrogate from MINAP dataset**
High-risk Criteria (Invasive strategy <24hrs)		
Haemodynamic instability or cardiogenic shock	Haemodynamic instability	Killip class 4
Life threatening arrhythmias or cardiac arrest	Sustained VT/ VF	Any cardiac arrest out of hospital or in-hospital
Acute heart failure	Signs or symptoms of HF	Killip class 3
Dynamic ST or T-wave changes (symptomatic or Silent)	New or presumably new ST depression	ST changes recorded on ECG
Rise or fall in cardiac troponin compatible with MI	Temporal change in troponin	Elevated troponin with at least one level above the 99th percentile
GRACE risk score >140	GRACE risk score >140	GRACE risk score >140
Intermediate risk criteria (Invasive strategy (24-72hrs)		
Diabetes mellitus	Diabetes mellitus	History of diabetes mellitus
Renal insufficiency (eGFR<60mL/min/1.73m2)	Renal insufficiency (eGFR<60mL/min/1.73m2)	History of CRF
LVEF <40% or CCF	LVEF <40% or CCF	History of CCF or LVEF<40%
Prior PCI	PCI within 6 month	Previous PCI
Prior CABG	Prior CABG	Previous CABG
GRACE risk score >109 and <140	GRACE score >109 and <140	GRACE risk score >109 and <140
Low-risk criteria (Invasive strategy >72hrs)		
Any characteristics not mentioned above	Any characteristics not mentioned above	All other patients

HF= heart failure, VT/VF= ventricular tachycardia/ventricular fibrillation, GRACE= Global Registry of Acute Coronary Events, CRF= chronic renal failure, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CCF= congestive cardiac failure, LVEF= left ventricular ejection fraction

6.3.3 *Study outcomes*

Time to the invasive strategy was calculated from the time of admission to the hospital and time of coronary angiography or PCI, which was then categorised into early (within 24 hours), intermediate (within 72 hours) and late (>72 hours) groups. As the timing is not always captured in hours within the MINAP dataset, hence it was not possible to accurately ascertain the timing of an invasive strategy for up to two hours. Therefore, the very high-risk category was merged into the high-risk category as patients meeting any of these criteria would still be required to undergo an invasive strategy within 24 hours of admission and this approach was felt to be the most pragmatic after discussions with the supervisory team.

6.3.4 *Study covariates*

In addition to the patient's risk factors, information on co-existing comorbidities, cardiac biomarkers, in-hospital and discharge medications, in-hospital outcomes including all-cause mortality, cardiac mortality, re-infarction, major bleeding, receipt of PCI and receipt of CABG was also collected. MINAP doesn't collect the actual calculated GRACE risk score as such, however, information available from variables within the dataset was used to calculate GRACE risk score which has been previously described and validated for use in this registry[2,168].

6.3.5 *Statistical analysis*

Baseline characteristics of all three groups were reported using numbers and percentages for categorical variables, or median and interquartile ranges for continuous variables across the three groups. Chi-square and Wilcoxon's rank sum were used to make the comparisons across three groups, whereas proportion tests were used to test statistical differences in proportions with the alpha level of significance of $p<0.05$. The data completion for mandatory fields and most of the variables included in the study

was more than 80% in most of the data fields. The missing information about each variable is provided in Appendix Table 5. An imputation framework based on chained equations to account for missing data for each group characteristic variables. Age, gender, hospital catheter laboratory status, ethnicity, timing of invasive strategy and in-hospital all-cause and cardiac mortality were registered as regular variables in the imputations model whereas all other variables including body mass index (BMI), GRACE risk-score >140, troponin elevation, acute heart failure, cardiogenic shock, seen by cardiologists, left ventricular (LV) systolic function or congestive cardiac failure, ECG changes defined as ST depression or transient ST elevation, prior history of PCI, coronary artery bypass graft (CABG), heart failure, hypercholesterolemia, angina, cerebrovascular disease, peripheral vascular disease, chronic renal failure, diabetes, hypertension, smoking status, asthma/COPD, family history of coronary disease, use of warfarin, loop diuretics, aspirin, P2Y12 inhibitors, statin, ACE inhibitor, beta-blocker were imputed. For the intermediate-risk group, high-risk group characteristics such as troponin elevation, acute heart failure, ECG changes, cardiogenic shock and GRACE risk score >140 were excluded from the imputation model. Similarly, intermediate-risk characteristics were excluded from the low-risk imputation model. Using these models, 10 imputed datasets were generated for each of the risk groups which were then used to perform all the analyses for multivariable logistic regression. Multivariable logistic regression models were used to study the independent predictors of the receipt of an invasive strategy within guideline recommended timeframes. The variables selected in the models included all the variables used in the imputations. Finally, for geographical variation analysis, patient geographical residence information was located according to clinical commissioning groups (CCGs) recorded in the MINAP dataset and stratified according to gender. Each patient's data was then

mapped to geographic information system CCGs layers accessed from NHS England to create choropleth maps of patients receiving an invasive strategy according to guidelines recommended time frames using spmap function in Stata.

6.4 Results

6.4.1 *Patient and hospital characteristics*

From a total of 137,265 patients that received an invasive management following admission with an NSTEMI, 3608 (2.6%) were categorised as low-risk, whereas 5,037 (3.7%) and 128,621 (93.7%) were categorised as intermediate and high-risk respectively, according to both ESC and AHA/ACC guidelines. Typically, patients in the low-risk category were younger (61.4years vs 68years, p<0.001), more likely to be women (31.5% vs 29.8%, p<0.001) and were less comorbid with lower prevalence of previous cerebrovascular disease (3.9% vs7.3%, p<0.001), peripheral vascular disease (2.6% vs 5.3%, p<0.001), hypertension (46.5% vs 55.9%, p<0.001), and asthma or COPD (12.5% vs 15.3%, p<0.001) compared to the high-risk group (Table 6.4). In the high-risk group the vast majority of patients had troponin elevation (n=125,070, 98.0%) whereas the prevalence of cardiogenic shock (n=463, 0.4%) and cardiac arrest on admission (n=3,092, 2.5%) was low. Within the intermediate-risk group, patients had higher prevalences of diabetes (42.2% vs 25.0%, p<0.001), previous coronary artery bypass surgery (16.0% vs 8.9%, p<0.001) and previous PCI (49.0% vs 16.8%, p<0.001) compared to the high-risk group. Finally, unadjusted all-cause mortality (1.0% vs 0.1%, p<0.001), cardiac mortality (1.0% vs 0.1%, p<0.001) and reinfarction (0.8% vs 0.4%, p=0.01) rates were significantly higher in the high-risk group compared to the low-risk group.

Table 6.4: Baseline Characteristics of patient stratified into low, intermediate and high-risk groups according to ESC and AHA/ACC guidelines

Variables	Low risk n=3608 (2.6%)	Intermediate risk n=5,037 (3.7%)	High Risk n=128,621 (93.7%)	P value
Age (Years)	61.4[52.4-70]	66[57-74]	68[58-77]	<0.001
Women (%)	1,137 (31.5%)	1,383 (27.5%)	38,291 (29.8%)	<0.001
Caucasians (%)	2,805 (77.7%)	3,592 (71.3%)	103,644 (80.6%)	<0.001
BMI median [IQR]	27.7 [24.9-31.0]	28.4 [25.4-3.6]	27.5 [24.5-31.1]	<0.001
High-risk Characteristics				
Cardiogenic shock	-	-	463 (0.4%)	
ECG ST changes	-	-	34,288 (26.9%)	
Cardiac arrest	-	-	3,092 (2.5%)	
Acute heart failure	-	-	9,203 (7.2%)	
GRACE score >140	-	-	35,298 (44.2%)	
Troponin positive	-	-	125,070 (98.0%)	
Intermediate risk characteristics				
Intermediate risk 109-140	-	1,423 (49.3%)	25,388 (31.9%)	<0.001
Chronic renal failure	-	215 (4.4%)	7,148 (5.8%)	0.01
Percutaneous coronary intervention	-	2,426 (49.0%)	20,713 (16.8%)	<0.001
Coronary artery bypass graft	-	789 (16.0%)	11,015 (8.9%)	<0.001
Diabetes	-	2,106 (42.2%)	31,729 (25.0%)	0.001
LVEF<40% or CCF	-	837 (34.5%)	24,548 (35.7%)	<0.001
Other clinical characteristics				
Hypercholesterolemia	1,306 (43.5%)	2,904 (59.6%)	50,757 (41.7%)	0.10
Angina	764 (26.5%)	2,609 (54.0%)	34,840 (28.4%)	<0.001
Cerebrovascular disease	119 (3.9%)	351 (7.2%)	9,019 (7.3%)	<0.01
Peripheral vascular disease	77 (2.6%)	219 (4.6%)	6,501 (5.3%)	<0.001
Hypertension	1,423 (46.5%)	3,224 (65.2%)	69,088 (55.9%)	<0.001
Smoking status				
Previous smoker	1,026 (33.0%)	2,064 (42.4%)	46,156 (37.1%)	<0.001

Current smoker	842 (27.1%)	846 (17.4%)	32,305 (26.0%)	<0.001
Asthma / COPD	378 (12.5%)	779 (15.9%)	18,776 (15.3%)	<0.001
Seen by cardiologist	3,367 (98.56%)	4,912 (98.8%)	126,664 (99.1%)	0.03
Heart rate, bpm, median (IQR)	70 [61-80]	70 [60-80]	75 [65-88]	<0.001
Systolic blood pressure, median (IQR)	140 [125-155]	138 [122-155]	140 [124-159]	<0.001
Family history of CHD	1,191 (44.8%)	1,686 (39.2%)	38,970 (35.6%)	0.001
Hospital catheter lab status				
No onsite laboratory	292 (8.1%)	319 (6.3%)	8,999 (7.0%)	0.01
Onsite diagnostic laboratory	354 (9.8%)	457 (9.1%)	16,262 (12.6%)	
Onsite PCI laboratory	2,962 (82.1%)	4,261 (84.6%)	103,360 (80.4%)	
In-hospital Pharmacology				
Low molecular weight heparin	1,208 (41.5%)	2,129 (46.8%)	57,214 (50.8%)	<0.001
Warfarin	61 (2.2%)	245 (4.1%)	5,713 (5.2%)	0.001
Loop Diuretic	196 (7.0%)	708 (15.9%)	22,529 (20.7%)	<0.001
Glycoprotein use	117 (4.1%)	188 (4.1%)	6,869 (6.2%)	<0.001
Discharge Medications				
Aspirin	2,920 (96.9%)	4,440 (96.9%)	110,412 (97.0%)	0.79
P2Y12 inhibitors	3,098(94..1%)	4,673 (95.4%)	122,474 (96.9%)	0.001
Statins	2,869 (96.5%)	4,396 (96.0%)	108,940 (96.6%)	0.04
ACE inhibitors	1,619 (85.3%)	2,805 (89.3%)	69,293 (89.5%)	<0.001
Beta-Blockers	2,395 (83.7%)	3,785 (85.3%)	97,628 (87.2%)	<0.001
Crude outcomes				
Death	3 (0.1%)	6 (0.1%)	1,354 (1.0%)	0.001
Cardiac mortality	1 (0.1%)	3 (0.1%)	1,125 (0.9%)	0.001
Reinfarction	12 (0.4%)	33 (0.7%)	1,028 (0.8%)	0.01
Major bleeding	48 (1.4%)	97 (2.0%)	2,032 (1.6%)	0.06

GRACE= Global Registry of Acute Coronary Events, CRF= chronic renal failure, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CCF= congestive cardiac failure, LVEF= left ventricular ejection fraction, COPD= chronic obstructive airway disease.

Table 6.5 compares the differences in the baseline characteristics, in-hospital and discharge pharmacology and outcomes amongst men and women across the three risk groups. In the low-risk group, there were 2,471 (68.5%) men and 1,137 (31.5%) women. Compared to low-risk men, low-risk women had a higher prevalence of hypertension (44.9% vs 38.1%, p<0.001), history of asthma or chronic obstructive airway disease (16.2% vs 10.2%, p<0.001). Within the intermediate-risk group, men had a higher incidence of the previous PCI (51.8% vs 41.7%, p<0.001) and CABG (18.6% vs 8.9%, p<0.001) respectively. Finally, high-risk women were significantly older (72year vs 66 year, p<0.001) and were likely to have more adverse features on presentation in the form of higher prevalence of acute heart failure (9.3% vs 6.2%, p<0.001), GRACE risk score > 140 (48.0% vs 42.6%, p<0.001), chronic renal failure (6.1% vs 5.7%, p<0.001) and history of diabetes (26.1% vs 24.5%, p<0.001) compared to high-risk men. Notably, higher risk women were also less likely to receive secondary prevention medications on discharge in the form of aspirin (96.2% vs 97.4%, p<0.001), statins (95.5% vs 97.1%, p<0.001), ACE inhibitors (86.8% vs 89.5%, p<0.001) and beta-blockers (85.3% vs 88.1%, p<0.001).

Table 6.5 Baseline characteristics of the Men and Women stratified into low, intermediate and high-risk according to ESC and AHA/ACC guidelines

Variables	**Low risk**		**P value**	**Intermediate risk**		**P value**	**High Risk**		**P value**
	3,608 (2.6%)			**5,037 (3.7%)**			**128,620 (93.7%)**		
	Men (2,471)	*Women (1,137)*		*Men (3,654)*	*Women (1,383)*		*Men (90,330)*	*Women (38,291)*	
Age (Years)	60[52-68]	65[55-74]	<0.001	64[56-72]	69[60-76]	<0.001	66[56-75]	72[62-79]	<0.001
Caucasians (%)	1,912 (77.4%)	893 (78.5%)	0.26	2,594 (71.0%)	998 (72.1%)	0.439	72,248 (80.0%)	31,396 (82.0%)	<0.001
BMI median [IQR]	27.5 [25-30]	28.1 [24-32]	0.06	28 [25-32]	28 [24-32.4]	0.11	27 [24-30]	27 [23-31]	<0.001
High-risk characteristics									
Cardiogenic shock	-	-	-	-	-	-	330 (0.4%)	133 (0.4%)	0.62
ECG ST changes	-	-		-	-		23,970 (26.8%)	10,318 (27.2%)	0.11
Cardiac arrest	-	-	-	-	-	-	2,338 (2.7%)	754 (2.0%)	<0.001
Acute heart failure	-	-	-	-	-	-	5,632 (6.2%)	3,580 (9.3%)	<0.001
High risk >140	-	-	-	-	-	-	23,675 (42.6%)	11,623 (48.0-%)	<0.001
Troponin positive	-	-	-	-	-	-	87,892 (98.0%)	37,178 (97.7%)	0.002
Intermediate-risk									

characteristics									
Intermediate risk 109-140	-	-	-	1,032 (48.6%)	391 (51.3%)	0.20	18,531 (33.3%)	6,587 (28.3%)	<0.001
Chronic renal failure	-	-	-	144 (4.0%)	71 (5.3%)	0.06	4,930 (5.7%)	2,218 (6.1%)	0.01
Percutaneous coronary intervention	-	-	-	1,858 (51.8%)	568 (41.7%)	<0.001	15,644 (18.1%)	5,069 (13.8%)	<0.001
Coronary artery bypass graft	-	-	-	668 (18.6%)	121 (8.9%)	<0.001	9,070 (10.5%)	1,945 (5.3%)	<0.001
Diabetes	-	-	-	1,472 (407%)	634 (46.4%)	<0.001	21,872 (24.5%)	9,857 (26.1%)	0.004
LVEF<40% or CCF	-	-	-	630 (36.0%)	207 (30.6%)	0.01	17,573 (36.6%)	6,975 (33.6%)	<0.001
Other clinical characteristics									
Hypercholesterolemia	903 (44.0%)	403(42.6%)	0.47	2,099 (59.3%)	805 (60.3%)	0.52	35,779 (41.8%)	14,978 (41.3%)	0.10
Angina	496 (25.2%)	268 (29.2%)	0.02	1,906 (54.2%)	703 (53.6%)	0.72	24,808 (28.8%)	10,032 (27.5%)	<0.001
Cerebrovascular disease	84 (4.1%)	35 (4.0%)	0.58	240 (6.8%)	111 (8.3%)	0.06	6,072 (7.0%)	2,947 (8.1%)	<0.01
Peripheral vascular disease	57 (2.8%)	20 (2.1%)	0.27	162 (4.6%)	53 (4.3%)	0.63	4,792 (5.6%)	1,709 (4.7%)	<0.001

Hypertension	7,999 (38.1%)	4,040 (44.9%)	<0.001	17,907 (57.0%)	7,364 (63.3%)	<0.001	23,960 (59.7%)	12,465 (67.4%)	<0.001
Smoking status									
Previous smoker	749 (35.3%)	277 (28.1%)	<0.001	1,653 (46.7%)	411 (31.0%)	<0.001	35,337 (40.4%)	10,819 (29.3%)	<0.001
Current smoker	591 (27.9%)	251 (25.4%)	<0.001	646 (18.3%)	200 (15.1%)	<0.001	23,690 (27.4%)	8,345 (22.6%)	<0.001
Asthma / COPD	222 (10.8%)	156 (16.2%)	<0.001	505 (14.2%)	274(20.4%)	<0.001	11,701 (13.5%)	7,075 (19.4%)	<0.001
Seen by cardiologist	2,311 (98.5%)	1,056 (98.6%)	0.98	3,562 (98.8%)	1,350 (98.9%)	0.66	88,987 (99.2%)	37,677 (99.0%)	0.03
Heart rate, bpm, median (IQR)	69 [60-71]	71 [63-82]	<0.001	68 [60-80]	73[64-83]	<0.001	74 [64-87]	78 [67-91]	<0.001
Systolic blood pressure, median (IQR)	139 [124-154]	142 [126-159]	<0.001	135 [120-153]	144 [127-161]	<0.001	140 [123-157]	143 [126-164]	<0.001
Family history of CHD	806 (44.5%)	385 (45.4%)	0.67	1,211 (38.8%)	475 (401%)	0.45	27,477 (35.7%)	11,493 (35.3%)	0.14
Hospital catheter lab status									
No onsite laboratory	196 (7.9%)	96 (8.4%)	0.17	228 (6.2%)	91 (6.6%)	0.81	6,400 (7.1%)	2,599 (6.8%)	0.01
Onsite	228 (9.2%)	126 (11.1%)		336 (9.2%)	121 (8.8%)		11,292	4,970	

diagnostic laboratory							(12.5%)	(13.0%)	
Onsite PCI laboratory	2,047 (82.9%)	915 (80.5%)		3,090 (84.6%)	1,171 (84.6%)		72, 638(80.4%)	30, 722(80.2%)	
In-hospital Pharmacology									
Low molecular weight heparin	817 (41.1%)	391 (42.3%)	0.54	1,528 (46.1%)	601 (48.9%)	0.09	39,900 (50.4%)	17,314 (51.6%)	<0.001
Warfarin	38 (2.0%)	23 (3.6%)	0.31	183 (5.6%)	62 (5.1%)	0.51	3,987 (5.2%)	1,726 (5.3%)	0.48
Loop Diuretic	109 (5.7%)	87 (9.7%)	<0.001	477 (14.7%)	231 (19.1%)	<0.001	14,421 (18.8%)	8,108 (24.9%)	<0.001
Glycoprotein use	82 (4.2%)	35 (3.8%)	0.63	145 (4.4%)	43 (3.4%)	0.16	5,120 (6.5%)	1,749 (5.3%)	<0.001
Discharge Medications									
Aspirin	2,013 (97.2%)	907 (96.2%)	0.11	3,234 (97.3%)	1,206 (95.9%)	0.01	77,595 (97.4%)	32,817 (96.2%)	<0.001
P2Y12 inhibitors	2,128(94.2%)	970 (93.7%)	0.58	3,396 (95.4%)	1,277 (95.4%)	0.92	86,026 (96.9%)	36,448 (96.9%)	0.76
Statins	1,978 (97.2%)	891 (95.3%)	0.01	3,206 (96.1%)	1,190 (95.5%)	0.33	76,743 (97.1%)	32,197 (95.5%)	<0.001
ACE inhibitors	1,619 (85.3%)	690 (82.2%)	0.04	2,805 (89.3%)	1,023 (86.2%)	0.006	69,293 (89.5%)	28,613 (86.8%)	<0.001
Beta-Blockers	1,688 (85.5%)	707 (79.8%)	<0.001	2,769 (86.0%)	1,016 (83.7%)	0.05	69,072 (88.1%)	28,556 (85.3%)	<0.001
Crude									

outcomes									
Death	3 (0.1%)	0 (0.0%)	0.24	2 (0.1%)	4 (0.3%)	0.03	902 (1.0%)	452 (1.2%)	0.003
Cardiac mortality	1 (0.1%)	0 (0.0%)	0.49	1 (0.1%)	2 (0.1%)	0.12	751 (0.8%)	374 (1.0%)	0.01
Reinfarction	8 (0.4%)	4 (0.4%)	0.89	25 (0.7%)	8 (0.6%)	0.71	717 (0.8%)	311 (0.9%)	0.72
Major bleeding	28 (1.2%)	20 (1.9%)	0.12	69 (2.0%)	28 (2.1%)	0.75	1,301 (1.5%)	731 (2.0%)	<0.001

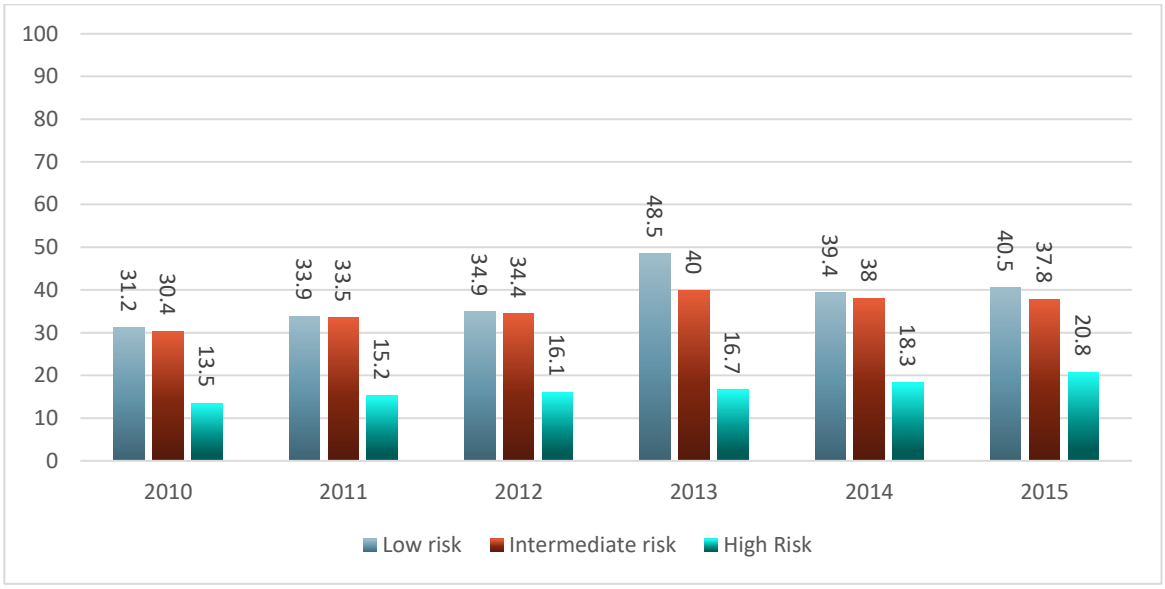
GRACE= Global Registry of Acute Coronary Events, CRF= chronic renal failure, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, CCF= congestive cardiac failure, LVEF= left ventricular ejection fraction, COPD= chronic obstructive airway disease.

6.4.2 *Temporal trends & regional variations*

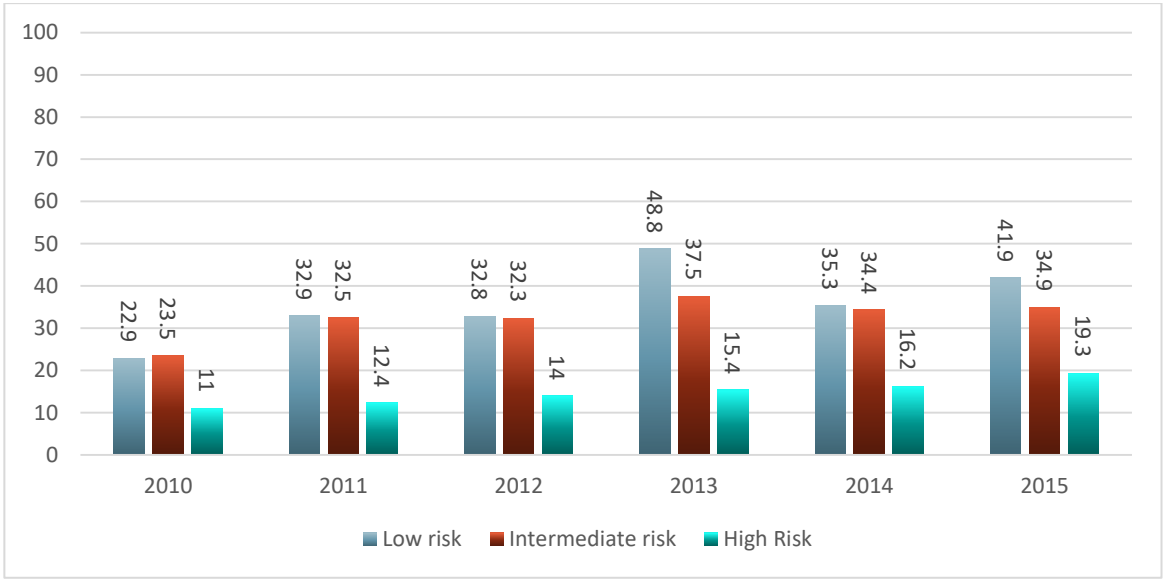
Analysis of temporal trends showed an increase in uptake of invasive strategy in all groups, but with a greater proportional in low-risk women (22.9% to 41.9%, p<0.001), whereas high-risk women had the least increase from 11% to 19.3%, p<0.001 during the study period (Figure 6.4).

Figure 6.2 Temporal trends in proportions of men and women receiving an invasive strategy within guidelines recommended time frame according to their risk.

A) Men



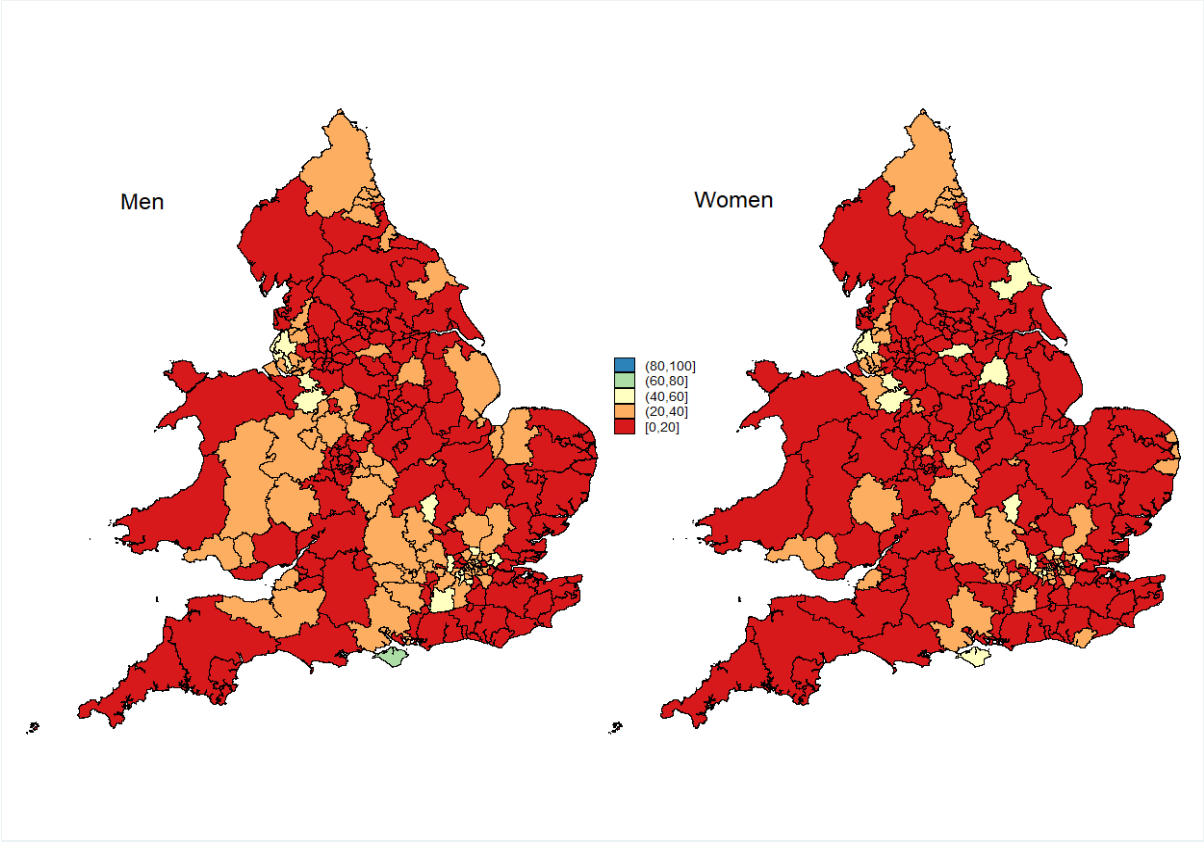
B) Women



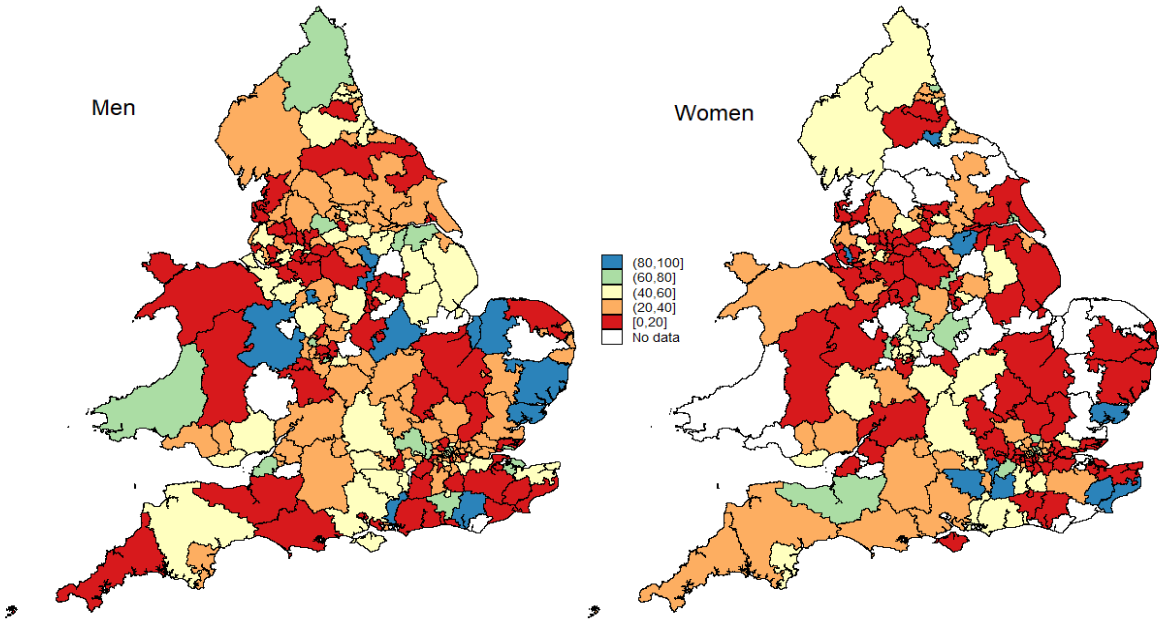
Regional variations in the attainment of targets recommended in the guidelines across different CCGs and healthcare board areas in England and Wales are illustrated in Figure 6.3. In the high-risk group, almost equal proportions of women (38%) and men (39%) received treatment in the Northeast of England whereas greater differences were observed in Wales (57%) and Southwest (59%) of England, where higher proportions of high-risk men received guidelines indicated invasive strategy. In the low-risk group, greater proportions of men in the Northeast (78%) and Southwest (75%) received timely treatment whereas lower proportions of women in the Midlands (20%) were treated in the recommended time frames.

Figure 6.3 Proportion of Men and Women stratified according to their risk receiving an invasive strategy within guidelines recommended time frame across the clinical commissioning group in England and Wales

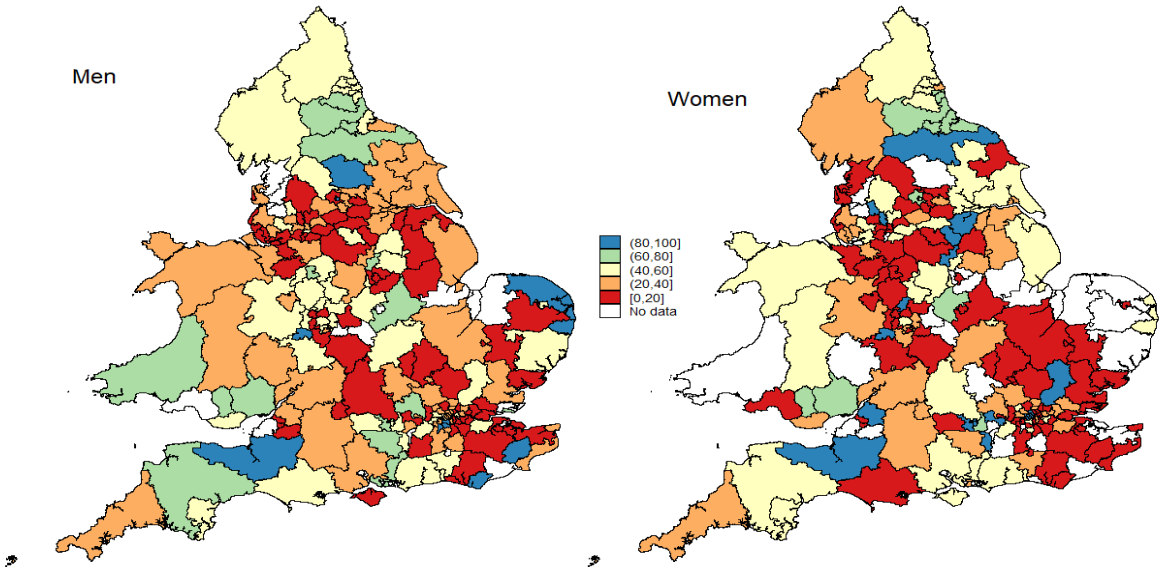
A) High risk



B) Intermediate risk



C) Low risk



6.4.3 *Independent predictors of receipt of invasive strategy within the recommended time*

Independent predictors of attainment of an invasive strategy within the recommended timeframe for high, intermediate and low-risk are reported in Table 6.6. In the high-risk group, the presence of cardiogenic shock (OR 0.35 95%CI 0.27-0.44), ST-segment ECG changes (OR 0.60 95%CI 0.57-0.63) and cardiac arrest (OR 0.43 95%CI 0.38-0.47) were associated with reduced odds of receiving an invasive strategy with 24hours. In contrast, troponin elevation was associated with more than two-fold increase in odds of receiving an invasive strategy within 24 hours (OR 2.35 95%CI 2.08-2.66. The presence of onsite PCI facilities was a strong positive predictor of receiving an invasive strategy within recommended time in the high-risk group (OR 2.49 95%CI 2.43-2.63) whereas they were less likely to receive an invasive strategy (OR 0.75 95%CI 0.68-0.83) in the diagnostic hospitals.

Table 6.6: Independent Predictors of receiving invasive coronary strategy within guidelines recommended time frames in high, intermediate and low-risk groups.

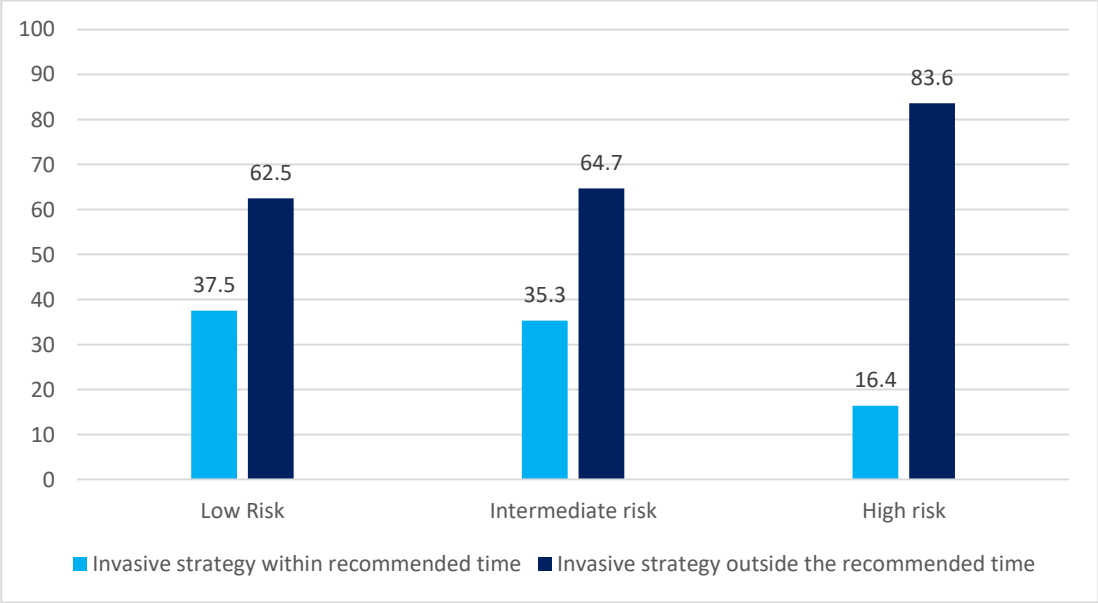
Variables	High-risk group	Intermediate risk group	Low-risk group
High-risk characteristics		**Odd ratio (95%CI)**	
Cardiogenic shock	2.78 (2.28-3.39)	-	-
ECG ST changes	1.67 (1.61-1.73)	-	-
Cardiac arrest	2.44 (2.24-2.64)	-	-
Acute heart failure	0.65 (0.61-0.70)	-	-
Troponin positive	0.39 (0.36-0.43)	-	-
Intermediate risk characteristics			-
Chronic Renal Failure	0.74 (0.68-0.80)	0.88 (0.63-1.23)	-
Previous Percutaneous coronary intervention	1.08 (1.02-1.13)	0.94 (0.79-1.11)	-
Previous CABG	0.87 (0.82-0.93)	1.37 (1.11-1.67)	-
Diabetes	0.81 (0.78-0.84)	1.05 (0.91-1.22)	-
LVEF <40% or CCF	1.26 (1.21-1.32)	0.61 (0.48-0.76)	-
Other predictors			-
Female gender	0.91 (0.88-0.94)	1.09 (0.93-1.27)	1.06 (0.89-1.25)
Age	0.98 (0.986-0.988)	1.00 (1.00-1.01)	1.00 (0.99-1.00)
Black Ethnicity	1.22 (1.06-1.39)	1.35 (0.77-2.33)	1.45 (0.74-2.83)
Hypercholesterolemia	1.25 (1.21-1.30)	0.75 (0.64-0.87)	0.63 (0.52-0.76)
Angina	0.95 (0.92-0.99)	1.05 (0.91-1.21)	1.40 (1.15-1.70)
Cerebrovascular disease	0.89 (0.83-0.93)	1.12 (0.85-1.47)	0.79 (0.53-1.19)
Peripheral vascular disease	1.10 (1.02-1.18)	0.79 (0.57-1.08)	0.91 (0.51-1.53)
Hypertension	1.02 (0.98-1.06)	0.95 (0.81-1.12)	0.97 (0.82-1.15)
Asthma/ COPD	0.84 (0.84-0.88)	0.95 (0.79-1.14)	1.09 (0.84-1.42)
Seen by cardiologist	0.88 (0.79-1.04)	1.03 (0.53-2.00)	1.51 (0.76-2.96)
Family history of heart disease	1.13 (1.09-1.17)	1.14 (0.98-1.32)	1.12 (0.93-1.36)
Hospital catheter lab status (Ref no laboratory centres)			
Diagnostic centre	0.75 (0.68-0.83)	1.37 (0.94-2.00)	2.00 (1.42-2.81)
PCI centres	2.49 (2.43-2.63)	0.74 (0.56-0.98)	2.16 (1.67-2.79)

CCF= congestive cardiac failure, LVEF= left ventricular ejection fraction, COPD= chronic obstructive airway disease, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft,

6.4.4 *Level of compliance with the guidelines*

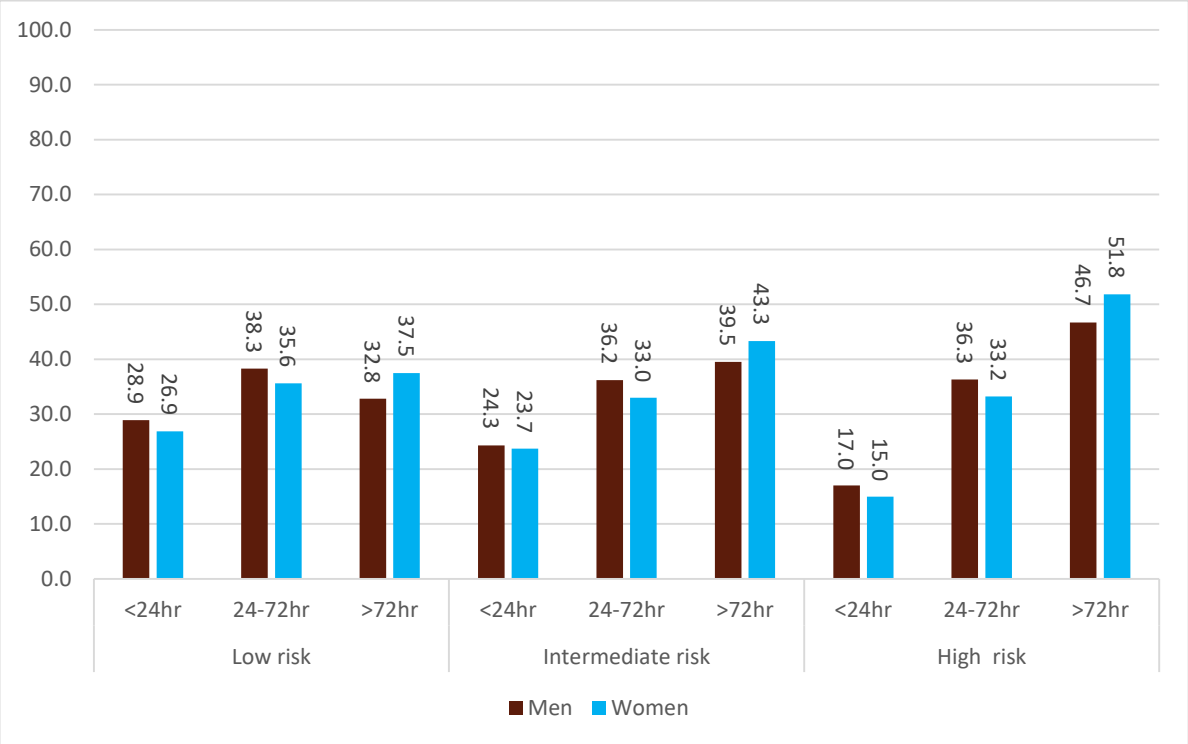
Overall, more than two thirds (83.6%) of patients in the high-risk group did not receive an invasive strategy within the recommended target time (<24 hrs), whilst it was provided within the recommended time targets (within 72 hours) in 35.3% of the intermediate and 37.5% of the low-risk cohorts category respectively (Figure 6.4).

Figure 6.4 Overall proportion of patients receiving an invasive strategy within guidelines recommended time frame according to their risk



Both men and women in the low-risk category were almost twice as likely to receive early an invasive strategy (within 24 hours) compared to high-risk men (28.9% vs 17%, p<0.001) and women (26.9% vs 15%, p<0.001) (Figure 6.5). Women were also consistently less likely to receive an invasive strategy within the recommended time points across all groups; low-risk (35.6% vs 38.3%, p=0.02) intermediate-risk (33.0% vs 36.2%, p=0.03) and high-risk group (15.0% vs 17.0%, p<0.001) compared to men. Paradoxically, Women in the high-risk group also experienced greater delays: 51.2% of women were treated beyond 72 hours compared to 46.7% men (Figure 6.5).

Figure 6.5 Proportion of Men and Women receiving an invasive strategy within guidelines recommended time frame according to their risk



Major differences were observed in the timing of invasive strategy amongst patients with high-risk features as defined by ESC or AHA/ACC guidelines. Early invasive strategy within the recommended time was most commonly used in patients presenting with cardiac arrest (49.8%) or cardiogenic shock (22.1%) but lesser proportion of patients with a GRACE score >140 (14.0%) or presenting with acute heart failure (11.8%) received an invasive strategy within the recommended target time (Figure 6.6). Furthermore, women in very high or high-risk categories (cardiogenic shock, cardiac arrest, acute heart failure, ST depression on the ECG, elevated troponin and GRACE risk score >140) were consistently less likely to receive an appropriately early invasive strategy compared to men (Figure 6.8). In addition, subgroup analysis demonstrated important differences in access to the invasive strategy in intermediate-risk patients (Figure 6.7). For example, women with history of diabetes (29.3% vs 35.0%, p=0.007) and congestive cardiac failure (23.2% vs 29.4%, p<0.001) were less likely to receive an invasive strategy within 24-72 hours compared to men, whereas

receipt of an invasive strategy within recommended time frames were similar in women with history of chronic renal disease (29.6% vs 26.4%, p=0.2) and intermediate GRACE risk-score (38.9% vs 38.6%, p=0.8) compared to men.

Figure 6.6: Men, women and overall proportions in the high-risk group receiving an invasive strategy within guidelines recommended time points

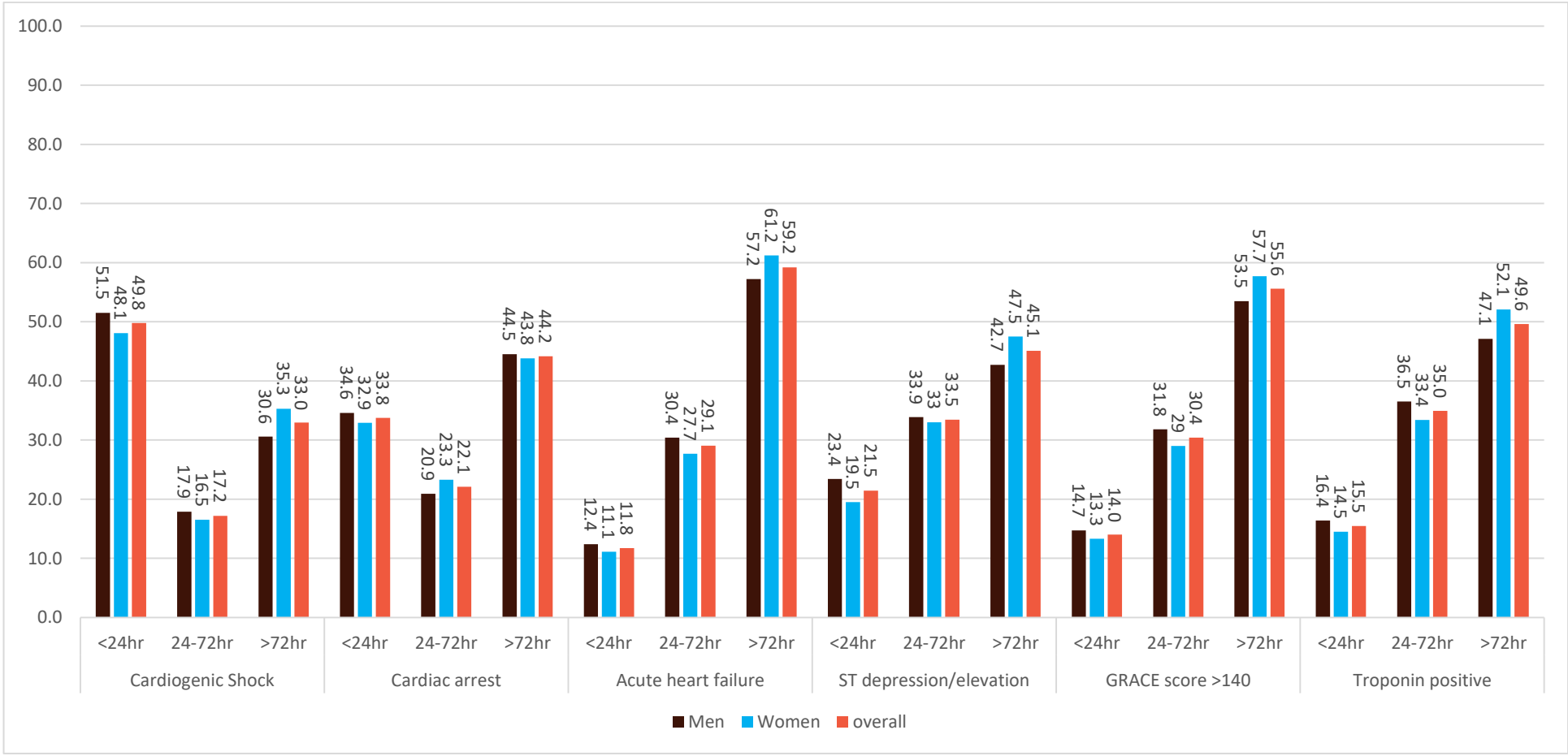
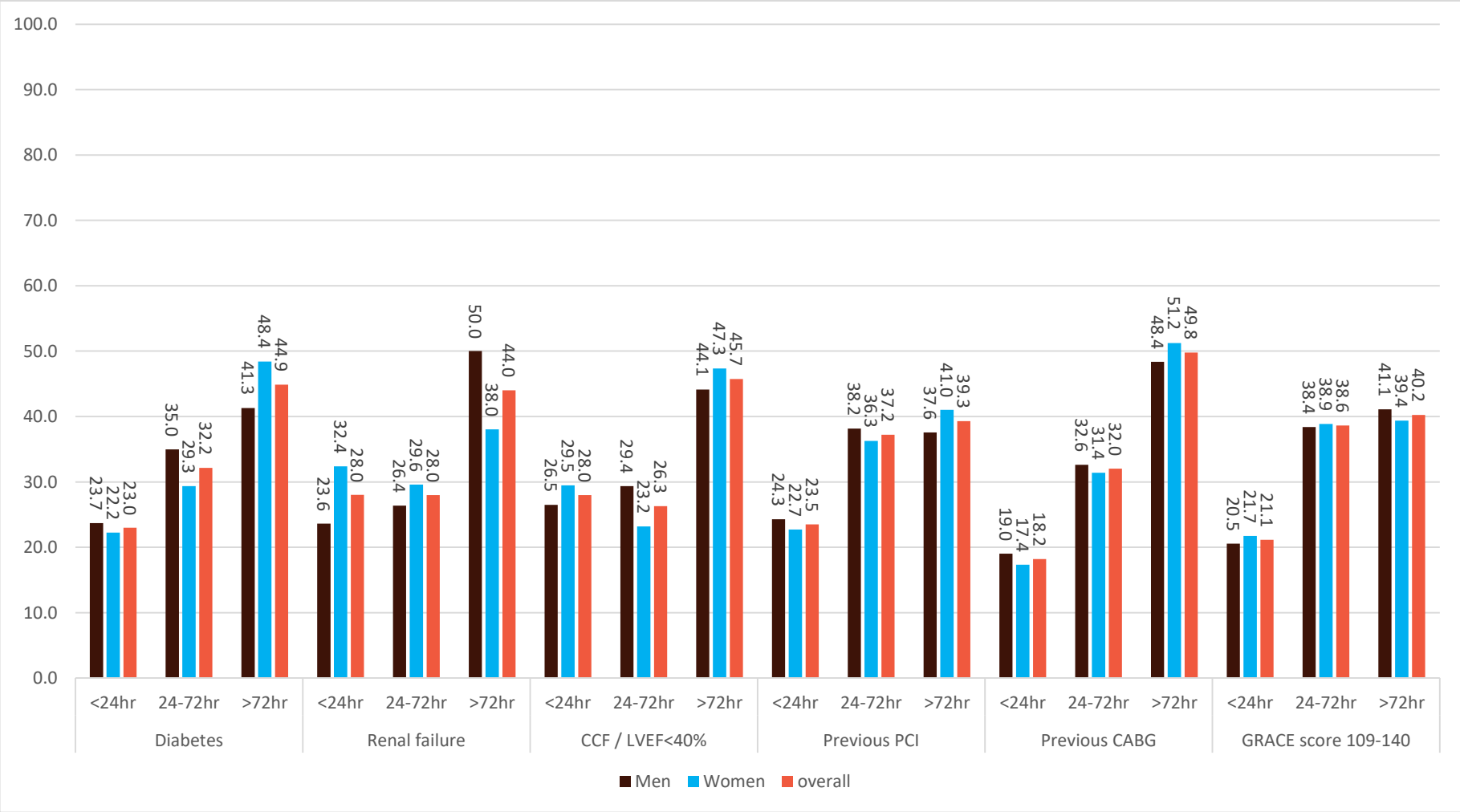


Figure 6.7: Men, women and overall proportions in the intermediate-risk group receiving an invasive strategy within guidelines recommended time points



6.5 Discussion

In this analysis of nearly 140,000 NSTEMI patients from a national AMI registry, there was a significant disconnect between targets for the timing of invasive strategy based upon baseline risk according to the guidelines. In this study population, over 90% of NSTEMI patients admitted within the United Kingdom are deemed to be high-risk according to ESC or AHA/ACC guidelines, and in this cohort, the recommendation is for an early invasive strategy (within 24 hours). In reality, only one in ten such high-risk NSTEMI patients actually received an invasive strategy within this target time. Paradoxically, patients in the lowest risk category were twice as likely to receive an early invasive strategy compared to high-risk patients. Finally, access to an invasive strategy within guideline recommended time targets was significantly lower in women than men. Specifically, high-risk women were more likely to present with adverse baseline clinical characteristics and were less likely to receive an invasive strategy within the recommended time points compared to men. These gender differences in attainment of guideline recommendations for an invasive strategy were apparent across different CCGs and healthcare boards in England and Wales. In fact, the findings from this study show a wide variation in adherence to guidelines, particularly amongst high-risk women.

Current ESC guidelines around the management of NSTEMI recommend an early invasive strategy within 24 hours in patients with high-risk features, with an aim to offer it no later than 72 hours in patients with intermediate-risk. The AHA/ACC risk stratification criteria and time points for offering an invasive strategy are similar to the ESC guidelines[3]. Almost 93% of the NSTEMI cohort in this study were deemed high-risk, in the majority of whom this was based upon them having at least one troponin

level above the 99th percentile. Both ESC and AHA/ACC guidelines recommend that at least one elevated troponin level above the 99th percentile cut off is required to make a diagnosis of NSTEMI. However, offering an early invasive strategy within 24 hours to patients meeting these criteria will have major resource implications and is likely to require a restructuring of national ACS services. Firstly, condensed data from RCTs shows that only high-risk patients with GRACE risk score >140 benefits from an early invasive strategy and have better clinical outcomes whereas the optimal timing of invasive strategy in patients with other high-risk features such as troponin positive or ECG changes is less clear [60,150]. Secondly, utilisation of increasingly highly sensitive troponin assays has resulted in increased detection of low-risk NSTEMI patients and concurrent fall in the diagnosis of Unstable angina[169-171]. Furthermore, the advent of highly sensitive troponin assays has resulted in the misinterpretation of apparently raised assay results to indicate Type 1 MI, when in fact the result may reflect Type 2 MI or myocardial injury[172]. Although, rise or fall in cardiac troponin is important from a diagnostic point of, optimal timing of intervention in this cohort requires further research. Therefore, mandating an invasive strategy within 24 hours to such large proportions of patients would require a major expansion in service structure and delivery in an already stretched healthcare system. The other second largest proportions (48%) of patients in the high-risk group were those with a GRACE risk score >140, yet both men and women with GRACE risk score >140 experienced greater delays in receiving an invasive strategy within 24 hours. Further research is required to elucidate an optimal time of intervention in patients with different high-risk features as currently prescribed by guidelines.

The results from this national heart attack registry analysis show a clear disassociation between the recommendations for target times for invasive strategy

access on one hand and what is actually offered to patients on the other. There was a consistently lower real life use of an invasive strategy in all risk groups. Remarkably, over 80% of patients in the high-risk group did not receive an invasive strategy within the recommended time frame of 24hours. More importantly, there was a significant risk-treatment paradox in that low and intermediate-risk patients were far more likely to get an early invasive strategy than those estimated to be at high-risk. This discrepancy may be explained by several factors such as treating physician bias, patient-related factors such as age, comorbidities and organisational factors such availability of onsite catheter lab facilities[173]. The results of chapter 4 of this thesis demonstrate that patients with increased comorbid burden, old age were less likely to receive angiography compared to their younger and less comorbid counterparts. In the current analysis, we found that low-risk patients were almost three times more likely to receive an invasive strategy when admitted to hospitals with onsite cardiac catheter laboratory facilities. Further efforts are required to develop a multifaceted approach in dissemination of guidelines, as well as to improve adherence and clinical care[46]. The association between the presence of onsite cardiac catheter facilities and the use of an invasive strategy will be explored in the next chapter (chapter 7.0) of this thesis.

The most striking observation in this analysis was around inequalities in the receipt of appropriate, guidelines based invasive strategy amongst women and men. It appears that women presenting with high-risk features were not only less likely to receive an invasive strategy within recommended time points but experienced greater delays compared to men. Furthermore, there was also significant heterogeneity in the application of guidelines based invasive approach in women with an intermediate-risk profile. Disparities in cardiovascular care and outcomes amongst men and women are widely reported in the literature [27,32,34,93]. The lower survival in women presenting with

ACS is not entirely explained by the differences in their presentation, symptomology and comorbidities[37]. Whilst previous studies have reported significant discrepancies in the use of an invasive strategy amongst women[93,174], this study is the first one to highlight heterogeneity between the use of an invasive strategy and guideline prescribed risk criteria. These findings indicate that women are only more likely to experience biases in receipt of guidelines-based invasive strategy compared to men but this gender gap appears to be greater with increasing baseline risk amongst women which may explain the poor outcomes in women admitted with NSTEMI.

There was also a significant disconnect between the clinical practice and guidelines-base delivery of an invasive strategy amongst women across different CCGs and healthcare boards in England and Wales. These disparities may partly be related to differences in institutional practices and the availability of services such as cardiac catheter laboratory facilities[43,175,176]. However, differences within the institute reflect that treating physician bias and may be a barrier to the delivery of guideline-based care in this cohort[177,178]. In addition, current NICE guidelines in the UK adopt a more conservative approach of undertaking an invasive strategy within 96 hours if the patient's predicted mortality is above 3.0% apart from high ischemic risk or haemodynamically unstable patients[8]. The guidance around risk stratification is less clear in NICE recommendations and may explain such wide variation in practice in the UK as risk stratification is left at physician discretion. It is also important to note that NICE guidelines on early management of NSTEMI and unstable angina were originally developed in 2010 and last updated in 2013. There has been a significant development in the management of NSTEMI. Development of quality improvement programmes and regionalisation of care for NSTEMI patients may help to alleviate some of these differences[175].

6.6 Study strengths and limitations

To best of my knowledge, this is the first study to provide a comprehensive illustration of the real-world practice of guidelines recommended invasive strategy amongst men and women in a single national healthcare system. However, certain limitations should be considered whilst interpreting these observations. A majority of these patients were in a high-risk group due to a significant number of patients having positive cardiac biomarkers. MINAP dataset doesn't collect information about dynamic changes in the cardiac troponin, therefore the guideline recommended criteria of the rise in cardiac troponin with at least one value above the 99th percentile was used to define these patients. Secondly, the patients with very high-risk features such as cardiogenic shock, cardiac arrest, acute heart failure and dynamic ECG changes were included into a high-risk category because information around the timing of CA was not available in hours for all patients in the MINAP dataset. Current ESC and AHA/ACC guidelines actually recommend an immediate invasive strategy within 2 hours in these patients, therefore after discussion with the supervisory team, it was felt that the logical approach would be to combine the very high-risk criteria with high-risk criteria as they would be requiring CA within 24 hours anyway.

6.7 Conclusion

In this NSTEMI cohort, there was a significant disconnect between guidelines recommended risk and the use of an invasive strategy in clinical practice. Specifically, over two thirds of high-risk NSTEMI patients did not receive an invasive strategy within guidelines recommended time points. There also appear to be significant sex-based inequalities in that women were not only more likely to experience higher delays in receipt of invasive strategy, women presenting with high-risk characteristics were significantly less likely to be treated invasively in the recommended time points

compared to men. Future efforts need to focus on the development of quality improvement programmes and educational interventions to promote uniform delivery of guidelines-based care in this cohort.

Chapter 7

Association between onsite cardiac catheter laboratory facilities and use of an invasive strategy in the management of NSTEMI

7.1 Introduction

The previous chapter of this thesis described the use of an invasive strategy in the management of patients admitted with a diagnosis of NSTEMI based on the risk criteria of international guidelines namely European Society of Cardiology (ESC) and American Heart Association / American College of Cardiology (AHA/ACC). The current chapter aims to study the association between the presence of cardiac catheter laboratory facilities at the first admitting hospital and use of an invasive strategy in patients admitted with the diagnosis of NSTEMI in England and Wales. The analysis from this chapter is also currently under review for consideration of a publication in a peer reviewed cardiology journal.

Invasive CA is the gold standard diagnostic modality for the assessment of coronary artery disease in patients admitted with ACS. Patients who present with STEMI are urgently transferred for primary PCI even when they initially present to hospitals without onsite cardiac catheter laboratory facilities based on current guideline recommendations[3,4]. Consequently, patients presenting to hospitals without onsite catheter laboratory are transferred to the nearest hospital with PCI facilities within a target time of 90 minutes from first medical contact. In contrast, the decision to undertake an invasive strategy in the form of CA in patients admitted with NSTEMI is based on initial presentation, ECG changes, risk factors, presence of haemodynamic instability and co-existing comorbidities[3,4,146]. Organisational factors, such as the availability of cardiac catheter laboratory facilities at the presenting hospital, are important determinants of utilisation of an invasive strategy and further management[42,43,179].

A proportion of patients with NSTEMI are admitted to hospitals without PCI capability and in some cases without diagnostic catheter laboratory facilities[180-183].

Previous studies have reported a positive association between the presence of an on-site catheter laboratory and receipt of an invasive strategy in patients with ACS[24,42,43,184-186] but the association between catheter laboratory facilities at the admitting hospital with clinical outcomes were inconsistent [42,43,184-188]. In an analysis of the GRACE registry, Van de Werf et al reported that the presence of on-site cardiac catheter laboratory was associated with the increased use of PCI but no differences in in-hospital mortality compared to the hospitals without an on-site cardiac catheter laboratory in patients admitted with ACS. In contrast, a study of 718,028 beneficiaries admitted with a diagnosis of ACS found that admission to a hospital with on-site cardiac catheter laboratory facilities was associated with lower 30-day mortality compared with admission without on-site cardiac catheter laboratory[189]. The interpretation of these data is challenging because the majority of previous studies are based on mixed cohorts of ACS patients including STEMI as well as NSTEMI patients and the availability of diagnostic only and PCI capable interventional facilities, in particular, is not considered separately. Furthermore, as described in chapter 6, current guidelines recommend an early invasive strategy within 24 hours in patients presenting with high-risk features, however, such time target times are unlikely to be met without the presence of onsite cardiac catheter laboratory facilities[3,4]. More importantly, there is a paucity of data around the use of an invasive strategy and clinical outcomes stratified according to admitting hospital catheter laboratory facilities in high-risk NSTEMI patients such as those with GRACE risk score >140. As such, it remains unclear how the types of cardiac catheter laboratory facilities at the first admitting hospital might influence the utilisation of invasive strategy in the form of CA or PCI and outcomes of patients with NSTEMI.

The main aim of the present study was to describe associations between use of an invasive strategy and outcomes in patients with NSTEMI and how these associations are influenced by the catheter laboratory and interventional (PCI) facilities of admitting hospitals. In order to further delineate the association between baseline NSTEMI risk and clinical outcomes, a pre-specified subgroup analysis of high-risk patients with a GRACE score >140 was also undertaken.

7.2 Objectives

The main objectives of this chapter were,

I. To describe the difference in the baseline characteristics stratified according to the types of cardiac catheter laboratory facilities at the first admitting hospital in patients admitted with a diagnosis of NSTEMI in England and Wales.
II. To study the association between the presence of different types of cardiac catheter laboratory facilities at the first admitting hospital and the use of an invasive strategy.
III. To study whether there is an association between different types of cardiac catheter laboratory facilities and in-hospital clinical outcomes.
IV. To study the association between different types of cardiac catheter laboratory facilities and in-hospital clinical outcomes in high-risk patients with GRACE risk score >140.
V. To study the independent predictors of receipt of CA and PCI according to hospital cardiac catheter laboratory status.

7.3 Methods

7.3.1 *Study design*

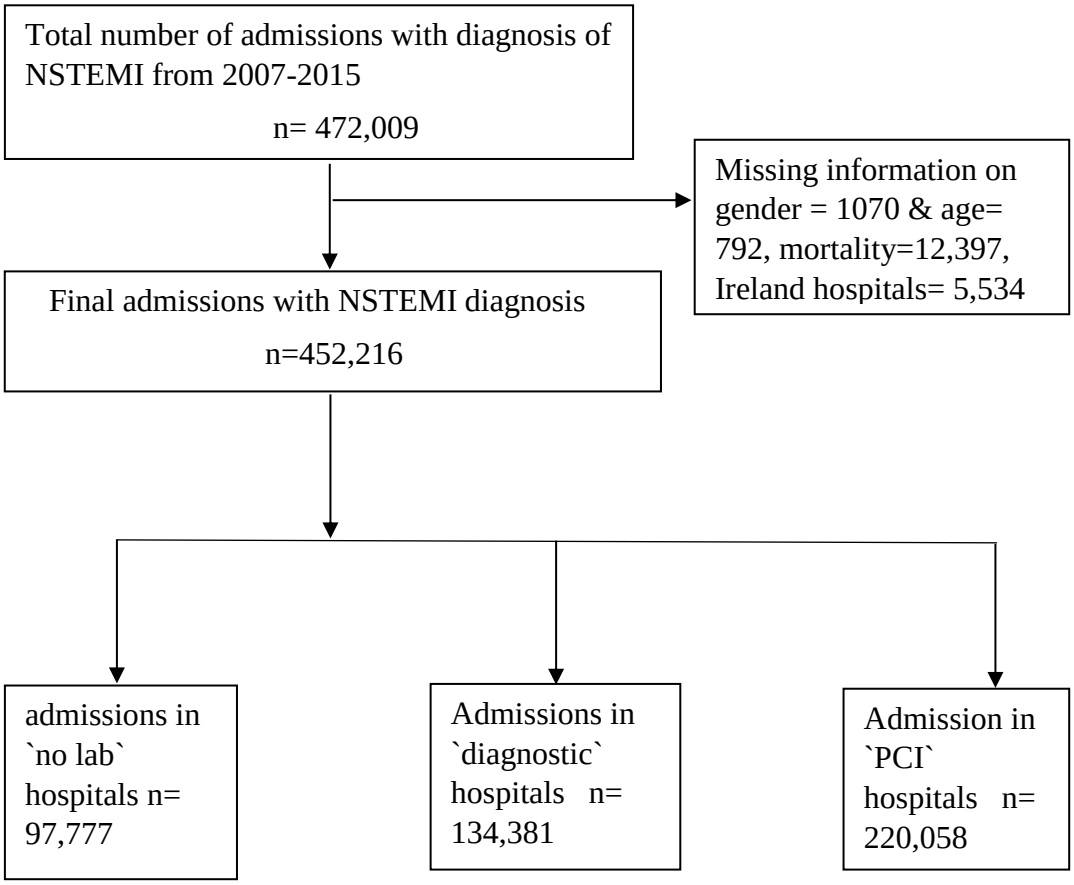
The design of this study was similar to previous chapters in this thesis in the form of an observational, retrospective cohort study comprising of all adults admitted with a diagnosis of NSTEMI in England and Wales. MINAP dataset was used to define this cohort, details of which have been provided in chapter 3. Briefly, MINAP is a national audit which prospectively collects information around the management of ACS in England and Wales to meet the audit requirements of the National Service Framework (NSF) for coronary heart disease[23,190,191]. MINAP amasses almost 85,000 hospital admissions per year with a diagnosis of ACS admitted to acute National Health Service (NHS) hospitals in England and Wales[80]. Each entry in the MINAP dataset provides comprehensive information about patient's journey encompassing patient demographics, coexisting comorbidities, admission method/route, clinical characteristics and investigations, in-hospital drug treatments, primary reperfusion treatment, interventional treatments, in-hospital outcome, diagnosis on discharge and discharge (secondary prevention) treatment[21,101,166].

7.3.2 *Study population*

The analytical cohort for this study included all patients over the age of 18 years, admitted with a diagnosis of NSTEMI in one of the 235 hospitals in the England and Wales from 1st Jan 2007 and 31st Dec 2015. Only the first admission of each patient in the dataset was included in the analysis which was then matched to the first admitting hospital catheter laboratory facilities. All patients were then stratified into three groups; according to the catheter laboratory facilities of the admitting hospital as follows: `no lab` hospitals – hospital without catheter laboratory; `diagnostic` hospitals – hospitals with diagnostic catheter laboratory only; PCI hospitals – hospital with interventional

(PCI) laboratory facilities Patients with missing age, gender, in-hospital mortality information or those admitted to hospitals in Northern Ireland were excluded from the analysis (Figure 7.1). The Northern Ireland hospitals were excluded because participation in the MINAP registry is not mandated in Northern Ireland and hence the data collection is not complete for those hospitals in the registry. In order to examine the association between different types of cardiac catheter laboratory facilities and clinical outcomes in patients admitted with high-risk NSTEMI, a subgroup analysis of patients with GRACE risk score > 140 was undertaken. For this analysis, all other patients were removed from the analysis except patients with GRACE risk score >140. They were then stratified into three groups according to the admitting hospital cardiac catheter laboratory facilities as described above. The patients admitted to 'no lab' hospitals will be either medically managed or referred to nearest 'PCI hospital' for an invasive strategy, whereas patients admitted to 'diagnostic hospitals' may follow different treatment pathways in the form of either medical management alone, onsite CA only, onsite CA and referral to nearest 'PCI hospital' for PCI or direct referral to 'PCI hospitals' for CA+/- PCI. Therefore, in order to further delineate the differences in treatment practices of high-risk NSTEMI patients admitted first in the diagnostic hospitals, a sensitivity analysis of patients receiving an invasive strategy onsite at the diagnostic hospitals compared to those transferred out directly to PCI hospitals from the diagnostic hospitals for an invasive strategy was performed. In this analysis, high-risk NSTEMI patients with GRACE risk score > 140 admitted to 'diagnostic hospital' and received an invasive strategy were divided into two groups based on whether they received an invasive strategy at the 'diagnostic hospital' or referred to 'PCI hospital' after admission to 'diagnostic hospital'.

Figure 7.1: Flow diagram of the study selection



7.3.3 *Study outcomes*

The outcomes of interest were in-hospital all-cause mortality, cardiac mortality, and major bleeding which are collected within the MINAP dataset.

7.3.4 *Study covariates*

Further information on the patient's baseline characteristics, details of the presentation, comorbidities, in-hospital and discharge pharmacology, receipt of invasive strategies in the form of CA, PCI or CABG during admission and GRACE risk score was also collected. GRACE 2.0 score was calculated as previously described[2] and patients were categorised into low (<109), intermediate (109-140) and high-risk (>140) categories as per international guidelines[3,4].

The MINAP database is collected and used for research purposes without informed patient consent by the NICOR under section 251 of the National Health Service Act 2006. Therefore, ethical approval was not required for this study under current arrangements by the NHS research governance.

7.3.5 *Statistical analysis*

The baseline characteristics across the three groups were described using the number and percentages for categorical variables and median and interquartile ranges for continuous variables. In order to limit the influence of biases related to missing data, multiple imputation techniques with chained equations were used to account for the missing data. Full details of the percentage of missing data of each variable included in the study are provided in Appendix Table 6. Age, gender, hospital catheter laboratory status, ethnicity and in-hospital all-cause and cardiac mortality were registered as regular variables in the imputations model whereas all other variables including body mass index (BMI), GRACE risk score, seen by cardiologists, left ventricular (LV) systolic function, ECG changes defined as ST depression or transient ST elevation or T wave inversion, prior history of PCI, coronary artery bypass graft (CABG), heart failure, hypercholesterolemia, angina, cerebrovascular disease, peripheral vascular disease, chronic renal failure, diabetes, hypertension, smoking status, asthma/COPD, family history of coronary disease, in-hospital use of low molecular weight heparin, warfarin, loop diuretics, glycoprotein 2b3a inhibitors, discharge medications including aspirin, P2Y12 inhibitors, statin, ACE inhibitor, beta-blocker, in-hospital major bleeding, receipt of CA and receipt of PCI were imputed. Using these models, 10 imputed datasets were generated which were used to perform all the analyses. Multivariable logistic regression models were used to study the independent predictors of the receipt of an invasive strategy in the form of CA or PCI. In order to account for

variations at the hospital level, multilevel logistic regression models were fitted as patients were clustered by the hospitals in these analyses. The multilevel logistic regression model captures any unobserved hospital components factors that were omitted but may influence the outcomes. All models included the same aforementioned variables used in the multiple imputation models as well as the year of admission. Full details of statistical modelling have been discussed in chapter 3 of this thesis. Estimates in the form of odds ratios and 95% confidence intervals were reported.

7.4 Results

7.4.1 *Patient and hospital characteristics*

The analytical cohort of this study consisted of 452,216 patients admitted with a final diagnosis of NSTEMI across 235 acute hospitals in England and Wales during the study period. Of these patients, 97,777 (21.6%) were admitted to hospitals with 'no lab' hospitals, whereas 134,381 (29.7%) and 220,058 (48.7%) were admitted to 'diagnostic' and 'PCI hospitals' respectively. Table 7.1 shows the differences in the baseline characteristics of the patients stratified according to the type of cardiac catheter laboratory facilities at the first admitting hospital. Typically, patients admitted to 'PCI hospitals' were younger [median age 72 interquartile range (60.8-81)], had worst baseline cardiovascular profiles with increased prevalence of hypercholesterolemia (39.9%), peripheral vascular disease (5.8%), current smoking (22.4%) and family history of coronary heart disease (32.1%) compared to those patients admitted to `no lab` and `diagnostic` hospitals. In contrast, patients admitted to 'no lab' hospitals were more likely to be high risk with GRACE risk score >140 (59.6%) and had increased prevalence of out hospital cardiac arrest (1.2%), acute ECG changes (79.6%), poor LV systolic function (13.6%) compared to 'PCI hospitals'. Patients admitted to `no lab` hospitals were less likely to be seen by a cardiologist compared with those admitted to

'PCI hospitals' (87.6% vs 95.6%). Rates of CA were higher in 'PCI hospitals' (77.3%) compared with `diagnostic` and `no lab` (63.2% and 61.4%) hospitals respectively. Likewise, patients in 'PCI hospitals' were almost twice as likely to receive PCI (45.9%) compared to `no lab` (28.3%) and `diagnostic` hospitals (22.4%). Finally, patient admitted to 'no lab' hospitals were less likely to receive guidelines recommended medications on discharge in the form of aspirin (89.9%), P2Y12 inhibitors (86.3%), statins (91.8%), ACE inhibitors (80.8%) and beta-blockers (77.7%) compared to the other two groups.

Table 7.1: Baseline characteristics of the patients stratified according to `no lab`, `diagnostic` and PCI hospitals.

Variables	**No lab 97,777 (21.6%)**	**Diagnostic hospitals 134,381 (29.7%)**	**PCI hospitals 220,058 (48.7%)**	**P value**
Age	74 [63-83]	74 [63-83]	72 [60.8-81]	<0.001
Male (%)	60,422(61.8%)	82,210 (61.2%)	144,096 (65.5%)	<0.001
Caucasians (%)	82,809 (84.7)	118,426 (88.2%)	179,008 (81.4%)	<0.001
BMI median [IQR]	27.0 [23.8-30.7]	26.9 [23.9-30.6]	27.2 [24.2-30.7]	0.0001
Presenting Characteristics				
Heart rate, bpm, median (IQR)	80 [67-94]	80 [67-94]	77 [65-91]	<0.001
Systolic blood pressure, median (IQR)	140 [121-158]	139 [121-158]	140 [121-158]	0.001
ECG changes	75,885 (79.6%)	104,960 (80.1%)	169,050 (78.6%)	0.001
Trop positive	88,066 (92.5%)	122,484 (94.1%)	196,414 (91.8%)	0.001
Out of hospital cardiac arrest	1,105 (1.2%)	1,175 (0.9%)	2,285 (1.1%)	<0.001
Creatinine, median	93 [77-119]	94 [77-118]	90 [74-114]	<0.001

(IQR)				
Seen by cardiologist	79,522 (87.6%)	111,775 (90.9%)	202,235 (95.6%)	<0.001
Left ventricular systolic function				<0.001
Good	21,533 (58.2%)	29,450 (59.3%)	56,750 (60.4%)	
Moderate	10,438 (28.2%)	13,975(28.2%)	26,380(28.1%)	
Poor	5,002 (13.6%)	6,202 (12.5%)	10,836 (11.5%)	
GRACE risk score				<0.001
Low <109	6,120(17.2%)	7,178 (17.3%)	20,742 (20.1%)	
Intermediate 109-140	8,251 (23.2%)	9,863 (23.8%)	27,351 (26.5%)	
High >140	21,226 (59.6%)	24,448 (58.9%)	55,224 (53.4%)	
Previous medical history				
Percutaneous coronary intervention	11,527(12.4%)	14,559(11.8%)	35,519 (16.6%)	<0.001
Coronary artery bypass graft	8,149 (8.7%)	11,352 (9.2%)	21,248 (10.2%)	<0.001
Heart failure	8,711 (9.3%)	10,930 (8.8%)	14,659 (7.1%)	0.001
Hypercholesterolemia	30,475 (33.2%)	44,900(36.4%)	82,128 (39.9%)	<0.001
Angina	34,059 (36.5%)	48,243(38.9%)	69,637 (33.5%)	0.001
Cerebrovascular disease	10,594 (11.1%)	13,771 (11.1%)	20,469 (9.8%)	<0.001
Peripheral vascular disease	4,980 (5.4%)	6,714 (5.5%)	11,758 (5.8%)	<0.001
Chronic renal failure	8,013 (8.6%)	10,100 (8.2%)	17,375 (8.4%)	0.04
Diabetes	24,212 (25.3%)	32,395 (24.6%)	56,291 (26.1%)	0.001
Hypertension	51,125 (54.6%)	67,945 (54.3%)	119,921 (57.0%)	0.001
Smoking status				<0.001
Previous smoker	36,946 (39.6%)	48,324 (38.3%)	78,747 (38.0%)	

Current smoker	18,941 (20.9%)	26,136 (20.8%)	46,456 (22.4%)	
Asthma / COPD	16,738 (18.0%)	23,049 (18.8%)	33,638 (16.3%)	0.001
Family history of CHD	20,315 (27.4%)	27,909 (27.6%)	57,252 (32.1%)	<0.001
In-hospital Pharmacology				
Low molecular weight heparin	58,058(64.3%)	77,468 (64.4%)	109,781 (57.2%)	<0.001
Warfarin	6,105 (6.9%)	8,649 (7.3%)	11,215 (6.1%)	<0.001
Loop Diuretic	28,666 (32.0%)	38,048 (32.1%)	52,755 (28.7%)	<0.001
Glycoprotein use	2,098 (2.3%)	2,554 (2.2%)	11,067 (5.9%)	<0.001
Coronary angiography	49,755 (61.4%)	72,277 (63.2%)	153,668 (77.3%)	<0.001
Discharge Medications				
Aspirin	61,470 (89.9%)	83,883 (89.0%)	181,828 (94.7%)	<0.001
P2Y12 inhibitors	82,895 (86.3%)	112,105 (84.9%)	192,776 (90.0%)	<0.001
Statins	61,600 (91.9%)	85,890 (91.8%)	178,985 (94.4%)	<0.001
ACE inhibitors	52,967 (80.8%)	71,151 (77.6%)	154,188 (83.9%)	<0.001
Beta-Blockers	52,108 (77.7%)	72,641 (77.6%)	156,595 (83.5%)	<0.001

BMI= body mass index, bmp= beats per minute, GRACE= global registry of acute coronary events, COPD= chronic obstructive airway disease, ACE= angiotensin converting enzyme

The differences in the characteristics of patients receiving an invasive strategy according to admitting hospital cardiac catheter laboratory facilities compared to medically managed patients are elucidated in Table 7.2 and Table 7.3. Among patients receiving an invasive strategy, patients admitted to 'PCI hospitals' were more likely to be older, male and have electrographic changes on admission. There were no differences in baseline GRACE scores across the three groups (Table 7.2). Patients with high-risk features such as those with high GRACE risk score >140, out of hospital

cardiac arrest or electrographic changes on admission were more likely to be medically managed in `no lab` hospitals compared to `diagnostic` and PCI capable hospitals (Table 7.3). These patients were also less likely to receive in-patient cardiology input in the form of a consultant cardiologist review in the `no lab` hospitals compared to the other two groups.

Table 7.2: Baseline characteristics of the patients receiving coronary angiography stratified according to `no lab`, `diagnostic` and PCI hospitals.

Variables	No lab 50,043 (18.3%)	Diagnostic hospitals 71,995 (26.3%)	PCI hospitals 151, 306 (55.4%)	P value
Age	67 [57-76]	67 [57-76]	67.9 [58-76]	<0.001
Male (%)	34,533(69.0%)	49,379 (68.6%)	105,971 (70.0%)	<0.001
Caucasians (%)	41,412 (82.7)	62,523 (86.9%)	121,342 (80.2%)	<0.001
BMI median [IQR]	27.7 [24.7-31.3]	27.7 [24.8-31.2]	27.4 [24.6-31.0]	0.0001
Presenting Characteristics				
Heart rate, bpm, median (IQR)	76 [65-90]	76 [65-90]	75 [65-88]	<0.001
Systolic blood pressure, median (IQR)	142 [125-160]	141 [125-160]	140 [124-159]	0.001
ECG changes	37,412 (76.3%)	54,059 (76.6%)	114,547 (77.1%)	0.001
Trop positive	45,540 (93.4%)	66,325 (94.8%)	135,539 (91.9%)	0.001
Out of hospital cardiac arrest	368 (0.7%)	501 (0.7%)	1,495 (1.0%)	<0.001
Creatinine, median (IQR)	88 [74-105]	88 [74-105]	87 [73-105]	<0.001
Seen by cardiologist	44,709 (94.9%)	65,819 (97.9%)	145,423 (98.9%)	<0.001
LV systolic function				<0.001
Good	14,239 (65.8%)	20,400 (66.9%)	45,195 (64.5%)	
Moderate	5,452 (25.2%)	7,683 (25.2%)	18,529(26.3%)	
Poor	1,937 (9.0%)	2,397 (7.9%)	6,378 (9.1%)	
GRACE risk score				0.66
Low <109	5,184 (24.6%)	6,239 (24.7%)	18,207 (24.8%)	
Intermediate 109-140	6,544 (31.0%)	7,947 (31.5%)	22,929 (31.2%)	
High >140	9,368 (44.4%)	11,031 (43.7%)	32,396 (44.1%)	
Previous medical history				
Percutaneous coronary intervention	6,931 (14.5%)	9,035 (13.6%)	25,420 (17.7%)	<0.001
Coronary artery bypass graft	3,842 (8.0%)	5,326 (8.0%)	13,580 (9.5%)	<0.001
Heart failure	2,122 (4.4%)	2,711 (4.1%)	6,193 (4.4%)	0.003
Hypercholesterolemia	17,897 (37.9%)	25,717 (38.6%)	61,041 (43.1%)	<0.001

Angina	14,790 (30.8%)	21,612 (32.4%)	43,931 (30.7%)	0.001
Cerebrovascular disease	3,419 (6.9%)	4,532 (6.8%)	10,651 (7.4%)	<0.001
Peripheral vascular disease	2,147 (4.5%)	2,742 (4.2%)	7,299 (5.2%)	<0.001
Chronic renal failure	2,313 (4.8%)	2,965 (4.4%)	8,200 (5.8%)	0.001
Diabetes	11,342 (23.1%)	15,747 (22.2%)	37,091 (25.0%)	0.001
Hypertension	25,494 (52.9%)	35,022 (52.1%)	81,626 (56.5%)	0.001
Smoking status				<0.001
Previous smoker	18,259 (38.0%)	25,398 (36.7%)	54,605 (37.5%)	
Current smoker	12,806 (26.7%)	18,460 (26.7%)	37,262 (25.7%)	
Asthma / COPD	7,296 (15.4%)	10,453 (15.9%)	20,916 (14.8%)	0.001
Family history of CHD	14,335 (35.1%)	20,295 (35.3%)	46,695 (37.0%)	<0.001
In-hospital Pharmacology				
Low molecular weight heparin	28,746 (62.3%)	40,955 (64.3%)	75,174 (56.6%)	<0.001
Warfarin	2,138 (4.7%)	2,940 (4.7%)	6,450 (5.1%)	<0.001
Loop Diuretic	8,645 (18.9%)	11,639 (18.5%)	26,913 (21.4%)	<0.001
Glycoprotein use	1,655 (3.6%)	2,069 (3.3%)	10,024 (7.7%)	<0.001
Discharge Medications				
Aspirin	29,844 (95.6%)	41,888 (94.5%)	133,715 (97.0%)	<0.001
P2Y12 inhibitors	45,513 (93.1%)	63,945 (90.9%)	137,751 (93.4%)	<0.001
Statins	29,949 (96.4%)	42,492 (96.0%)	132,337 (96.5%)	<0.001
ACE inhibitors	26,785 (88.7%)	36,940 (85.7%)	116,704 (87.9%)	<0.001
Beta-Blockers	26,046 (84.5%)	36,958 (84.1%)	116,074 (86.2%)	<0.001
Outcomes				
Death	229 (0.5%)	277 (0.4%)	1,512 (1.0%)	<0.001
Cardiac mortality	188 (0.4%)	233 (0.3%)	1,203 (0.8%)	<0.001
Major bleeding	399 (0.8%)	355 (0.5%)	2,491 (1.7%)	<0.001

BMI= body mass index, bmp= beats per minute, GRACE= global registry of acute coronary events, COPD= chronic obstructive airway disease, ACE= angiotensin converting enzyme

Table 7.3: Baseline characteristics of medically managed patients stratified according to `no lab`, diagnostic` and PCI hospitals.

Variables	**No lab N=32,455 (27.2%)**	**Diagnostic hospitals N =42,119 (35.2%)**	**PCI hospitals N=44,917 (37.6%)**	**P value**
Age	81 [72-87]	81 [73-87]	81 [72-87]	<0.001
Male (%)	17,523 (54.0%)	22,012 (52.3%)	24,302(54.1%)	<0.001
Caucasians (%)	28,289 (87.2)	37,366 (88.7%)	37,517 (83.6%)	<0.001
BMI median [IQR]	25.6 [22.3-29.4]	25.7 [22.5-29.4]	25.8 [22.6-29.4]	0.03

Presenting Characteristics				
Heart rate, bpm, median (IQR)	83 [70-100]	84 [70-100]	82 [70-99]	<0.001
Systolic blood pressure, median (IQR)	136 [118-156]	136 [117-156]	136 [118-156]	0.76
ECG changes	27,136 (85.8%)	35,213 (85.9%)	36,986 (84.8%)	0.001
Trop positive	29,220 (92.3%)	37,789 (93.1%)	39,781 (91.2%)	0.001
Out of hospital cardiac arrest	464 (1.5%)	350 (0.9%)	433 (1.1%)	<0.001
Creatinine, median (IQR)	104 [82-137]	104 [83-138]	103 [81-140]	0.003
Seen by cardiologist	23,200 (79.5%)	30,321 (81.2%)	36,070 (87.4%)	<0.001
Left ventricular systolic function				<0.001
Good	4,898(48.6%)	6,006 (48.2%)	6,179 (45.1%)	
Moderate	3,249 (32.3%)	4,116(33.1%)	4,709(34.3%)	
Poor	1,922 (19.1%)	2,329 (18.7%)	2,822 (20.6%)	
GRACE risk score				<0.001
Low <109	332 (4.9%)	375 (4.9%)	848 (5.5%)	
Intermediate 109-140	714 (10.5%)	862 (11.3%)	1,863 (12.2%)	
High >140	5,746 (84.6%)	6,380 (83.8%)	12,627 (82.3%)	
Previous medical history				
Percutaneous coronary intervention	2,842(9.4%)	3,513 (9.0%)	5,947 (14.1%)	<0.001
Coronary artery bypass graft	2,891 (9.5%)	4,047 (10.3%)	5,152 (12.2%)	<0.001
Heart failure	4,497 (14.7%)	5,320 (13.6%)	5,659 (13.5%)	0.001
Hypercholesterolemia	8,720 (28.9%)	13,391(34.4%)	13,681 (32.9%)	<0.001
Angina	13,295 (43.3%)	18,415(46.9%)	17,549 (41.3%)	0.001
Cerebrovascular disease	4,882 (15.8%)	6,138 (15.6%)	6,609 (15.7%)	<0.001
Peripheral vascular disease	1,940 (6.4%)	2,586 (6.8%)	2,900 (7.1%)	<0.001
Chronic renal failure	3,683 (11.9%)	4,481 (11.5%)	6,150 (14.7%)	0.04
Diabetes	8,262 (27.2%)	11,098 (27.0%)	12,725 (29.1%)	0.001
Hypertension	17,435 (56.7%)	22,268 (56.3%)	25,312 (59.0%)	0.001
Smoking status				<0.001
Previous smoker	12,271 (42.1%)	15,410 (40.4%)	15,987 (39.3%)	
Current smoker	4,283 (14.7%)	5,167 (13.5%)	5,782 (14.2%)	
Asthma / COPD	6,375 (20.9%)	8,436 (21.7%)	8,293 (19.9%)	0.001
Family history of CHD	4,196 (18.5%)	5,454 (18.2%)	6,994 (20.1%)	<0.001
In-hospital Pharmacology				
Low molecular weight heparin	21,114 (70.2%)	26,352 (67.8%)	23,860 (61.2%)	<0.001
Warfarin	2,777 (9.4%)	2,884 (10.2%)	3,278 (8.7%)	<0.001
Loop Diuretic	13,701 (45.6%)	18,222 (47.7%)	17,807 (47.1%)	<0.001
Glycoprotein use	284 (1.0%)	295 (0.8%)	532 (1.4%)	<0.001
Discharge Medications				

Aspirin	22,545 (85.2%)	29,370 (84.2%)	32,274 (88.2%)	<0.001
P2Y12 inhibitors	25,500 (78.9%)	32,900 (78.3%)	36,056 (81.1%)	<0.001
Statins	22,557 (88.2%)	30,344 (87.7%)	31,778 (88.3%)	0.04
ACE inhibitors	18,751 (73.9%)	24,145 (70.7%)	25,068 (72.2%)	<0.001
Beta-Blockers	18,030 (69.7%)	24,514 (70.6%)	26,628 (74.7%)	<0.001
Outcomes				
Death	4,100 (12.6%)	5,048 (12.0%)	4,716 (10.5%)	<0.001
Cardiac mortality	3,077 (9.5%)	3,960 (9.4%)	3,737 (8.3%)	<0.001
Major bleeding	957 (3.0%)	612 (1.5%)	8,47 (2.0%)	<0.001

BMI= body mass index, bmp= beats per minute, GRACE= global registry of acute coronary events, COPD= chronic obstructive airway disease, ACE= angiotensin converting enzyme

In the subgroup analysis looking at the utilisation of an invasive strategy and clinical outcomes in 100,898 high-risk NSTEMI patients (defined as GRACE score >140) 21,226 (21.0%) were admitted to `no lab` hospitals, whereas 24,448 (24.3%) and 55,224 (54.7%) to `diagnostic` and 'PCI hospitals' respectively. Out of the 24,448 admitted to `diagnostic` hospitals, 5,184 (21.2%) were transferred out to the nearest PCI hospital for an invasive strategy, whereas 19,264 (78.8%) were managed onsite at the first admitted diagnostic hospital. Patients transferred out to a 'PCI hospital' displayed a significantly worse baseline cardiovascular profile with increased prevalence of out of hospital cardiac arrest, electrographic changes, history of previous PCI or CABG, hypertension and current smoking status compared to those that remained and were managed in the diagnostic hospital. The patients who were treated onsite in `diagnostic` hospitals had a higher prevalence of non-cardiac comorbidities such as chronic renal failure, asthma or COPD, previous cerebrovascular accident and peripheral vascular disease. (Appendix Table 7)

7.4.2 *Temporal trends*

In the whole NSTEMI cohort, overall rates of invasive strategy increased from 50.8% to 86.0% during the study period (Figure 7.2). While the number of 'PCI hospitals' increased from 87 to 99, the 'diagnostic hospital' declined from 70 to 56 whereas the

'no lab hospitals' almost remained constant from 74 to 78 from 2007 to 2015 (Figures 7.3).

Figure 7.2: Trends in utilisation of invasive strategy in England and Wales between 2007-2015.

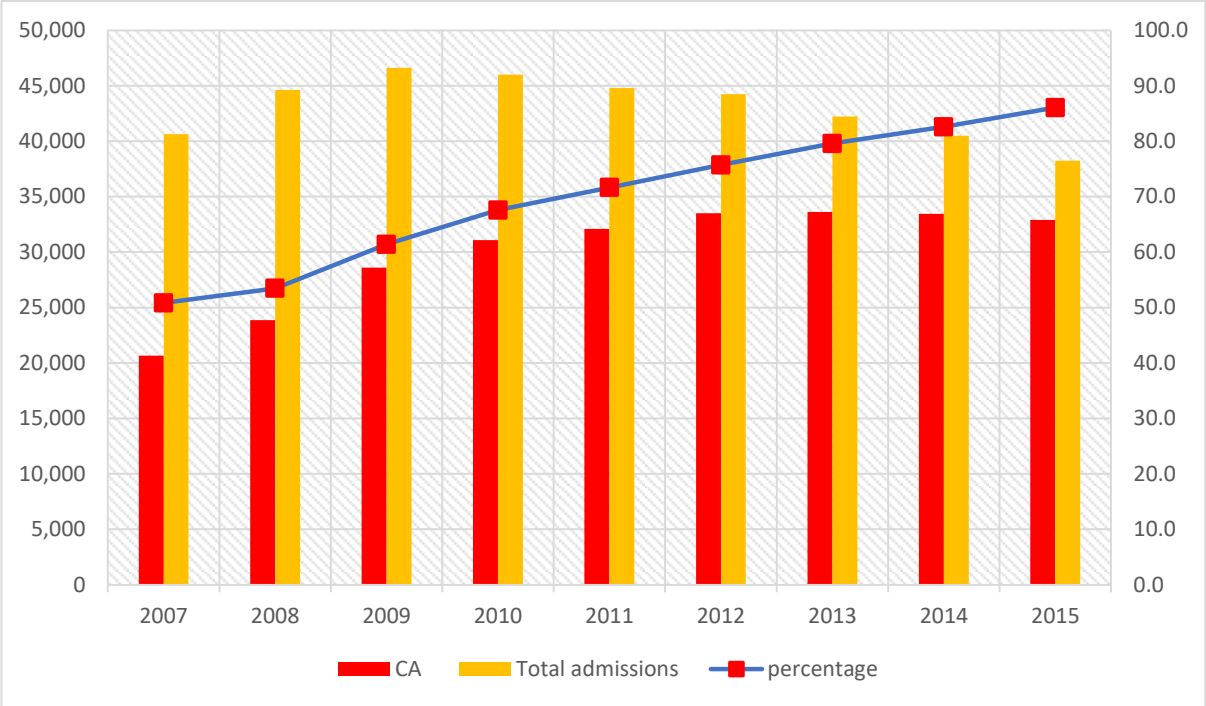
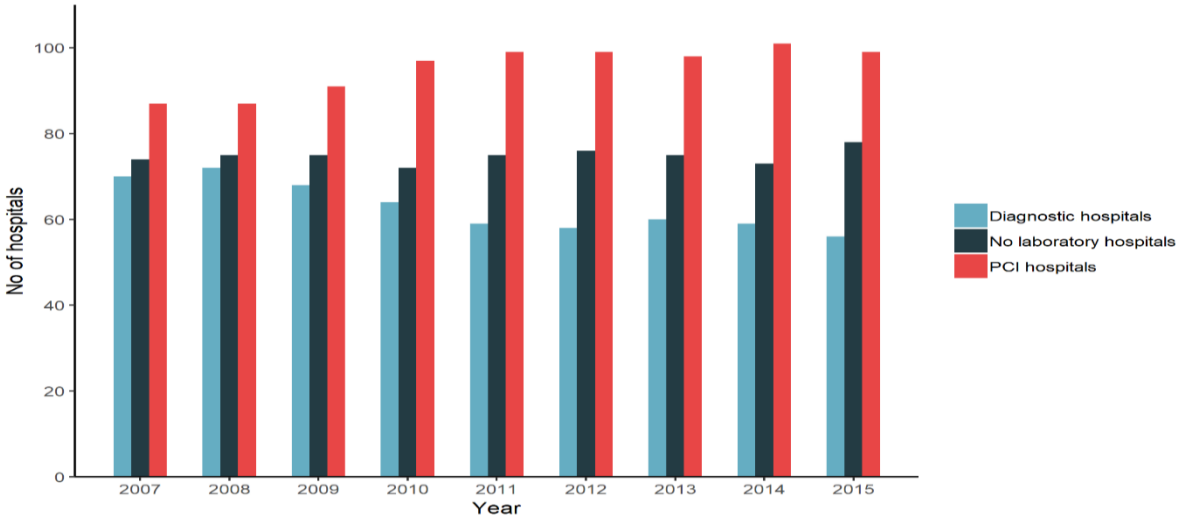


Figure 7.3: Growth in Catheter lab facilities in England and Wales hospitals between 2007-2015



The utilisation of an invasive strategy in the form of CA or PCI increased across all the hospitals and by 2015 were similar in `no lab`, `diagnostic` and PCI hospitals (86.4%,

86.0% and 85. 6%) (Figure 7.4). However, although receipt of PCI alone also increased across all hospitals during the study period it remained consistently lower in `diagnostic` hospitals compared to PCI hospitals and by 2015, was also lower compared to `no lab` hospitals (Figure 7.5). A similar pattern was seen for receipt of any revascularisation (composite of PCI or CABG) procedures in the patients admitted to `diagnostic` hospitals (Figure 7.6).

Figure 7.4: Receipt of coronary angiography stratified according to hospital cardiac catheter laboratory facilities between 2007-2015.

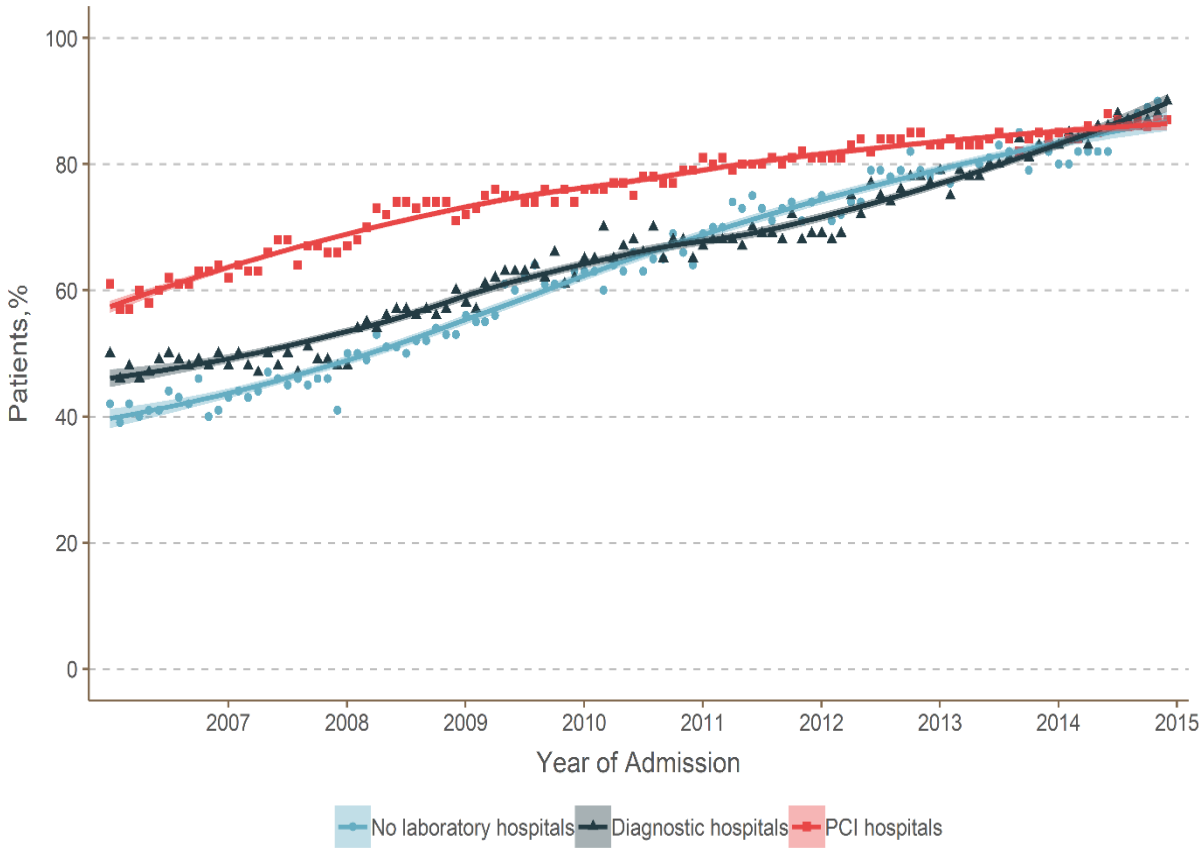


Figure 7.5: Receipt of percutaneous coronary intervention stratified according to hospital cardiac catheter laboratory facilities between 2007-2015.

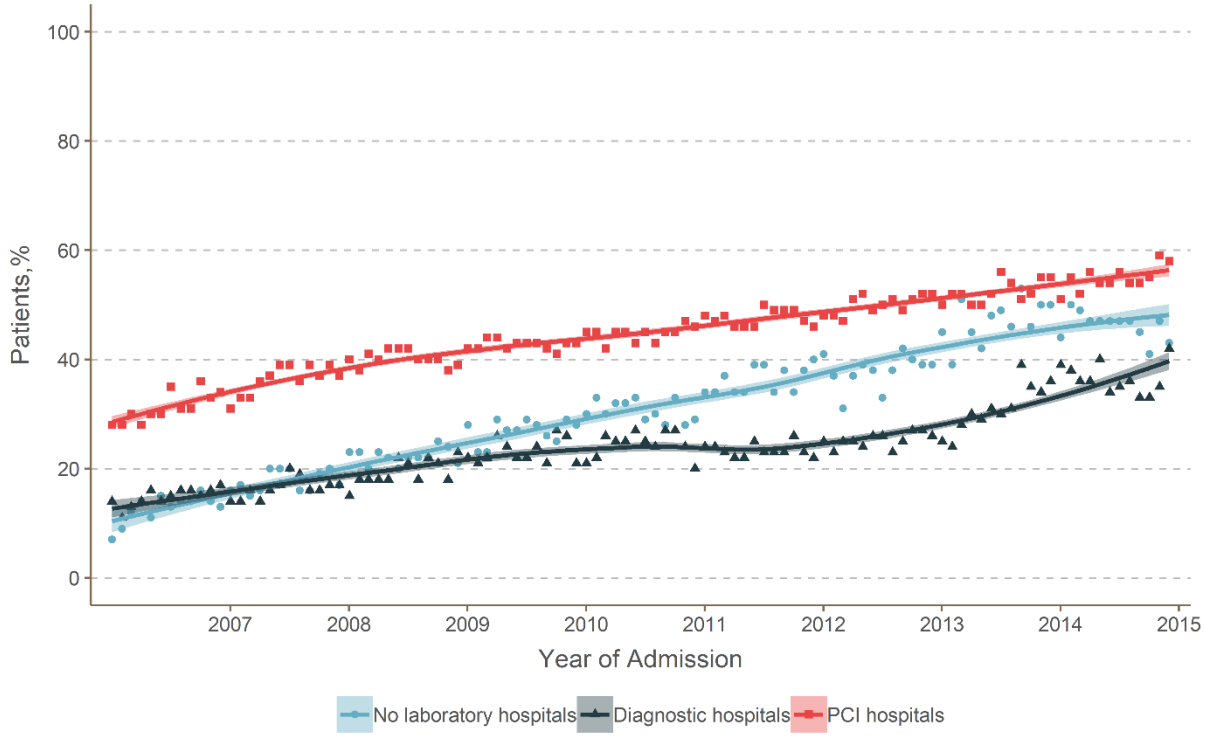
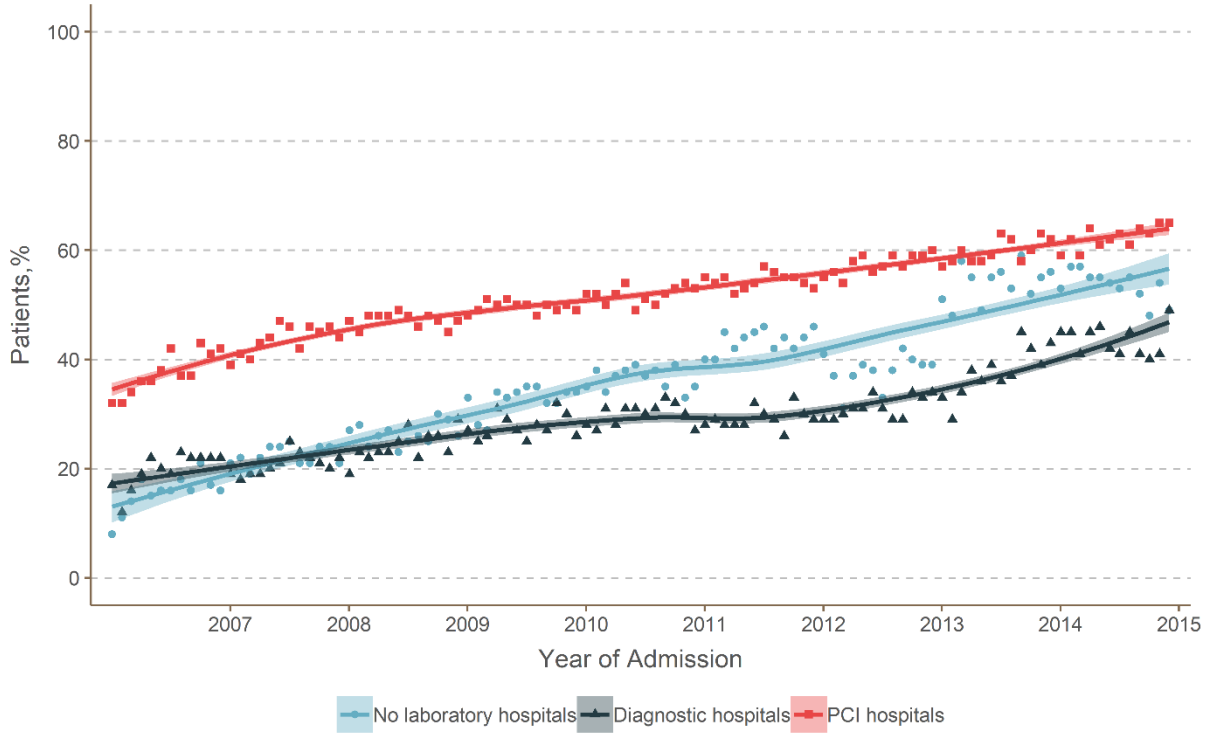


Figure 7.6: Receipt of percutaneous coronary intervention or coronary artery bypass graft surgery stratified according to hospital cardiac catheter laboratory facilities between 2007-2015.



7.4.3 *Independent predictors*

Independent predictors of receipt of an invasive strategy in the form of CA and PCI are reported in Table 7.4. High-risk NSTEMI patients defined by GRACE score >140 were less likely to receive CA (OR 0.89 95%CI 0.83-0.95) or PCI (OR 0.84 95%CI 0.84-0.94). Female sex and was also associated with reduced odds of receiving CA (OR 0.73 95%CI 0.71-0.74) and PCI (OR 0.76 95%CI 0.75-0.77). Patients with prior history of PCI were more likely to receive CA (OR 1.28 95%CI 1.24-1.32) and PCI (OR 1.36 95%CI 1.32-1.40). Receipt of cardiology care in the form of consultant cardiologist review as an in-patient was the strongest independent predictor of receipt of CA (OR 6.09 95%CI 5.79-6.41) and PCI (OR 4.27 95%CI 4.01-4.55). Finally, compared to patients treated in `no lab` hospitals, the odds of receiving CA were greater for those treated at `diagnostic` (OR 1.14 95%CI 1.11-1.16) and PCI hospitals (OR 1.64 95%CI 1.60-1.68). Conversely, the odds of receiving PCI were lower in `diagnostic` hospitals (OR 0.88 95%CI 0.86-0.90) but higher in PCI hospitals (OR 1.69 95%CI 1.66-1.73) compared to `no lab` hospitals.

Table 7.4: Independent predictors of receipt of coronary angiography and percutaneous coronary intervention

	Predictors of Receipt of CA	**Predictors of Receipt of PCI**
Variables	OR (95% CI)	OR (95% CI)
GRACE risk Score (low-risk baseline)		
Intermediate (109-140)	1.17 (1.12-1.23)	1.09 (1.06-1.13)
High (>140)	0.89 (0.83-0.95)	0.89 (0.84-0.94)
Female Gender	0.73 (0.71-0.74)	0.76 (0.75-0.77)
Age	0.94 (0.944-0.946)	0.97 (0.978-0.981)
Previous acute myocardial infarction	0.65 (0.63-0.66)	0.70 (0.69-0.72)
Previous coronary artery bypass grafting	0.92 (0.89-0.95)	0.99 (0.96-1.02)
Previous percutaneous coronary intervention	1.28 (1.24-1.32)	1.36 (1.32-1.40)
History of angina	0.86 (0.84-0.88)	0.86 (0.84-0.88)

Hypertension	1.07 (1.05-1.08)	0.99 (0.97-1.07)
Hypercholesterolemia	1.24 (1.22-1.26)	1.26 (1.23-1.28)
Peripheral vascular disease	0.96 (0.92-0.96)	1.03 (0.99-1.07)
Asthma/ COPD	0.94 (0.92-0.96)	0.99 (0.97-1.01)
Chronic renal failure	0.73 (0.70-0.76)	0.88 (0.85-0.91)
Heart failure	0.70 (0.68-0.73)	0.82 (0.79-0.85)
Cerebrovascular accident	0.67 (0.65-0.68)	0.75 (0.73-0.77)
Diabetes	0.84 (0.83-0.86)	0.86 (0.84-0.88)
Left ventricular dysfunction		
Moderate	0.86 (0.83-0.89)	0.94 (0.92-0.96)
Severe	0.67 (0.64 -0.70)	0.71 (0.68-0.74)
Family history of coronary heart disease	1.33 (1.30-1.36)	1.23 (1.21-1.25)
Seen by cardiologist	6.09 (5.79-6.41)	4.27 (4.01-4.55)
Catheter laboratory facilities (ref=no lab)		
Diagnostic hospitals	1.14 (1.11-1.16)	0.88 (0.86-0.90)
PCI hospitals	1.64 (1.60-1.68)	1.69 (1.66-1.73)

CA= coronary angiography, PCI= percutaneous coronary intervention, GRACE= global registry of acute coronary events, COPD= chronic obstructive airway disease,

7.4.4 *Clinical outcomes*

Figure 7.7 illustrates unadjusted in-hospital outcomes stratified according to admission to the three different types of hospital. In-hospital mortality was lowest (10.5%) in PCI hospitals compared with `diagnostic` (12.0%) and `no lab` (12.6%) hospitals. After adjustment for differences in baseline clinical characteristics, no differences in-hospital mortality (OR 1.09 95%CI 0.96-1.24), cardiac mortality (OR 1.03 95%CI 0.90-1.18) or bleeding complications (OR 0.95 95%CI 0.73-1.23) were observed in 'PCI hospital' and 'diagnostic hospital' (in-hospital all-cause mortality (OR 0.93 95%CI 0.83-1.04), cardiac mortality (OR 0.95 95%CI 0.84-1.07) and bleeding (OR 0.99 95%CI 0.77-1.26) (Table 7.5). In the subgroup analysis of the high-risk NSTEMI patients with a GRACE score > 140, the odds of in-hospital mortality (OR 1.36 95% 1.06-1.75) and cardiac mortality (OR 1.28 95%CI 0.99-1.65) were higher but no difference in bleeding (OR 0.96 95%CI 0.65-1.43) in `diagnostic` hospitals compared to `no lab` and PCI hospitals.

(Table 7.5). However, the sensitivity analysis of high-risk NSTEMI cohort showed that patients from 'diagnostic hospitals' receiving an invasive strategy onsite at the admitting hospital had significant increase in in-hospital mortality (OR 1.45 95%CI 1.13-1.87) and cardiac mortality (1.35 95%CI 1.05-1.75) compared to those transferred to nearest PCI hospital, `no lab` and PCI hospitals. (Table 7.6)

Figure 7.7: Unadjusted in-hospital outcomes stratified according to hospital cardiac catheter laboratory facilities

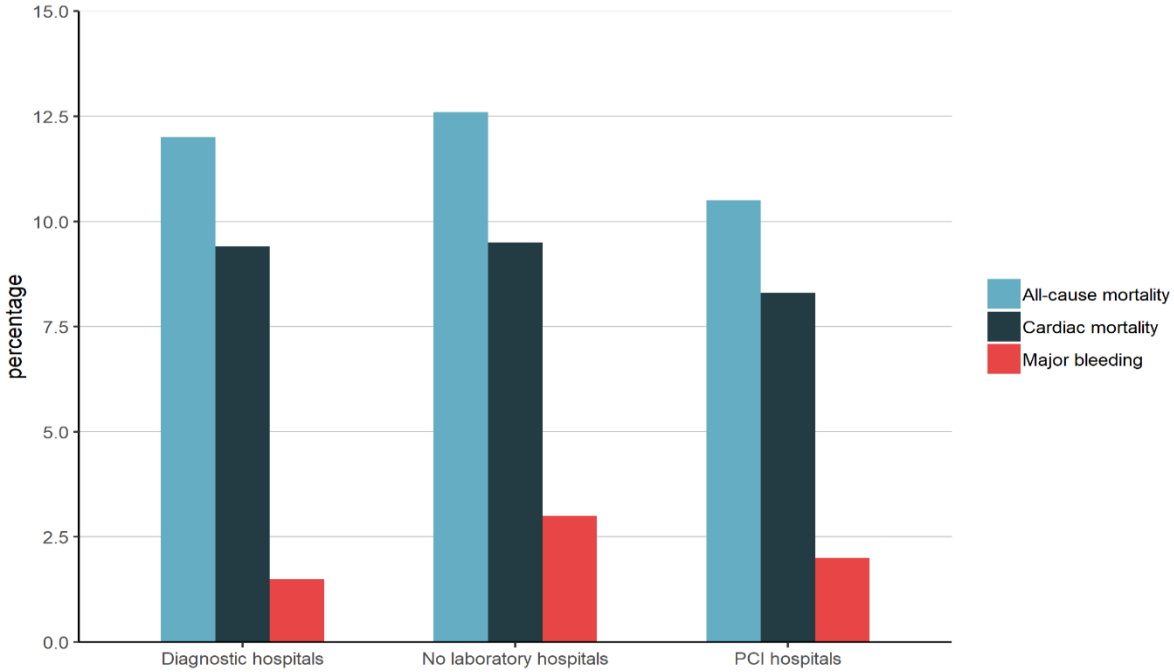


Table 7.5: Association between different types of cardiac catheter laboratory facilities and in-hospital clinical outcomes overall and high GRACE risk score.

Clinical outcomes	PCI hospitals Ref (no lab centres)	Diagnostic hospitals Ref (no lab centres)
In hospital death	1.09 (0.96-1.24)p=0.17	0.93 (0.83-1.04)p=0.22
Cardiac mortality	1.03 (0.90-1.18)p=0.61	0.95 (0.84-1.07)p=0.43
Bleeding	0.95 (0.73-1.23), p=0.70	0.99 (0.77-1.26),p=0.95
Clinical outcomes in patients with GRACE score >140		
In hospital death	1.10 (0.87-1.39)p=0.38	1.36 (1.06-1.75)p=0.01
Cardiac mortality	0.94 (0.75-1.18)p=0.62	1.28 (0.99-1.65)p=0.05
Bleeding	0.62 (0.37-1.03), p=0.06	0.96 (0.65-1.43),p=0.87

Table 7.6: Clinical outcomes in patients with high GRACE risk score > 140 receiving an invasive strategy onsite compared to those transferred to a PCI centre

Clinical outcomes Ref (no lab centres)	Diagnostic hospitals (treated off-site)	Diagnostic hospitals (treated on-site)	PCI centres
In-hospital mortality	0.35 (0.21-0.51)	1.45 (1.13-1.87)	1.06 (0.84-1.33)
Cardiac Mortality	0.40 (0.24-0.65)	1.35 (1.05-1.75)	0.90 (0.72-1.14)
Bleeding	0.24 (0.12-0.47)	0.72 (0.43-1.20)	0.96 (0.65-142)

7.5 Discussion

In this national analysis of patients admitted with a diagnosis of NSTEMI in England and Wales, patients admitted to hospitals with onsite cardiac catheter laboratory facilities have similar outcomes compared to those admitted at hospitals without such facilities. In high-risk NSTEMI patients (with GRACE score >140), admission to a diagnostic hospital was associated with an increased risk of in-hospital all-cause and cardiac mortality particularly in those receiving CA locally compared to those transferred to the nearest PCI hospital. This also analysis suggests that the presence of onsite catheter laboratory facilities was associated with increased utilisation of an invasive strategy, although paradoxically patients admitted to diagnostic hospitals were less likely to receive PCI or CABG compared to hospitals without onsite catheter laboratory facilities or PCI hospitals. These findings have important implications in developing regional treatment pathways for NSTEMI care to allow effective access to an invasive strategy.

Several studies have reported the influence of on-site catheter laboratory facilities on invasive strategy in ACS patients[43,175,186-189,192,193]. Unsurprisingly, the majority of these studies show increased use of an invasive strategy in patients admitted

to hospitals with onsite cardiac catheter laboratory facilities. There are no data studying the relationship between the type of catheter laboratory facilities of the admitting hospital and receipt of an invasive strategy in an exclusively NSTEMI national cohort. The referral patterns and utilisation of an invasive strategy are likely to be different in NSTEMI patients, compared to STEMI patients where referral pathways are focussed on transfer to a PCI capable hospital for primary PCI and early reperfusion. In the current study, a uniform uptake in the use of CA in patients admitted with a diagnosis of NSTEMI in England and Wales independent of catheter laboratory facilities of the admitting hospital was observed, however, patients admitted to diagnostic hospitals were less likely to receive an invasive strategy in the form of PCI or CABG. This is likely to be due to selection bias and variation in referral patterns of the admitting hospital, as patients admitted to hospitals without any laboratory facilities are likely to be referred to a nearest tertiary hospitals with onsite PCI facilities[194]. In contrast, patients admitted to diagnostic hospitals receive CA locally before a decision about further revascularisation is made by the treating physician, who may not necessarily be an interventional cardiologist. Consequently, such patients may be potentially denied early access to guideline-recommended invasive strategies[3,4]. The lower rates of PCI and CABG in patients admitted to diagnostic hospitals suggests that in clinical practice, physicians are likely to adopt a risk-averse strategy even after obtaining information from CA particularly in patients admitted first to diagnostic hospitals.

In this prospective observational cohort study of over 450,000 patients, there were no differences in in-hospital all-cause and cardiac mortality or bleeding complications and type of catheter laboratory facilities at the first admitting hospital. The effect of onsite site versus off site cardiac catheter laboratory facilities in ACS patients was compared in the GRACE registry showing that patients admitted to

hospital with onsite cardiac catheter laboratory facilities had similar outcomes as compared to those admitted to hospital without such facilities[188]. Similar findings were reported by the European Network of Acute Coronary Treatment (ENACT) and National Registry of Myocardial Infarction investigators showing no benefit of onsite cardiac catheter laboratory facilities on clinical outcomes in ACS[195,196]. To the best of my knowledge, this is the first study comparing association with different levels of hospital cardiac catheter laboratory facilities and clinical outcomes in an exclusive NSTEMI cohort. These findings also highlight important differences in institutional practices and treatment gaps, particularly in high-risk NSTEMI patients. In the high-risk NSTEMI cohort, patients admitted to diagnostic hospitals first were at increased risk of in-hospital all-cause and cardiac mortality, which may be related to a significantly lower use of invasive strategies in the form of PCI or CABG in these hospitals. We observed a similar mortality hazard in high-risk NSTEMI patients receiving CA onsite in diagnostic hospitals compared to those referred for CA to PCI hospitals from the diagnostic hospitals. Previous studies from international registries have shown that the use of invasive strategies is independently associated with improved survival in NSTEMI patients[21,197]. Ideally, hospitals treating these patients should be able to offer effective care and uniform access to CA and revascularisation as per guidelines recommendations. Therefore, regionalisation of care for NSTEMI patients whereby merging the diagnostic hospitals with PCI hospitals and direct referral of patients to PCI hospitals after appropriate risk stratification may translate into early, uniform access to an invasive strategy, better resource allocation and improved patient care[175,189].

Current guidelines emphasise an early invasive approach followed by revascularisation either in the form of PCI or CABG in patients with GRACE score ≥140 or other high-risk features[3,4]. The results from this analysis indicate that patients presenting with high-

risk features such as those with LV dysfunction, heart failure, history of diabetes and high GRACE score ≥140 were least likely to receive CA or PCI independent of the type of admitting hospitals. This finding is consistent with well-known treatment-risk paradox whereby patient who most likely to benefit from an intervention are least likely to receive it[198]. A recent individual patients' level meta-analysis of eight RCTs including 5,324 patients found significantly lower mortality in high-risk patients such those with history of diabetes, age above 75 years and GRACE score ≥ 140 when treated with early invasive strategy[150]. Appropriate risk stratification, recognition of this paradox and development of quality improvement programmes are required to offer guidelines recommended treatment to patients presenting with high-risk features.

7.6 Study strengths and limitations

This analysis is subject to certain limitations that should be borne in mind whilst interpreting these findings. The follow-up data beyond hospital discharge was not available so only in-hospital outcomes were evaluated. However, previous studies have reported similar comparable outcomes at shorter and longer-term follow up in patients who were admitted to hospitals with or without cardiac catheter laboratory facilities in all ACS patients[43,186]. Although completion of mandatory data fields has improved considerably in MINAP over time, there was a significant amount of missing data in important variables such as LVEF and GRACE risk score that could have biased the estimates. However, in order to limit the influence of bias from missing data we implemented an imputation strategy as previously described and validated for use in this registry[88]. Finally, the observational nature of the study is susceptible to unmeasured confounding and only associations rather than causal relationships can be inferred.

7.7 Conclusion

In this large, contemporary analysis from a national healthcare system, there were significant disparities in utilisation of an invasive strategy, which is influenced by the type of cardiac catheter laboratory facilities of the admitting hospital. This study serves to highlight important differences in institutional practices and treatment gaps whereby high-risk NSTEMI patients admitted to diagnostic hospitals were less likely to receive an invasive strategy in the form of PCI or CABG and were at increased risk of in-hospital mortality. These differences in the care of NSTEMI may be improved by developing a stronger network of a regional system of care with transfer algorithms and implementation of guidelines directed invasive strategies for high-risk NSTEMI patients.

Chapter 8

Appropriate radial access site selection and clinical outcomes in the use of invasive strategy in ACS

8.1 Introduction

The previous chapters in this thesis systematically studied the use of invasive strategy amongst different groups of patients admitted with a diagnosis of NSTEMI, the timing of an invasive strategy, the independent predictors of invasive strategy and hospital factors such as the presence of cardiac catheter laboratory facilities. Given the central role of an invasive strategy in the management of NSTEMI patients, it is important to understand if there are any procedural aspects of an invasive strategy that may influence the clinical outcomes of patients, and in particular access site choice. Therefore, this chapter focuses on access site selection and clinical outcomes in patients that underwent PCI in the UK. The findings from this chapter were published in the Journal of American College of Cardiology (JACC): Cardiovascular Interventions[199]. Furthermore, the manuscript was selected as Continued Medical Education (CME) choice by the editor and was awarded CME points by the editorial board for the accompanying CME questions (appended in chapter 10). There was also an editorial to highlight the importance of this work (Appendix 10.3)

The radial artery is now the most common vascular access site utilised for percutaneous coronary interventions (PCI) across many European[4], Canadian and South Asian countries [200,201] and continues to gain popularity in the US [202,203]. According to most recent audit figure published by British Cardiovascular Intervention Society (BCIS), the transradial access (TRA) is now being used in almost 90% of patients undergoing PCI procedures in the UK and similar surge in use of TRA has been noted in the USA where use of TRA has increased fourfold to almost 40% in the last 5 years[204,205]. The main advantages of transradial access (TRA) over transfemoral access (TFA) include a lower incidence of vascular complications, significant reductions in major bleeding, a lower rate of MACE and, in some settings, death [72,73,206] as well as earlier ambulation, shorter

hospital stay and greater patient satisfaction [207,208]. The most recent guidelines from the European Society of Cardiology also emphasis on the use of TRA with class 1A indication[15]. Most radial operators use the right radial access (RRA) as their initial access site due to the ease of working on the right hand side of the patients and catheter lab setup [63]. However, radial operators may need to switch to the left side in the event of radial artery spasm [74], radial artery occlusion [75], the presence of arteriovenous shunt in the right arm, or presence of extreme tortuosity in the right forearm or right subclavian artery [209,210]. Left radial access (LRA) also offers much more favourable vascular anatomy compared to RRA particularly in short stature patients or those with previous coronary artery bypass grafts resulting in lesser catheter manipulation, shorter procedure time and a theoretically smaller risk of procedure related stroke[79,211-213]. However, lack of training dedicated cardiac catheter lab equipment and increase operator discomfort particularly in the early stages is a significant limitation in the use of LRA and has limited the use of LRA to selected cases in clinical practice. This has also meant that many operators will switch to a default femoral approach when right radial access is not possible, with inherently worse outcomes such as the increased risk of major bleeding and vascular access site complications.

Data from published studies comparing the RRA versus LRA have only compared the procedural efficacy such as procedure time, contrast use, fluoroscopy time and crossover to femoral access reporting conflicting results[212,214]. The TALENT study investigators randomised 1,540 patients in two hospitals to RRA or LRA for either diagnostic coronary angiography or PCI. The primary endpoint was fluoroscopy time for diagnostic coronary angiography and for PCI measured independently for each group. In the diagnostic group, LRA was associated with lower fluoroscopy time and lower dose area product (a surrogate of radiation exposure to the patient); however,

there were no differences in either of these primary endpoints in patients undergoing PCI[215]. Another study comparing RRA versus LRA for primary endpoints of radiation exposure and operator discomfort reported decreased radiation exposure to the operators in the LRA group albeit at the expense of increase operator discomfort [79]. The majority of these studies were limited to single centres and small sample sizes, therefore, one cannot determine whether there are any clinically relevant differences between either access site. Very importantly, there is no data comparing clinical outcomes such as in-hospital, 30-day mortality and procedural related complications such as access site complications or peri-procedural stroke in LRA versus RRA.

As the population requiring PCI grows and ages, it is likely that LRA will become commonplace for performing CA or PCI. There are few data that describe the differences in patient and clinical characteristics relating to the use of LRA compared to RRA, whether this practice is changing over time nationally, how multiple successive procedures influence the use of LRA or importantly whether the use of LRA is associated with different risks to patients. This study used a large national registry of all PCI procedures to answer these questions.

8.2 Objectives

The main objectives of this chapter were as follows

I. To compare the clinical and procedural characteristics of patients receiving LRA versus RRA.
II. To study the temporal trends in the use of LRA and RRA
III. To examine changes in access site practice in patients undergoing successive procedure after the first RRA procedure.
IV. To investigate differences in clinical outcomes with the use of LRA compared to RRA

8.3 Methods

8.3.1 *Study design*

This observational study was a retrospective analysis of a prospectively collected data in the British Cardiovascular Intervention Society (BCIS) registry.

8.3.2 *Study population*

The data from the British Cardiovascular Intervention Society (BCIS) registry was used to define the patient cohort and study variables. Full details of BCIS registry, strengths and limitations are provided in chapter 3. Briefly, the BCIS registry is a national registry that prospectively collects data around the clinical, procedural and outcome of almost all PCI undertaken in the United Kingdom and is managed by the National Institute of Cardiovascular Research Outcome (NICOR)[68,82,216]. All cause-mortality outcomes are robustly tracked via a linkage to the Office of National Statistics (ONS) using the unique national health system (NHS) number of all patients in England and Wales only. All data collected in the BCIS registry are a part of a national audit initiative by NICOR and are anonymised with no patient identifiable information provided to the researcher in the dataset; therefore, ethical approval was not required for this study. The initial cohort selection was made by including all patients undergoing an invasive strategy in the form of at least one PCI via either RRA or LRA in the United Kingdom, however, as the out of hospital mortality data is not available for patients in Scotland, therefore they were excluded from the outcome analyses. Patients with femoral, brachial, multiple, unknown or missing access site information were excluded. Further data restrictions were applied to patients with missing information around age and gender. For the outcomes analysis, the patients with missing information on mortality or in-hospital complications were also excluded from the analysis.

8.3.3 *Study outcomes*

The primary endpoints were in-hospital and 30-day mortality, in-hospital major bleeding (defined as a composite of blood or platelet transfusion, intracerebral haemorrhage, retroperitoneal haemorrhage, bleed resulting in cardiac tamponade, or an arterial access site bleeding requiring surgery or intervention), in-hospital Major Adverse Cardiovascular Events (MACE defined a composite of in-hospital mortality, in-hospital myocardial infarction or re-infarction and revascularization in the form of emergency PCI or CABG) and In-hospital Stroke complications (defined as haemorrhagic, ischemic, embolic stroke or transient ischemic attack). All the in-hospital complications are operator reported and not adjudicated independently.

8.3.4 *Study covariates*

In addition to the information around clinical outcomes and complications, further data were collected on each patient's baseline demographics such as age, gender, ethnicity, clinical and cardiovascular risk profile, indication for PCI, and all other aspects of interventional and pharmacological treatment administered. In order to explore the access site practice in patients undergoing repeat PCI in successive procedures in the dataset, a sub-group analysis of patients with RRA procedure as their first procedure was undertaken. The access site at each subsequent procedure was tracked to see how the access site selection changes in patients having first procedure via RRA. The RRA was selected as the first access site because it is most widely practised radial access.

8.3.5 *Statistical analysis*

First, the characteristics were compared between patients with RRA and LRA used in the first procedure. Analysis of variance (ANOVA) for continuous variables and Fisher's exact tests for binary/categorical variables were used. The independent predictors of use of LRA were determined to use multivariable logistic regression

(MLR), model. This predictive analysis was undertaken using a backward stepwise approach by including all the variables and potential confounders in the MLR and then removing the variables with significance above the defined threshold of ($p>0.011$).

In order to protect against the biases arising from informative missing data mechanisms, multiple imputations with chained equations framework were used to impute for all variables with missing information. The patients with missing information on mortality outcomes were excluded before the imputation since the inclusion of these cases in the imputation model makes no difference[89]. Complete variables registered in the imputation model were age, sex, access site and study outcome variables and imputed variables were indication for PCI, previous AMI, previous CABG, history of diabetes mellitus, peripheral vascular disease, previous PCI, hypercholesteraemia, hypertension, cerebrovascular accident, renal disease, body mass index, left ventricular systolic function, smoking status, mechanical ventilation, use of intra-aortic balloon pump, pharmacological inotropic support, use of GP2b3a inhibitor, Ticagrelor, Prasugrel, bivalirudin, PCI to left main stem, multi-vessel PCI, cardiogenic shock, stent use and operator status.

The final analyses were run on the 10 datasets generated under the multiple imputation framework. The approach can deal with data missing completely at random (MCAR) or on missing at random (MAR), and not necessarily missing not at random (MNAR) scenarios, while levels of missingness are high for certain variables. However, it has been previously illustrated that multiple imputation frameworks are robust even with high levels of missingness and can offer some protection with MNAR data as discussed in detail in chapter 3[89]. MLR modelling was used for risk estimation of all outcomes across both groups, adjusting for age, sex and all the other variables included in the multiple imputations. To account for any systematic differences in the baseline

characteristics between the two groups, multiple imputations with propensity score matching were used to calculate the average treatment effects using the same variables as in our main MLR model. The coefficients were converted to odds ratio to aid interpretation under assumptions for right radial access risk presented in Table 8.1. Finally, although it is technically possible to undertake PCI procedure in patients with previous CABG via the RRA, it is common practice to use LRA in these patients as the left internal mammary artery (LIMA) graft can be easily cannulated with a catheter from the LRA. Therefore, in order to minimise selection bias in the LRA group, we performed a sensitivity analysis by excluding patients with a previous history of CABG (Appendix Table 7-10). In order to study the regional variations in the use of LRA across primary care trusts and healthcare boards in England, Scotland and Wales, proportions of LRA procedures per year were calculated for each area from the BCIS dataset. Each patient's data was then mapped to geographic information system primary care trust layers accessed from NHS England, Scotland and healthcare board across NHS Wales to create choropleth maps of patients receiving LRA procedure using the spmap function in Stata.

8.4 Results

8.4.1 *Patient and hospital characteristics*

There were 343,725 patients undergoing PCI using radial access during the study period from which 328,495 (96%) were undertaken through the RRA and 14,311(4%) via the LRA (Figure 8.1). The relationship between different demographic characteristics and LRA use are illustrated in Figures 8.2-8.6. It can be seen that LRA PCI was undertaken in Asians (27.9% n=1854) far more than in Caucasians (4.2% n=228,908) and other ethnic groups (Figure 8.2). Similarly, LRA access was used relatively common in patients with a previous history of CABG (23.4% vs 3%) (Figure 8.3). In contrast, LRA

access was used infrequently for patients requiring PCI for STEMI indication compared to elective PCI (1.8% vs 5.5%). Finally, there was a strong inverse relationship between height and the use of LRA access with 6.8% of procedures undertaken via the LRA in short stature patients (height <150cm) compared to only 3.4% in taller patients (height >190cm).

Figure 8.1: Flow diagram of the study selection

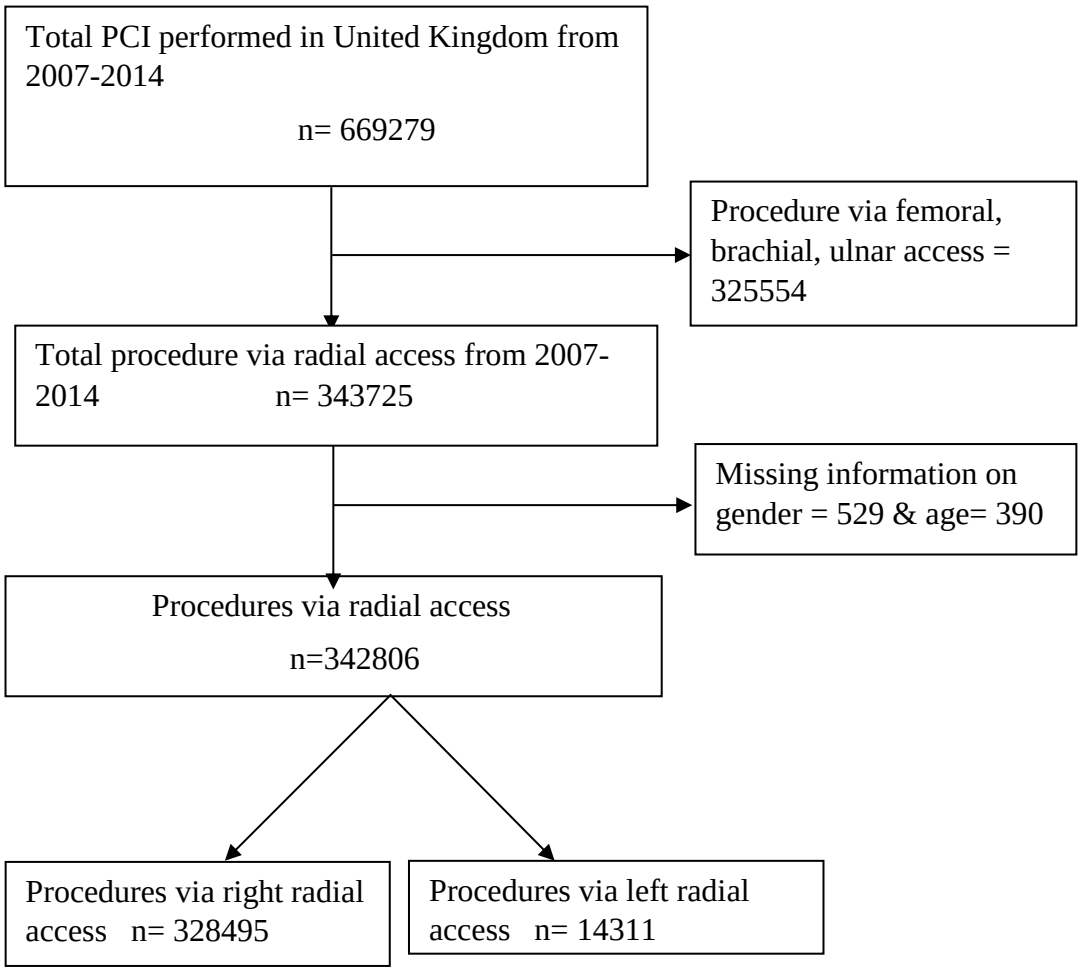


Figure 8.2**:** Left Radial access use by Ethnicity

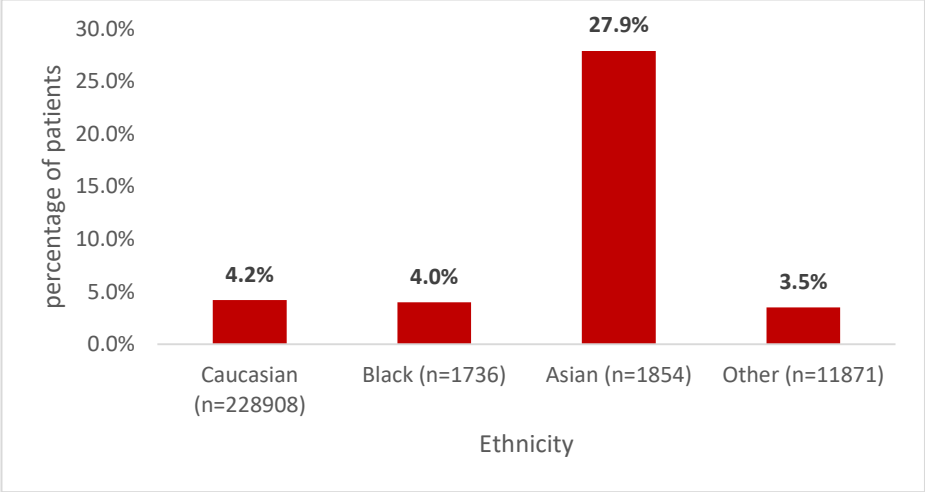


Figure 8.3: Left Radial access use by the history of CABG

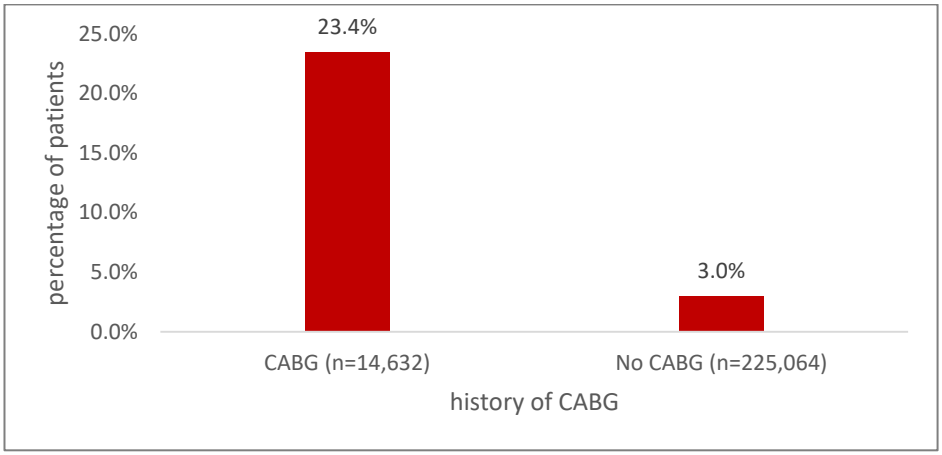


Figure 8.4: Left Radial access use by indication of PCI

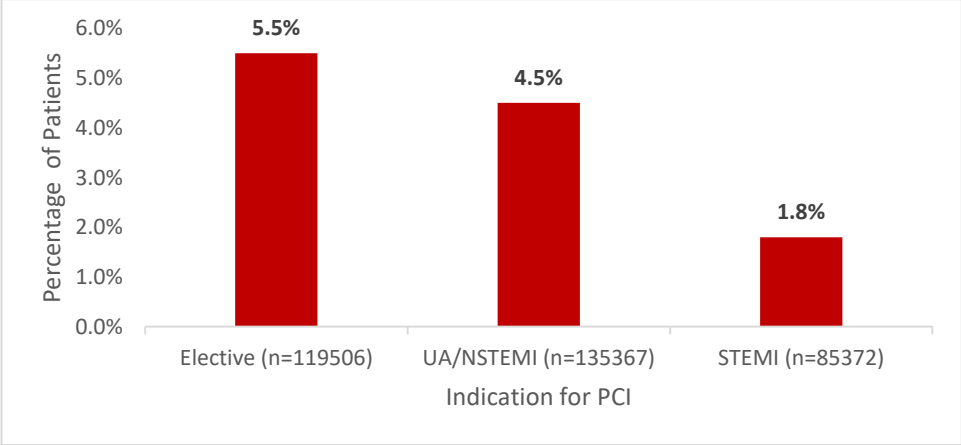


Figure 8.5: Left Radial access use by the patient's height.

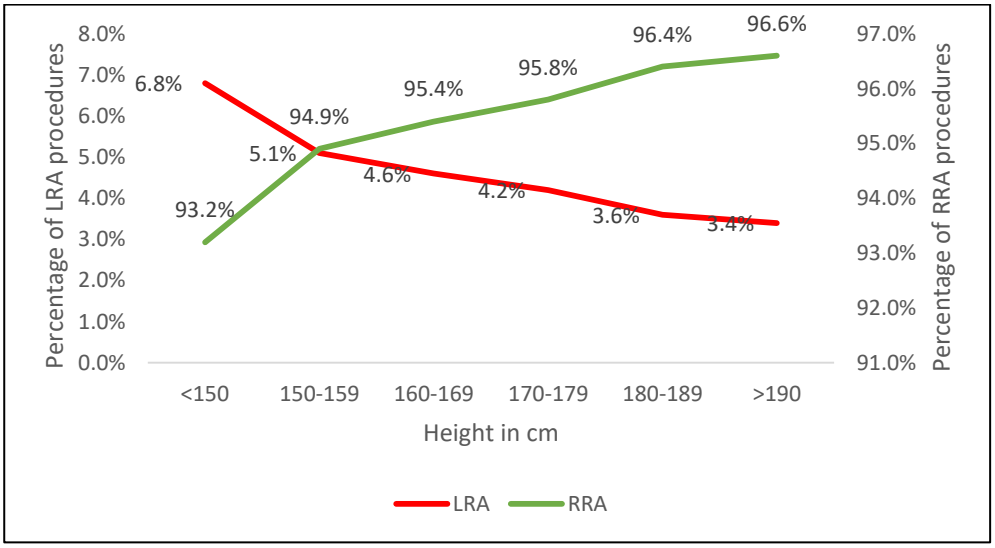


Table 8.1 shows the demographics, cardiovascular risk profile, procedural characteristics and crude outcomes differences across the two groups. Patients in the LRA group were older and had a higher risk baseline cardiovascular profile, with an increased incidence of diabetes (27.7% vs 18.2%, p<0.001), hypertension (64.8% vs 52.7%, p<0.001), history of previous cerebrovascular event (CVA) (7.4% vs 4.0%, P<0.001), acute myocardial infarction (47.6% vs 24.4%, p<0.001), coronary artery bypass grafting (CABG) (33.2% vs 4.9%, p<0.001) and peripheral vascular disease (PVD) (12.8% vs 4.5%, p<0.001). Patients in the RRA access group received more aggressive pharmacotherapy with a higher use of Ticagrelor (7.7% vs 6.8%, p<0.001), Prasugrel (5.5% vs 3.6%, p<0.001), Glycoprotein 2b3a inhibitors (25.0% vs 16.7%, p<0.001) and bivalirudin (4.4% vs 1.9%, p<0.001). From the operator skill perspective, more trainees were likely to undertake LRA procedures compared to consultants (34.0% vs 31.2%, p<0.001). Missing data information about each variable is provided in Appendix Table 8.

Table 8.1 Baseline characteristics and procedural details of patients undergoing left and right radial percutaneous coronary intervention in the United Kingdom

	Right Radial access n=328,495	**Left Radial access n=14,311**	**P value**
Age (y), mean (SD)	63.8±11.8	66.2±11.0	<0.001
Male, n(%)	249,974 (76.1%)	10,572 (73.9%)	<0.001
BMI mean, (SD)	28.5±5.16	29.1±5.61	<0.001
Hypercholesterolemia (%)	167,993 (54.3%)	8,995 (66%)	<0.001
Hypertension (%)	163,160 (52.7%)	8,840 (64.8%)	<0.001
Diabetes (%)	57,616 (18.2%)	3,848 (27.7%)	<0.001
Previous CABG (%)	11,169(4.9%)	3,413 (33.2%)	<0.001
Previous CVA (%)	12,463 (4.0%)	1,014 (7.4%)	<0.001
Peripheral vascular disease (%)	14,003 (4.5%)	1,747 (12.8%)	<0.001
Previous AMI (%)	75,204 (24.4%)	6,393 (47.6%)	<0.001
Previous PCI (%)	63,413 (19.9%)	5,413 (39%%)	<0.001
LVSD (%)	53,320 (30.1%)	3,058 (36.0%)	<0.001
Smoking (%)			<0.001
Never smoked	107,671(35.9%)	4,480(34.2%)	
Current smoker	82,931(27.6%)	2,658(20.2%)	
Ex-smoker	109,457(36.4%)	5,961(45.5%)	
Renal Failure (%)	2,293 (0.74%)	215 (1.6%)	
Indication for PCI			<0.001
Stable Angina (%)	112,998 (34%)	6,508(46.1%)	
STEMI (%)	82,872 (25.7%)	1,500 (10.6%)	
UA/NSTEMI	129,269 (39.6%)	6,100 (43.2%)	
Operator status			<0.001
Consultant	200,251 (68.7%)	8,380 (65.9%)	
Trainee	91,083 (31.2%)	4,331 (34.0%)	
Multi vessel PCI (%)	43,685 (13.5%)	2,063 (14.6%)	<0.001
Cardiogenic Shock (%)	3,874 (1.84%)	165 (2.2%)	0.02
Pharmacological Inotropes	1.246 (0.4%)	69 (0.5%)	0.05
Intra-aortic balloon pump device (%)	2,122 (0.6%)	80 (0.6%)	0.19
Left main stem PCI (%)	9,216 (2.85%)	892 (6.3%)	<0.001

Mechanical ventilation (%)	2,484 (0.9%)	179 (1.4%)	<0.001
PCI to Grafts	5,166 (1.6%)	2,216(15.7%)	<0.001
Chronic total occlusion PCI	17,553 (5.7%)	897 (6.7%)	<0.001
Stent Use			<0.001
No Stents (%)	21,180 (6.7%)	1,495 (10.8%)	
BMS only (%)	63,479 (20%)	2,236 (16.2%)	
DES only (%)	222,017 (70.0%)	9,632 (70.0%)	
BMS & DES (%)	10,203 (3.2%)	385 (2.8%)	
Bivalirudin (%)	13,316 (4.4%)	249 (1.9%)	<0.001
GP2b3a use (%)	77,681 (25.0%)	2,248 (16.7%)	<0.001
Ticagrelor (%)	23,271 (7.7%)	900 (6.8%)	<0.001
Prasugrel (%)	16,647 (5.5%)	484 (3.6%)	<0.001
Warfarin (%)	3,418(1.1%)	375 (2.8%)	<0.001
Length of stay (days), median (IQR)	1 (0-2)	1 (0-1)	<0.001
In hospital death (%)	2,206 (0.7%)	120 (0.9%)	0.01
MACE (%)	4,234 (1.33%)	225 (1.62%)	0.004
Major Bleeding (%)	1,305 (0.41%)	75 (0.54%)	0.02
In hospital Stroke	363 (0.11%)	11 (0.08%)	0.230
30-day mortality (%)	3,881 (1.47%)	211 (1.88%)	<0.001

MACE=major adverse cardiovascular events defined as composite of in-hospital mortality, in-hospital myocardial infarction or re-infarction and revascularization- emergency percutaneous coronary intervention or CABG, LVSD= left ventricular systolic dysfunction, CABG= coronary artery bypass grafting, AMI= acute myocardial infarction, PCI= percutaneous coronary intervention, GP2b3a= glycoprotein 2b3a.

8.4.2 *Temporal trends*

Use of LRA access increased modestly from 3.2% (n=527) in 2007 to 4.6% (n=3110) in 2014 (Figure 8.6). Temporal changes and regional variation in LRA practices are depicted in Figures 8.7-8.8 showing a significant heterogeneity in the use of LRA access amongst different primary care trust areas across Scotland, England and Wales. During the study period, the highest proportions of LRA procedures were undertaken in England with some areas performing almost 20% of their radial procedures via the

LRA, whereas the use of LRA access was sporadically low in Scotland (10%) and Wales (7%).

Figure 8.6**:** Use of left radial access from 2007 to 2014 in the United Kingdom

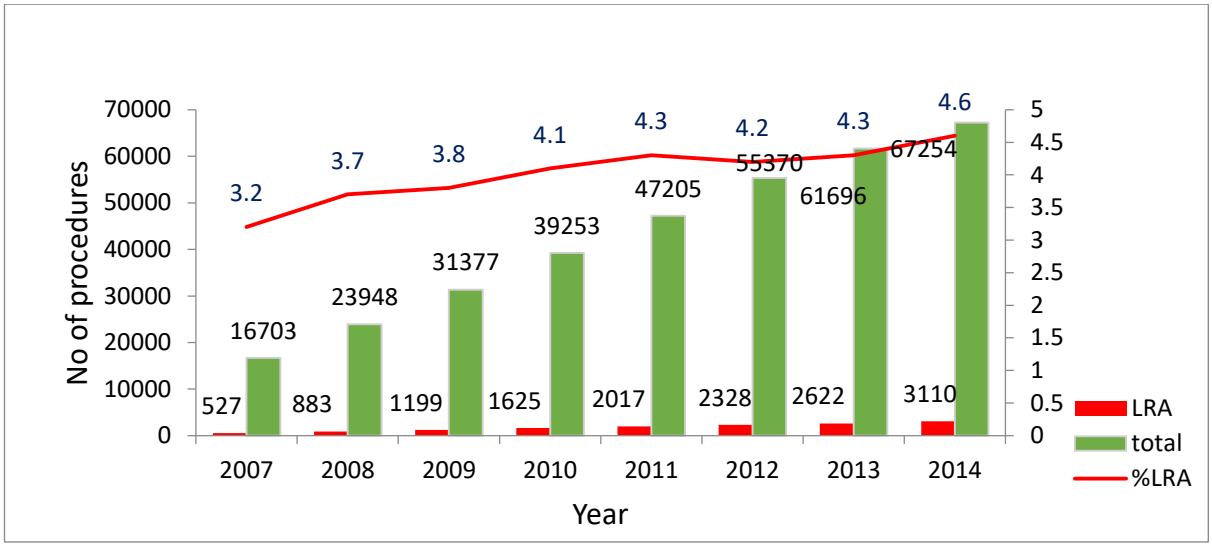


Figure 8.7: Overall proportions of left radial access procedures across different primary care trusts in the United Kingdom.

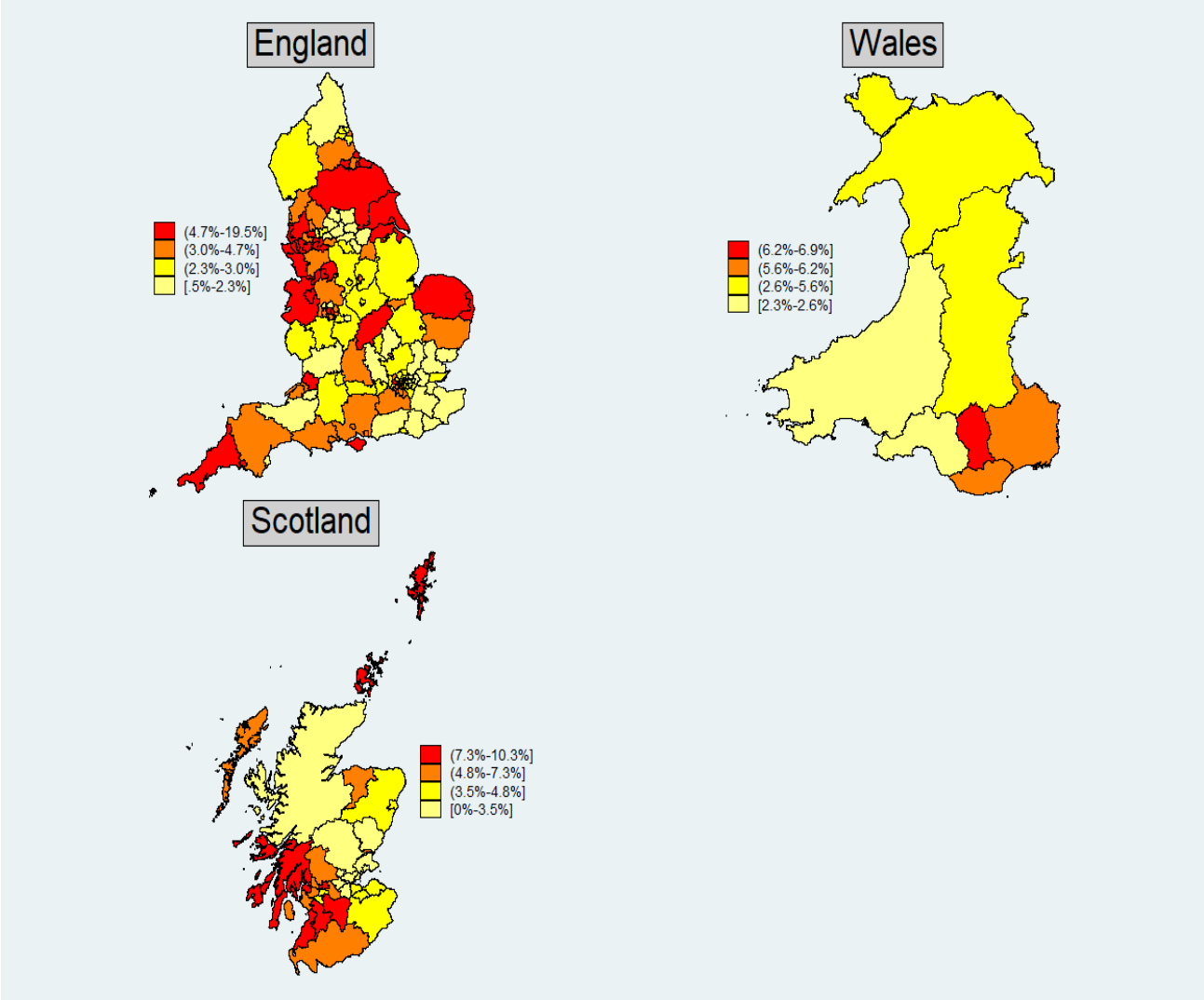
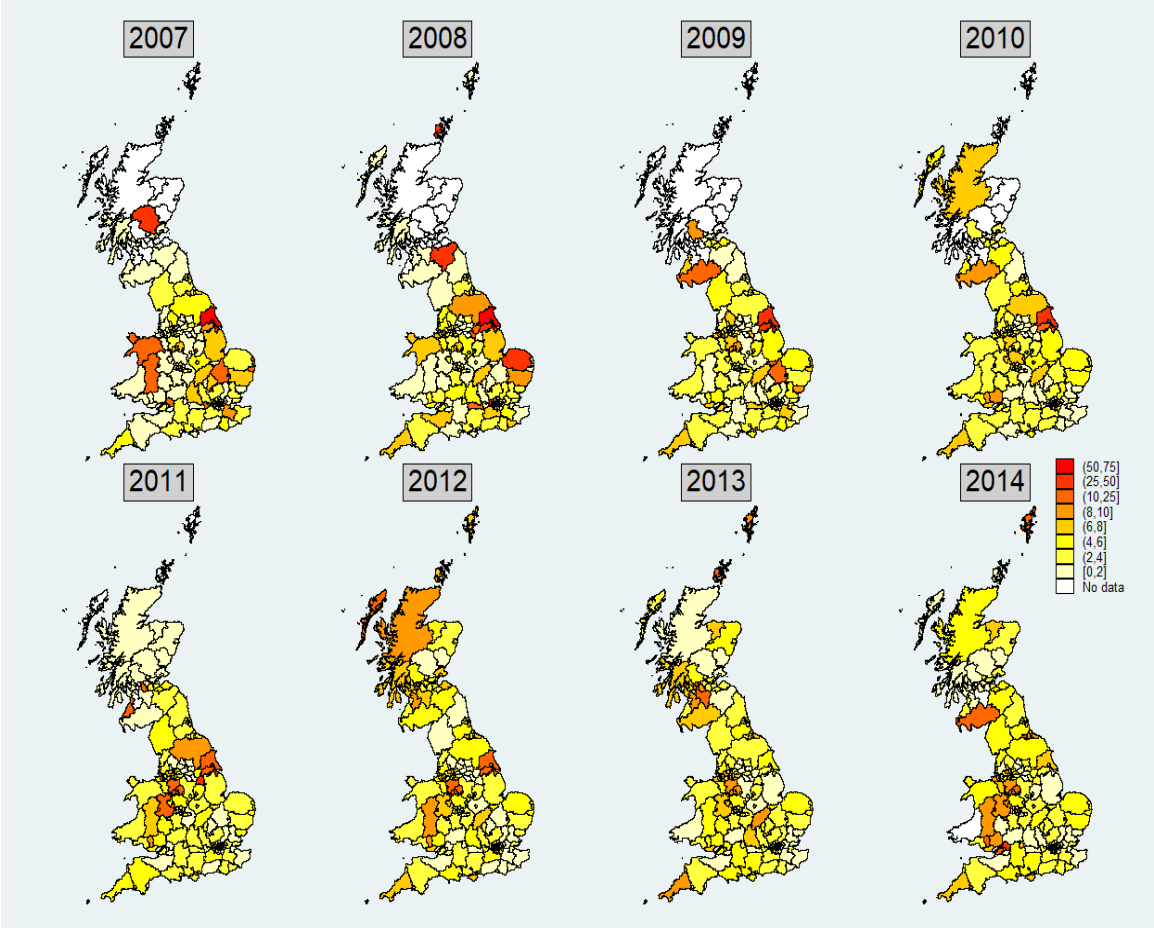


Figure 8.8: Proportions of left radial access procedures across different primary care trusts in the United Kingdom from 2007-2014.



8.4.3 *Access site switch in successive procedures*

During the study period, 35,388 patients from the radial cohort had more than one successive PCI procedures. RRA was used in 33,956 patients at their index PCI whereas 1,432 patients had their first PCI using LRA. In patients receiving their first PCI using RRA, subsequent successful RRA PCI was only possible in 72% of the patients. Notably, the majority of the switch from RRA was to femoral (23.5%) access instead of LRA (4.5%). However, LRA remained relatively stable between 4.5% to 6% at four or more procedures (Figure 8.9). The patterns of access site switch during successive procedures based on gender (male versus female) and age (age>75 vs age <75) was also studied. It appeared that females were less likely to undergo a subsequent procedure through the RRA approach compared to males (Figure 8.10-8.11). For example, almost 30% of female had their access site changed to TFA compared to only 19% in males at

the ≥4 PCI procedure. Similar trends were observed in the elderly age≥75 who were again more likely to have their access site switched to femoral instead of LRA at each successive procedure compared to their younger counterparts, aged <75. (Figure 8.12-8.13).

Figure 8.9**:** Access site switch in patients undergoing repeat percutaneous coronary intervention after right radial access in the United Kingdom

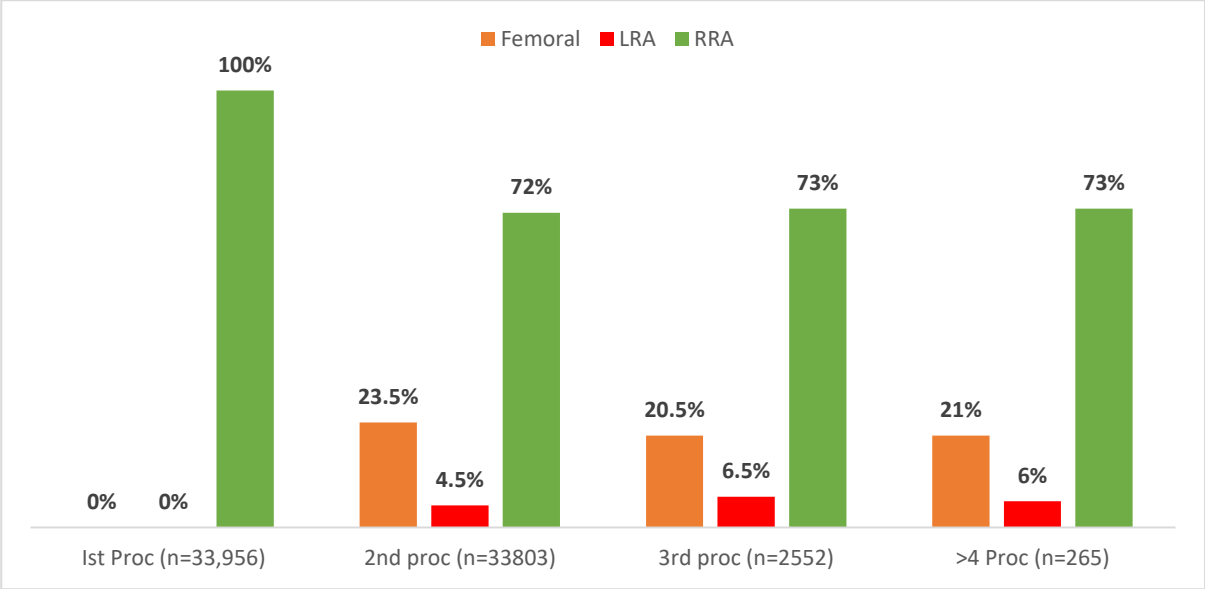


Figure 8.10**:** Access site switch in males undergoing repeat percutaneous coronary intervention after right radial access in the United Kingdom

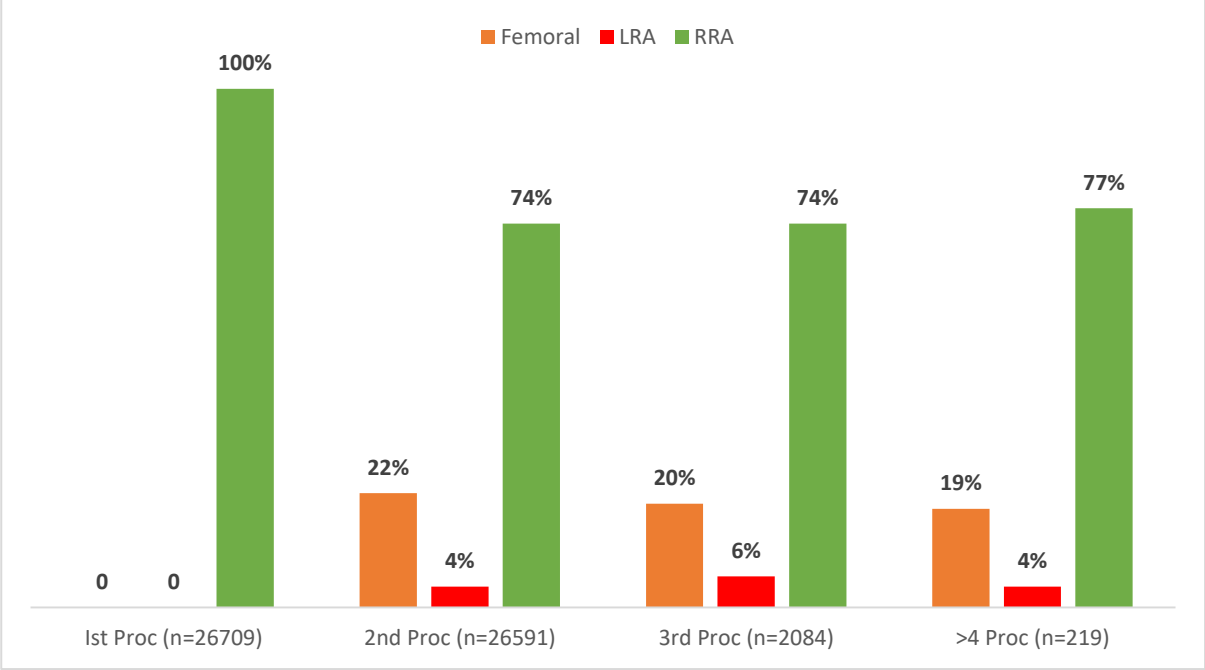


Figure 8.11**:** Access site switch in females undergoing repeat percutaneous coronary intervention after right radial access in the United Kingdom

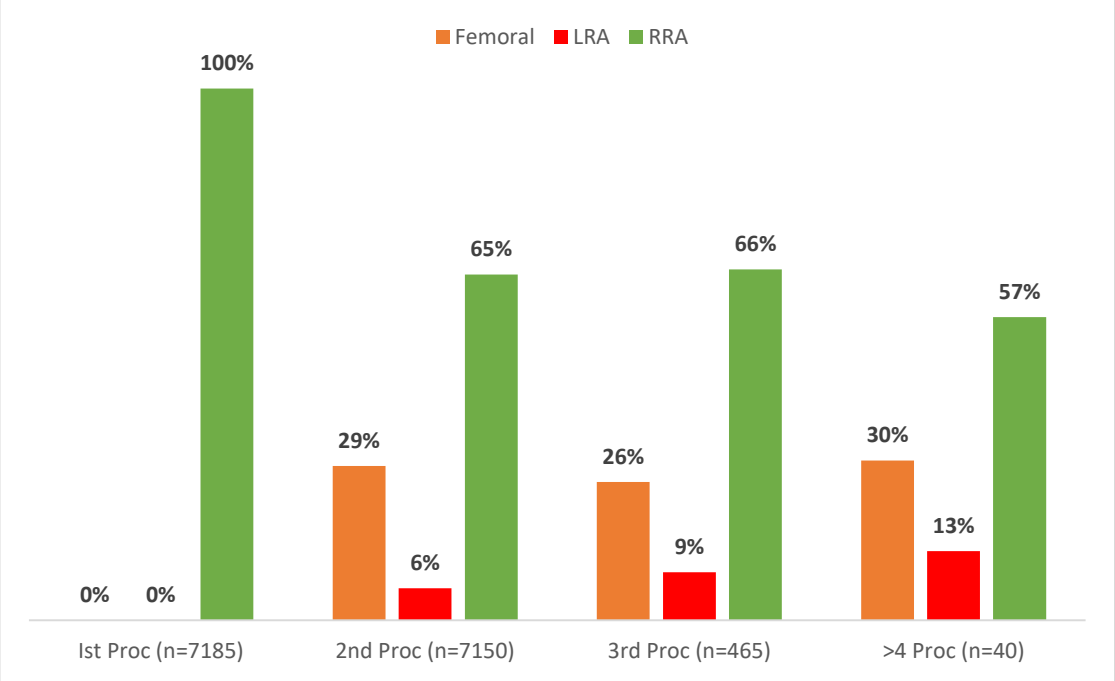


Figure 8.12**:** Access site switch in patients age < 75-year undergoing repeat percutaneous coronary intervention after right radial access in the United Kingdom

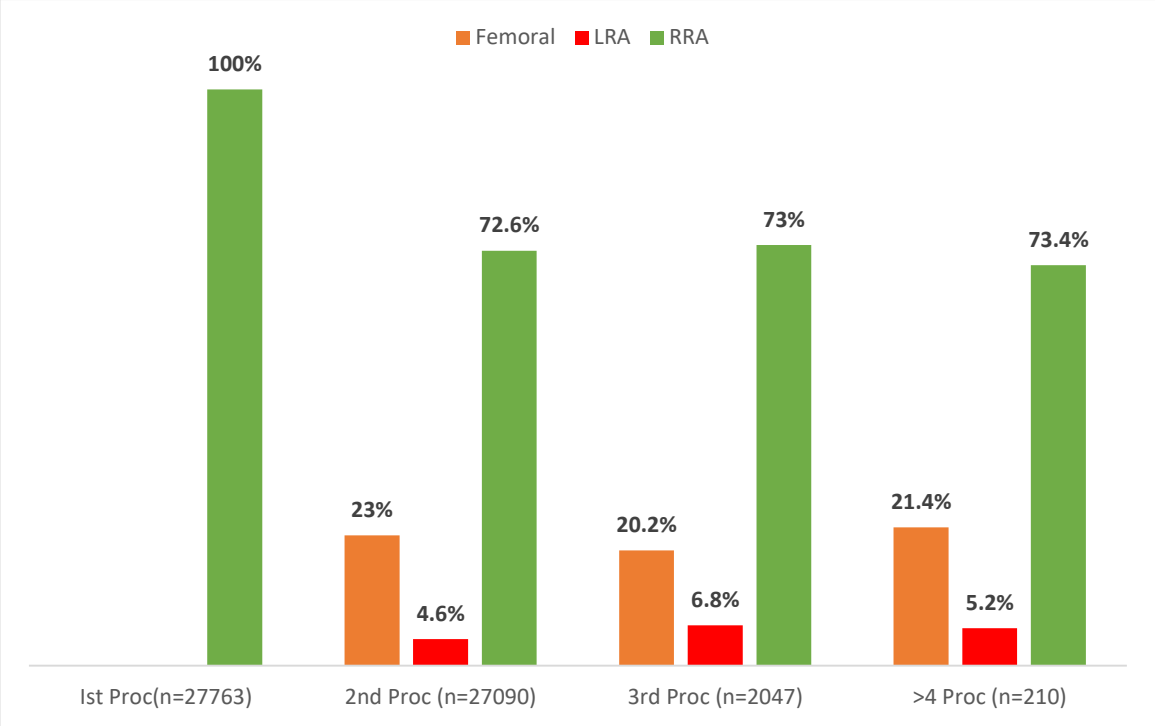
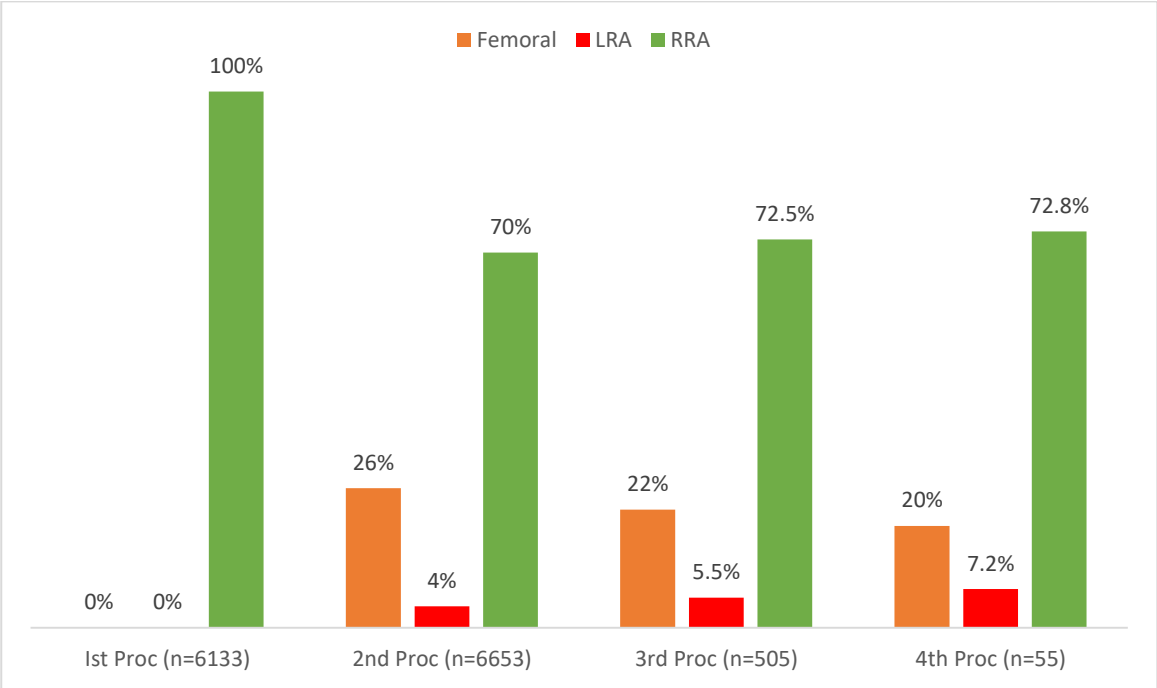


Figure 8.13**:** Access site switch in patients age > 75-year undergoing repeat percutaneous coronary intervention after right radial access in the United Kingdom



8.4.4 *Independent predictors*

The independent predictors of LRA at any time are reported in Table 8.2. It was found that previous CABG (OR 9.32 95%CI 7.72-11.24 P<0.001), PCI to vein graft (OR 2.10 95%CI 1.61-2.74 p<0.001), renal failure (OR 2.65 95%CI 1.63-4.30), mechanical ventilation (OR 2.61 95%CI 1.64-4.15 p<0.001), peripheral vascular disease (OR 1.81 95%CI 1.48-2.22 p<0.001), previous AMI (OR 1.29 95%CI 1.11-1.51 p<0.001), female sex (OR1.27 95%CI 1.10-1.46 p<0.001) and repeat PCI (OR 1.09 95%CI 1.05-1.35 p<0.006) were strong independent predictors of LRA access.

Table 8.2**:** Predictors of Left radial access

Predictors	Odds ratio (95%CI)	p-value
Previous CABG	9.32 (7.72-11.24)	<0.001
Female	1.27 (1.10-1.46)	<0.001
Repeat Procedures	1.09(1.05-1.35)	<0.006
Previous AMI	1.29 (1.11-1.51)	<0.001
Peripheral vascular disease	1.81 (1.48-2.22)	<0.001

Mechanical ventilation	2.61 (1.64-4.15)	<0.001
PCI to vein graft	2.10 (1.61-2.74)	<0.001
Renal Failure	2.65(1.63-4.30)	<0.001

CABG= coronary artery bypass grafting, AMI= acute myocardial infarction, PCI= percutaneous coronary intervention

8.4.5 *Clinical outcomes*

Crude MACE (1.6% n=225 vs 1.3% n= 4234, p=0.004), in-hospital (0.9% n=120 vs 0.7% n=2,206, p=0.01) and 30-day mortality (1.9% n=211 vs 1.5% n=3881, p<0.001) rates were significantly higher in the LRA group but there were no differences in stroke and bleeding complications (Table 8.1). In the MLR analysis after adjustments for all the baseline differences in clinical and procedural characteristics and other potential confounders (Table 8.3), there were no differences between use of either access site and clinical outcomes, in-hospital death (OR 1.19 95% CI 0.90-1.57, p= 0.20), 30-day mortality (OR 1.17 95%CI 0.93-1.74, p=0.16), MACE (OR 1.06 95%CI 0.86-1.32, p=0.56), in-hospital stroke complication (OR 0.45 95%CI 0.16-1.26, p=0.13) and major bleeding (OR 1.22 95%CI 0.87-1.77, p=0.24). Notably, in the propensity score matching analysis (Table 8.4), LRA was associated with a significant decrease in in-hospital stroke risk (OR 0.52 95%CI 0.37-0.82, p=0.005) whereas all the other outcomes results were consistent with the MLR analysis.

Table 8.3**:** Adjusted outcomes following Left radial versus right radial access

Clinical outcome	**Odds ratio (95%CI)**	**p-value**
In hospital death	1.19 (0.90-1.57)	0.20
Major bleeding	1.22 (0.87-1.71)	0.24
In hospital stroke	0.45 (0.16-1.26)	0.13
MACE	1.06 (0.86-1.32)	0.56
30- day mortality	1.17 (0.93-1.47)	0.16

MACE=major adverse cardiovascular events defined as a composite of in-hospital mortality, in-hospital myocardial infarction or re-infarction and revascularization- emergency percutaneous coronary intervention or CABG

Table 8.4 Propensity score matching analysis on 10 imputed datasets, reporting average treatment effects (ATE)

Right v Left Radial access	N	Coefficient	95% confidence interval		Odds ratio (95% confidence interval)	P value
In hospital death	153027	0.002324	-0.004819	0.009468	1.33 (0.31-2.37)	0.64
Major bleeding	152,956	0.002506	-0.003093	0.008106	1.61 (0.24-3.00)	0.89
In hospital stroke	152,956	-0.001045	-0.001858	-0.00232	0.52 (0.37-0.82)	0.005
MACE	152,956	0.003680	-0.004376	0.011737	1.28 (0.66-1.90)	0.90
30 day mortality	131,778	-0.009475	-0.003708	0.022658	1.33 (0.31-2.37)	0.15

MACE=major adverse cardiovascular events defined as composite of in-hospital mortality, in-hospital myocardial infarction or re-infarction and revascularization- emergency PCI or CABG

For sensitivity analysis, patients with the previous history of CABG were excluded from the dataset. The baseline characteristics and differences in procedural and in-hospital pharmacology were compared in patients undergoing RRA and LRA respectively. Similar to the main analysis, the patients receiving LRA PCI procedure in this subgroup were older, had increased prevalence of cardiovascular risk factors such as hypertension, diabetes, previous CVA, previous AMI, previous PCI and peripheral vascular disease (Appendix tables 8). The adjusted outcomes in this subgroup are reported in Appendix Table 9, showing no differences in clinical outcomes in patients receiving LRA compared to RRA PCI procedures. Finally, the multivariable predictive analysis again showed that female sex (OR 1.01 95%CI 1.0.-1.01, p<0.001), repeat procedure (OR 1.30 95%CI 1.22-1.37, p<0.001), previous AMI (OR 1.77 95%CI 1.65-1.90, p<0.001), peripheral vascular disease (OR 2.02 95%CI 1.84-2.21, p<0.001), mechanical ventilation (OR 2.09, 95%CI 1.71-2.56, p<0.001) and renal failure (OR

1.57, 95%CI 1.26-1.95, p<0.001) were strong independent predictors of LRA use (Appendix Table 10).

8.5 Discussion

To best of my knowledge, this is the first study describing the patterns of radial access use from a national perspective over a period where access site practice has transitioned to predominantly transradial in the United Kingdom. There are several important findings from this study. Firstly, these results show that use of LRA has modestly increased over time in UK practice and is used more often in females, the elderly, Asian ethnicity, patients with a previous history of CABG and short stature patients. Furthermore, the patients receiving LRA were multimorbid with a significantly higher prevalence of cardiovascular comorbidities and receiving less potent in-hospital pharmacology. Secondly, in patients undergoing repeat PCI, over one third of the patients (28%) had access site switched from RRA at each successive procedure to mainly femoral access with only a minority undergoing procedures through the contralateral arm (LRA). Finally, in the main MLR analyses, complications with LRA access were similar to those seen with RRA access with no difference in in-hospital or 30-day mortality, in-hospital MACE or major bleeding complications, although there was a significantly decreased odds of in-hospital stroke following PCI using the LRA approach in the propensity matched cohort.

In line with best available evidence from randomised trials, national bodies recommend the use of TRA instead of TFA access with the most recent guidelines placing a class 1A indication on the use of TRA[15,217,218]. RRA access is more commonly practised by radial operators because of ergonomics of the cardiac catheter lab, previous training experience and increased operator discomfort due to the need of having to bend over to the left side in patients requiring an LRA procedure. On the other hand, a recent meta-

analysis of 12 prospective randomised trials enrolling 6,450 patients confirmed that LRA access provides more favourable anatomy for catheter manipulation and coronary engagement translating into a small but statistically significant reduction in fluoroscopy time and contrast use[212]. Despite the advantages of offering similar anatomical considerations applicable to the TFA access even early in the training[215], uptake of LRA access remains low, although there has been a marginal increase over time in the UK (3.2% to 4.6% during the period of this study). There was significant heterogeneity in LRA usage across different regions of England, Scotland and Wales. The proportions of radial procedures undertaken via the LRA varied from as low as 0.5% to 20% in England, from 2.3% to 6.9% in Wales and 0.3% to 10.2% in Scotland showing a wide variation in uptake of LRA in clinical practice. In addition to the difference in patient's demographics, this variation in practice may be related to local culture, the operator's previous training experience and personal preference to adapt to innovations in procedural skills. In this analysis, trainees were more likely to use LRA compared to consultants and this exposure to using the contralateral arm for PCI may persist beyond the training stages. Whilst investigating the independent predictors of LRA usage in the multivariate predictive analysis, it was found that a history of previous CABG and PCI to a vein graft were the strongest predictors of LRA use. The most likely explanation for this is that LRA offers better access to grafts in patients with previous CABG compared to RRA and in some cases to TFA. Similarly, factors that are associated with an increased risk of radial artery spasm and access site failure such as female gender, repeat procedure and history of peripheral vascular disease were significant predictors of LRA use. Previous studies have reported that the anatomical course of the radial artery is likely to be straight forward with less incidence of the loop or touristy in the forearm[210].

The study also describes the access site practice in patients undergoing repeat PCI and found that when RRA is used at the first procedure, future use of the RRA for PCI drops by 28% overall, by 35% in females and 27% in patients aged >75 at a second procedure with a concomitant increase mainly in the use TFA access but with a slight increase in LRA usage. Although success rates and complication rates of repeat transradial access have been described in small case series from single centres [219-221], the utility of different radial access has not previously been reported at a national level. For example in an early series from Japan, Sakai et al described that the failure rate of repeat radial access was approximately 16% in male and 30% in women[221]. More recently published data from a high volume radial centre illustrated that TRA access can be safely attempted in about 60% of cases for up to 10 procedures [219]. Progressive luminal narrowing and radial artery occlusion are known to occur following transradial access and may limit the use of ipsilateral radial access for a repeat procedure[75,222]. This study shows a higher switch rate of an RRA approach in elderly and female patients with a concomitant increase in the use of TFA and LRA access. It is possible that the higher switch from RRA to TFA was observed because the subsequent procedure was undertaken by a femoral operator instead of a radial operator. However, this analysis is from an era where more than 80% of the PCIs in the United Kingdom are undertaken via TRA and most femoral operators have switched their access site practice to from TFA to TRA, which may suggest that this is less likely [68]. The key messages from these findings are that although repeat RRA access can safely be performed in the majority of cases, alternative access is used in a significant number of patients and currently, a transfemoral approach is undertaken more commonly than the contralateral radial artery, particularly in elderly and female patients. Given the established advantages of radial access in terms of reducing major bleeding and access site complications, there

may be benefits in using the LRA access site as the default in such circumstances. These observations also have important implications for training. Trainees should be exposed to LRA early in their training so that the potential benefits of TRA access can still be offered in the event of RRA failure.

Finally, in the clinical outcome analysis, there were no statistically significant differences between the use of the LRA and RRA and in-hospital or 30-day mortality, in-hospital major bleeding and MACE. However, statistically non–significant decreased odds of in-hospital stroke (OR 0.45 95%CI 0.16-1.26, p=0.13) were observed in the main MLR analysis albeit with wide confidence intervals that may reflect the low event rate, with a similar significant risk reduction in our propensity score matched cohort that was statistically significant (OR 0.52 95%CI 0.37-0.82, p=0.005). A number of previous studies have reported on procedural outcomes of LRA versus RRA showing that LRA offers a small advantage over RRA in terms of lower fluoroscopy time, radiation dose and contrast use [79,212,214,215,223]. There is very little information on the association of LRA or RRA with clinical outcomes[212,215]. There is a large body of evidence confirming the advantages of radial over femoral access in reducing major bleeding, vascular access site complications and MACE translating into mortality benefit as discussed before. With RRA access, the anatomical variations such as increased incidence of tortuosity and loops in the arm and subclavian artery may require extra catheter manipulation. Additionally, during RRA access the catheter needs to be passed from the innominate artery into the ascending aorta where the right carotid comes off resulting in a theoretically increased risk of embolization of plaque into the right carotid artery resulting in an embolic stroke. In contrast, LRA access offers very similar anatomy to the TFA approach as the left common carotid artery arises directly from the aortic arch. This analysis suggests that LRA access may be associated with a lower stroke risk than

the RRA and possible mechanisms behind this effect may relate to the anatomical reasons outlined above. Given that stroke is a relatively rare event[224,225], whilst there was a signal observed, we estimate that an operator would need to undertake 1,818 PCI procedures through the LRA to avoid 1 stroke (in comparison to RRA use). Given low event rates, it is unlikely that a randomised controlled trial will ever be adequately powered to investigate this further. Hence, this study for the first time in literature provides mechanistic insight into minimising a devastating complication of PCI procedure.

8.6 Study strengths and limitations

This study offers several key messages albeit with some limitations. This study illustrates the patterns of left and right radial access over almost a decade in a national registry. In addition to studying the independent predictors of LRA usage, the association between the use of LRA or RRA with clinical outcomes was also investigated in the national population. One of the limitations of the BCIS dataset is that it does not collect information around procedure outcomes such as fluoroscopy time, procedure time, contrast use and operator or patient radiation dose, therefore differences between procedural outcomes could not be reported. However, as mentioned earlier, data from randomised control and subsequent meta-analysis shows that LRA is associated with better procedural outcomes compared to RRA. Secondly, data around access site attempt and failure and crossover to the contralateral radial artery is not captured which makes it difficult to ascertain if the access was used as the primary default access or because of failure to cannulate the contralateral artery for other reasons. Furthermore, the BCIS registry only started collecting operator level data from the last two years of this study period; hence it was not possible to study the impact of operator volume or personal experience on the use of LRA. Therefore, the analysis was

limited to patient level data. Consequently, changes in access site practice in patients undergoing repeat PCI may actually reflect differences in operator practice. Finally, these findings are observational in nature and a possibility of biases from unmeasured confounders may have contributed to the results

8.7 Conclusion

Using a large and unique national PCI registry, I have shown that LRA access provides a safe and effective alternative access site choice compared to the RRA. There is significant variation in the use of the LRA across different health care regions in the UK with higher proportions of LRA PCI being undertaken in England compared to Wales and Scotland regions. In patients undergoing repeat PCI, although TRA access was safely used in about two thirds of patients, a change to a predominantly TFA approach, particularly in females and elderly patients, was used in up to one third of patients despite established advantages of radial access in this high-risk group. Finally, an important signal was observed in that the LRA access may be associated with a reduced risk of stroke compared to the RRA. Future efforts need to focus on education and training to preserve radial artery patency and increase skills in the use of LRA access.

Chapter 9

General Discussion

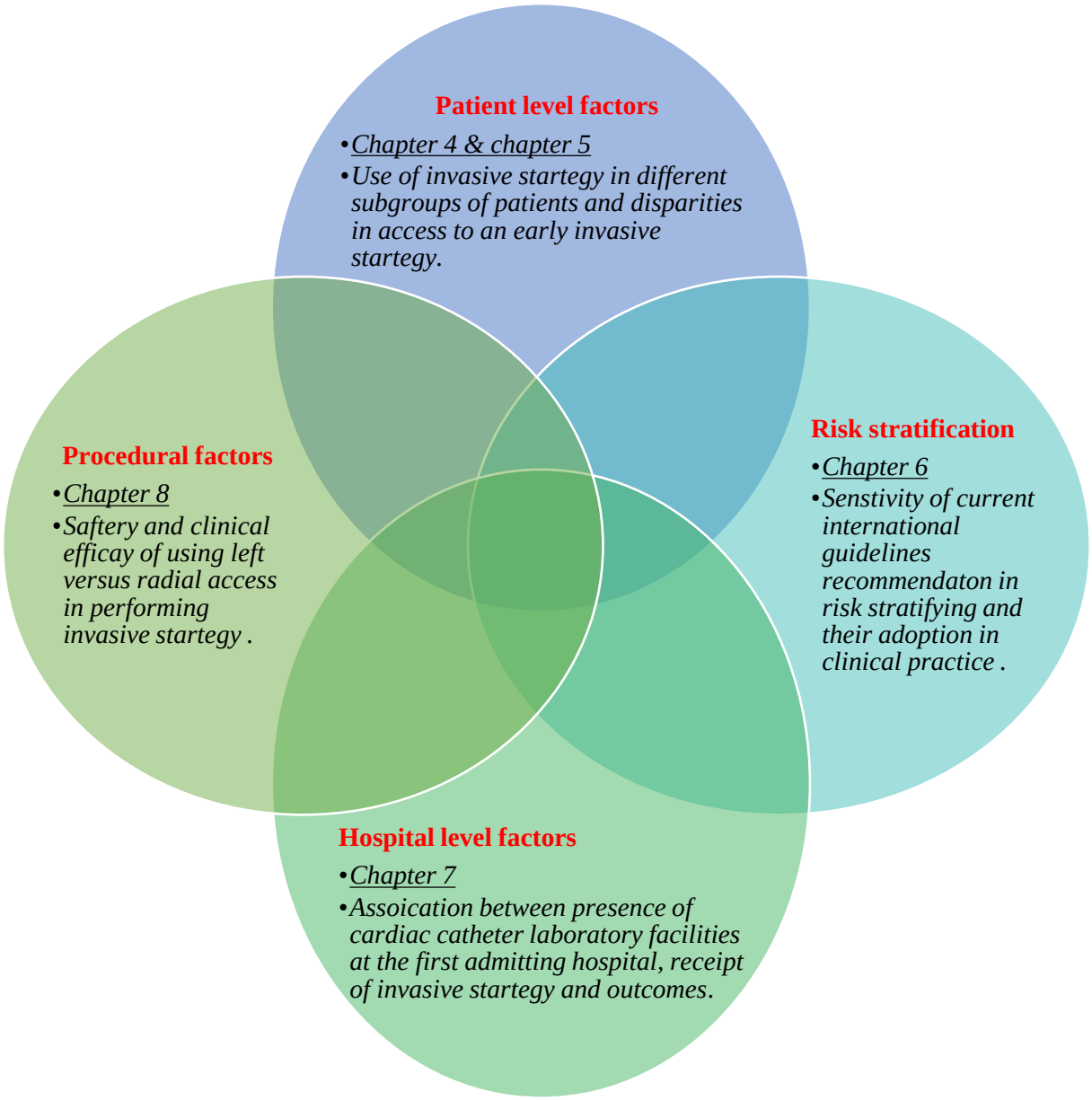
9.1 Introduction

This PhD thesis investigated the use of an invasive strategy in the form of either coronary angiography or PCI in the management of patients admitted with a diagnosis of an NSTEMI. As all the results have been discussed in detail in the respective chapter of this thesis, the focus in this chapter is to provide a brief summary of the key findings of each research question and identify further areas of research.

9.2 Main findings

The cornerstone of this thesis has been to comprehensively investigate the patient, hospital and procedural aspects associated with the use of an invasive strategy and the role of risk stratification in guiding the invasive management of patients admitted with NSTEMI. Generally, the thesis (i) reports important differences in the invasive management of patients admitted following an NSTEMI (ii) identifies different subgroups of patients who are at a disadvantage to receive an early invasive strategy despite having the potential to gain more benefit from it (iii) illustrates the lack of sensitivity of current guidelines to differentiate risk and leading to significant biases in the use of an invasive strategy particularly in high-risk patients (iv) reports an association between the presence of a cardiac catheter laboratory at the first admitting hospital and the receipt of an invasive strategy and clinical outcomes (v) optimal access site selection and the role of alternative access in performing an invasive strategy (PCI). Figure 9.1 illustrates the relationship between chapters and the research question, and some of the key findings are discussed in this section.

Figure 9.1 Pictorial illustration of how each chapter reports the different aspects influencing the use of an invasive strategy.


Patient level factors
•Chapter 4 & chapter 5
•Use of invasive startegy in different subgroups of patients and disparities in access to an early invasive startegy.
Procedural factors
•Chapter 8
•Saftery and clinical efficay of using left versus radial access in performing invasive startegy .
Risk stratification
•Chapter 6
•Senstivity of current international guidelines recommendaton in risk stratifying and their adoption in clinical practice .
Hospital level factors
•Chapter 7
•Assoication between presence of cardiac catheter laboratory facilities at the first admitting hospital, receipt of invasive startegy and outcomes.

9.2.1 *What are the patient level factors related to the use of an invasive strategy and variations in different subgroups?*

Chapter 4 & 5 of this thesis were designed to examine different patient level factors such as age, gender, ethnicity, cardiac and non-cardiac comorbidities and how they are associated with the use of an invasive strategy overall and the timing of an invasive strategy respectively. The key findings from chapter 4 showed that despite an increase in the utilisation of an invasive strategy over the past decade, there remain significant disparities across different subgroups of patients. For example, patients with increased comorbidity burden defined as CCI≥3 were almost 25% less likely to receive an invasive strategy compared to less comorbid patients defined as CCI=0. Similar underutilisation of the invasive strategy was noted in elderly patients age≥81 compared to those aged≤60 who were almost twice as likely to receive an invasive strategy. Subgroups such as gender (men vs women), ethnicity (Whites vs African American) also showed similar inequalities in the use of an invasive strategy in women and African American. This study also shows that patient features, which are known to be associated with an increased risk of adverse events in NSTEMI such as age, diabetes with complications, prior history of CABG, PCI or ACS actually have a strong inverse relationship with receipt of an invasive strategy. Importantly, certain non-cardiac comorbidities, which are associated with poor outcomes such as metastatic cancer, dementia, and chronic renal failure were also independently associated with lower odds of receipt of an invasive strategy.

Chapter 5 demonstrates that there is significant heterogeneity in access to an early invasive strategy (within 24 hours of admission). Together with the work in chapter 4.0, the results from this study illustrate that despite the increasing use of an early invasive strategy, there were significant inequalities in its use in different subgroups of patients.

Specifically, temporal trends in the timing of an invasive strategy stratified according to gender reveal that early invasive strategy was comparatively higher in men (74.2% to 68.6%) during the study period, although there was a greater proportional increase in the use of an early invasive strategy from 60.9% to 70.0% in women. Similar to the findings reported in chapter 4, only half of the patients with higher comorbidity burden defined as CCI≥3 were managed invasively within 24hours compared to patients without any comorbidity. Similar inequalities were noted in patients admitted on weekend compared to weekday admission and older patients (age >75) compared to their younger counterparts (age<65) were significantly less likely to receive an early invasive strategy. Temporal analysis of patient characteristics showed that there were significant changes in clinical characteristics and baseline risk profile of patients treated with an early invasive strategy compared to intermediate and late invasive strategy, so that the use of an early invasive strategy remains attenuated in elderly, complex and multi-morbid patients despite an overall increase in adoption of an early invasive strategy in NSTEMI. The presence of non-cardiac comorbidities such as liver disease, peripheral vascular disease, chronic renal failure, dementia and history of alcohol disease was inversely associated with receipt of an early invasive strategy. In the adjusted outcomes analysis, the use of an invasive strategy on day 2 from admission appears to be safe with the greatest reduction in odds of in-hospital mortality and major adverse cerebrovascular events.

9.2.2 *Risk stratification and adoption of guidelines in the use of an invasive strategy*

This study in chapter 6 was focused to evaluate the use of an invasive strategy in the management of NSTEMI according to risk criteria of international guidelines[3,4]. Adherence to guidelines recommended use of an invasive strategy was examined and the main findings of the study showed that almost 90% of patients admitted with the

diagnosis of NSTEMI in England and Wales were deemed to be high-risk based on the current guidelines recommended risk criteria. Although, the recommendation in this high-risk group is to undergo an invasive strategy within 24 hours, only one in ten patients actually received an invasive strategy within this time period. There was also a significant disconnect between the guidelines recommended timing of invasive strategy and baseline risk of all patients. For instance, patients in the low-risk group were twice as more likely to receive early invasive strategy within 24 hours compared to the high-risk group despite the fact that the recommendations in the low-risk cohort is to receive an invasive strategy within 72 hours from admission. In the subgroup analysis based on gender, access to guidelines recommended invasive strategy was significantly lower in the women compared to men. Specifically, high-risk women were not only less likely to receive an invasive strategy within 24 hours but experienced the greatest delay compared to high-risk women.

9.2.3 *Association between the presence of cardiac catheter laboratory facilities and the use of an invasive strategy in the management of NSTEMI*

Chapter 7 of this thesis was conceptualised to study the association between an important hospital factor in the form of the presence of cardiac catheter laboratory facilities, the use of an invasive strategy and clinical outcomes. This study highlights important differences in both the utilisation of an invasive strategy and the subsequent management of NSTEMI patients according to admitting hospital cardiac catheter laboratory facilities. The utilisation of an invasive strategy in the form of coronary angiography was similar in patients admitted to hospitals without any cardiac catheter laboratory facilities (no lab hospital; 85.6%), hospitals with only diagnostic cardiac catheter laboratory facilities (diagnostic hospitals; 86.0%) and hospital with facilities to perform PCI (PCI hospitals; 86.4%). However, patients admitted to diagnostic only

centres were at a significant disadvantage to receive PCI. Patients admitted to hospitals with onsite cardiac catheter laboratory facilities had similar outcomes compared to those admitted at hospitals without such facilities. In high-risk NSTEMI group (with GRACE score >140), admission to a diagnostic hospital was associated significantly lower receipt of PCI and with an increased risk of in-hospital all-cause and cardiac mortality particularly in those receiving invasive strategy locally compared to those transferred to the nearest PCI hospital.

9.2.4 *Appropriate radial access site selection for performing an invasive strategy*

The final part of this thesis reports on the safety and clinical efficacy of using left versus right radial access in performing an invasive strategy in the form of PCI procedure. Right radial access is the most commonly used access site (96%) compared to left radial access (4%). However, patients with Asian ethnicity (27.9%), previous CABG (23.4%) and short height <150cm (6.8%) were more likely to have left radial access used for PCI procedure. In patients undergoing repeat PCI, over one-third of the patients (28%) had access site switched from RRA at each successive procedure to mainly femoral access with only a minority (<5%) undergoing procedures through the left radial access. There were no differences between the use of access site and clinical outcomes, in-hospital death, 30-day mortality, MACE, in-hospital stroke complication and major bleeding. Notably, in the propensity score matching analysis, the left radial access was associated with a significant decrease in in-hospital stroke risk, whereas all the other outcomes results were consistent with the main analysis with no differences in in-hospital death, major bleeding, MACE and 30-day mortality. For the first time in literature, this study confirmed that left radial access offers a safe alternative access site and may help to reduce PCI related stroke complications.

9.3 Clinical implications

The results from studies conducted in this thesis provide novel information about various aspects of invasive management of NSTEMI, which may have important clinical implications.

Chapter 4 of this thesis presents important results, demonstrating that there are significant disparities in the adoption of an invasive strategy with particularly slower utilisation in different subgroups of patients. A similar pattern in inequalities in the timing of invasive strategy was observed in chapter 5, where slower utilisation of early invasive strategy within 24hours was noted in elderly, female and patients with higher comorbidity burden. These results could have important consequences for routine clinical practice, particularly because they not only highlight the need for developing pathways to improve overall invasive management of NSTEMI patients but provide important information for healthcare providers to develop strategies designed to ensure fair and appropriate access to the invasive strategy in different subgroups of patients. These findings are of major interest given NSTEMI is the most frequent manifestation of acute coronary syndromes and is likely to be encountered by many healthcare professionals such as those working accident and emergency, general internal medicine and cardiology.

Chapter 6 describes the level of compliance with the utilisation of an invasive strategy based on the risk criteria as per current ESC, AHA/ACC guidelines recommendations in the management of a national population of patients admitted following a diagnosis of NSTEMI. This shows that there is significantly lower compliance with the adoption of guidelines, particularly in high-risk patients. The significant rise in the number of patients being classified into the high-risk category was due to guidelines recommendations of offering an invasive strategy within 24 hours to patients with

elevated cardiac troponin levels. The increased sensitivity of newer generation troponin assays has translated into an increasing number of patients being detected with elevated cardiac troponins. As such offering an invasive strategy within 24 hours to every patient with positive troponin test would require a significant expansion in cardiac catheter laboratory services, workforce and financial resources. That aside, from the logistics and structure point of it will not be possible to offer an invasive strategy within recommended time frames in an under-resourced healthcare system. An alternative approach would be to develop regional pathways for the invasive management of NSTEMI patients as discussed in the next section. Future research also needs to focus on investigating whether patients with elevated cardiac troponin would benefit from an invasive strategy and determine the optimal timing of procedure in this cohort.

Chapter 7 of this thesis focuses on the institutional aspect of the invasive management of NSTEMI patients. It shows that the use of an invasive strategy varies according to the availability of cardiac catheterisation facilities at the first admitting hospital. The lower rates of invasive coronary strategy in patients admitted to diagnostic hospitals suggests that in clinical practice, physicians are likely to adopt a risk-averse strategy particularly in high-risk NSTEMI patients. In clinical practice, the physician performing a diagnostic procedure may not necessarily be an interventional cardiologist and may not be best placed to assess the risk & benefits of further revascularisation in the form of PCI or CABG. This may in return influence the decision to treat patients such as those with high-risk features conservatively. There is also a possibility that delays in treatment such as timely use of an invasive strategy may be culminating in a longer length of hospital stays and costs. Future efforts may need to be focused on institutionalising the invasive management of NSTEMI patients, particularly to develop

a regional pathway for uniform and early access to an invasive strategy, especially in high-risk NSTEMI patients.

Finally, chapter 8 investigated the procedural aspects of an invasive strategy. LRA was associated with a reduced risk of PCI-related in-hospital stroke complications due to favourable anatomy of the aortic arch on the left side, the lesser requirement for catheter manipulation and instrumentation in the aorta. Therefore, LRA offers a safe alternative access site and may help to reduce PCI-related stroke complications. Furthermore, a greater understanding for the reasons of higher access site switch from radial to femoral rather than the contralateral arm is needed with educational program development to improve familiarity amongst operators for the LRA approach at an early stage in their career and improve overall invasive management of NSTEMI patients.

9.4 Future area for research

There are several important findings presented in this thesis which can be extended to further research. As discussed earlier, the present analyses were derived from three different datasets to investigate various aspects of invasive management of patients admitted with an NSTEMI. Ideally, a dataset containing information around patient baseline profile, comorbidities, risk score, pharmacology, coronary anatomy and procedure details would serve well to conduct this type of research, however, the logistics and feasibility of such dataset on a national scale would very challenging and time consuming. An alternative approach would be to create a longitudinal cohort by linking electronic healthcare records to allow not only a comprehensive assessment of the patient's journey during hospital admission but also investigate long term outcomes. This will also be more feasible in a shorter time span by using existing datasets. As discussed earlier, an important limitation of current work is not being able to investigate the relationship between the exact timing of an invasive strategy and clinical outcomes.

Prospective large randomised control studies or better data collection with accurate timing of procedures with adequate power based on patient baseline risk are required to answer this question.

Current guidelines on risk stratification and timing of invasive strategy particularly on the high-risk group are mainly based on expert consensus or studies conducted pre-potent antiplatelet era. Also as discussed in chapter 6, the advent of high sensitive troponin assay has resulted in a significant increase in the detection of type 2 myocardial injury instead of true plaque rupture causing an NSTEMI. As such inclusion of cardiac biomarkers in the high-risk criteria certainly needs revisiting and future research needs to consider the role of cardiac biomarkers in risk stratification and the use of an invasive strategy. Additionally, there have been significant advancements in pharmacological treatments in the contemporary era such as more potent antiplatelet agents in the form of ticagrelor, prasugrel, cangrelor, which are associated with reduced ischemic complications of NSTEMI such as reinfarction. It is plausible that a proportion of patients being classified as high-risk in current risk criteria may benefit from an extended intense medical therapy rather than an early invasive strategy in contemporary practice. Therefore, future research needs to be focused to develop risk models in predicting risk along with the alignment of guideline's risk criteria to contemporary practice.

9.5 Overall strengths

The work presented in this thesis provides a comprehensive overview of all aspects of invasive management of patients admitted with a diagnosis of NSTEMI. This work focused on examining the differences in baseline demographics of patients receiving an invasive strategy in the form of coronary angiography or PCI, associations between different patient-level factors, guidelines recommended risk scores, hospital-level

factors and procedural aspects with receipt of an invasive strategy and clinical outcomes. This thesis illustrates the value of using the large national database in examining the temporal changes in the risk profile and disparities in receipt of an invasive strategy amongst different subgroups of patients admitted with NSTEMI.

The results from the thesis extend the knowledge about changes in population demographics, risk profile and subsequent invasive management in patients admitted with a diagnosis of an NSTEMI in the most recent past. Furthermore, novel results such as disparities in utilisation and timing of an invasive strategy in different subgroups of patients, associations between baseline risk and receipt of an invasive strategy and institutional differences in invasive management of high-risk NSTEMI patients are not only hypothesis generating but provide important information to healthcare policymakers.

Another important overall strength of this thesis stems from the utilisation of large national datasets in cohort derivation. The size and national reach of these databases was a key strength and enabled a real-world analysis of different subgroups of patients, which are usually excluded from the randomised clinical trials. The national data allowed to study temporal trends, changes in characteristics of patients in all-comers, real-world setting compared to a highly selected randomised control trials undertaken in a much smaller number of patients from selected larger hospitals only. The granularity of data around the comorbidities, timing of the procedure, baseline risk profile and information about GRACE risk score formed the basis for studying the influence of comorbidity burden on the decision making process and compliance of guidelines adherence in the utilisation of an invasive strategy for the very first time in literature.

9.6 Overall limitations

In addition to the individual limitations of each study discussed in each relevant chapter, there are some important overall limitations, which need to be considered whilst interpreting the findings presented in this thesis as discussed below.

First and foremost, the research question in the thesis was a comprehensive evaluation of invasive management of patients admitted with the diagnosis of NSTEMI and their clinical outcomes. As discussed in chapter 1, there are several key aspects of managing these patients and to draw robust and clinically meaningful results. We set to study all factors such as patient-level factors, hospital-level factors and procedural factors in this thesis. Although this approach seems logical and comprehensive, it resulted in using three different datasets to study the respective research questions. The strengths and limitations of each dataset are discussed at length in chapter 4. Ideally, a comprehensive dataset encompassing information around patient comorbidities, risk profile, pharmacological treatment and procedural detail would be able to conduct this type of research. However, the logistics of creating such dataset at the national scale will be not conducive and will need a long time to create a dataset over a decade. Therefore, creating a linked electronic healthcare record may be an alternative approach, as discussed already in this chapter.

Another important limitation of this thesis is the fact that the research conducted was observational in the form of retrospective cohort studies. Such design allowed to study several hospital-level factors such as, the presence of cardiac catheter laboratory facilities at the first admitting hospital and their associations with receipt of an invasive strategy, temporal trends in changes in baseline risk profile and regional variations in the invasive management of NSTEMI which is only possible in an observational setting. However, it is not possible to adjust for unmeasured confounders whilst studying the

clinical outcomes of these patients, therefore a causal relationship between the use of an invasive strategy, the timing of an invasive strategy and clinical outcomes cannot be established. These findings are hypothesis generating and will form the basis of future prospective studies.

It is also important to mention that the diagnostic thresholds for diagnosing NSTEMI with the aid of cardiac troponin assays have evolved significantly over the past few years as mentioned earlier. Consequently, there has been a significant increase in detecting various types of myocardial injury, which may not necessarily reflect a true plaque rupture event. It was not possible to examine this in the current thesis due to the unavailability of information on types of cardiac troponin assays used.

The clinical outcomes in this thesis were limited to in-hospital mortality and complications in the majority of the studies. It is possible that long term outcomes of patients receiving invasive strategy may be different compared to those receiving medical management only. Furthermore, the in-hospital complications in most instances were self-reported without independent adjudication of events, which may have resulted in an underestimation of event rates. Finally, the details about patient characteristics, risk factors, pharmacological and invasive treatments in this thesis were based on the assumption of acute capture of these details in each respective dataset. This approach may be prone to errors as the information collected as part of a national audit compared to those collected under restrict research conditions. Furthermore, none of these datasets was collected with a specific focus on invasive management of patients admitted with NSTEMI. Therefore, the possibility of unmeasured confounder cannot be ruled out. Not only that, the accurate information about blood tests, medications, patient's risk profile may also influence the indication of an invasive strategy and inform the decision making the process about the overall care of the patient.

9.7 Conclusion

In conclusion, this thesis investigated the invasive management of one of the commonest phenotype of ACS. The results show that there are significant disparities in the use and timing of invasive strategy in different subgroups of patients. More importantly, patients who are most likely to benefit from an overall invasive strategy or an early invasive approach are least likely to receive it. There is also a significant disconnect between guidelines recommended risk stratification and the use of an invasive strategy and this gap appears to be widening with increasing risk. At the hospital level, high-risk NSTEMI patients admitted to hospitals with diagnostic cardiac catheter laboratory only may be denied early access to an invasive strategy and have poor outcomes. Finally, from the procedure point of left radial access offers a very safe alternative approach for performing an invasive strategy with the potential added benefit of reduced risk of procedure-related stroke complication. These findings not only have important implications for risk assessment, developing interventions to allow uniform access to an invasive strategy and improve quality of care for patients presenting with NSTEMI but also offer promising areas for further research.

References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40(3):237-269.

2. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: Prospective multinational observational study (GRACE). *BMJ*. 2006;333(7578):1091.

3. Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: A report of

the american college of cardiology/american heart association task force on practice guidelines. *J Am Coll Cardiol*. 2014;64(24):e139-228.

4. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the european society of cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315.

5. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. gruppo italiano per lo studio della streptochinasi nell'infarto miocardico (GISSI). *Lancet*. 1986;1(8478):397-402.

6. Durand P, Asseman P, Pruvost P, Bertrand ME, LaBlanche JM, Thery C. Effectiveness of intravenous streptokinase on infarct size and left ventricular function in acute myocardial infarction. prospective and randomized study. *Clin Cardiol*. 1987;10(7):383-392.

7. Khan MI, Hackett DR, Andreotti F, et al. Effectiveness of multiple bolus administration of tissue-type plasminogen activator in acute myocardial infarction. *Am J Cardiol*. 1990;65(16):1051-1056.

8. National clinical guideline centre (UK). unstable angina and NSTEMI: The early management of unstable angina and non-ST-segment-elevation myocardial infarction. london: Royal college of physicians (UK); 2010. (NICE clinical guidelines, no. 94.) appendix B, the analysis of MINAP data for the cost–effectiveness analysis. . https://www.ncbi.nlm.nih.gov/books/NBK62740/. Accessed 19th May, 2017.

9. Rashid M, Kwok CS, Gale CP, et al. Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: A systematic review and meta-analysis. *Eur Heart J Qual Care Clin Outcomes*. 2017;3(1):20-36.

10. Gupta T, Kolte D, Khera S, et al. Contemporary sex-based differences by age in presenting characteristics, use of an early invasive strategy, and inhospital mortality in patients with non-ST-segment-elevation myocardial infarction in the united states. *Circ Cardiovasc Interv*. 2018;11(1):e005735.

11. Damman P, Jernberg T, Lindahl B, et al. Invasive strategies and outcomes for non-ST-segment elevation acute coronary syndromes: A twelve-year experience from SWEDEHEART. *EuroIntervention*. 2016;12(9):1108-1116.

12. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA*. 2000;284(7):835-842.

13. Aragam KG, Tamhane UU, Kline-Rogers E, et al. Does simplicity compromise accuracy in ACS risk prediction? A retrospective analysis of the TIMI and GRACE risk scores. *PLoS One*. 2009;4(11):e7947.

14. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: Sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J*. 2005;26(9):865-872.

15. Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The task

force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the european society of cardiology (ESC). *Eur Heart J*. 2017.

16. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A platelet inhibition and patient outcomes (PLATO) trial subgroup analysis. *Circulation*. 2010;122(21):2131-2141.

17. Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous coronary intervention. *Heart*. 2016;102(8):617-625.

18. Olier I, Sirker A, Hildick-Smith DJR, et al. Association of different antiplatelet therapies with mortality after primary percutaneous coronary intervention. *Heart*. 2018.

19. Bertrand ME, Rupprecht HJ, Urban P, Gershlick AH, CLASSICS Investigators. Double-blind study of the safety of clopidogrel with and without a loading dose in combination with aspirin compared with ticlopidine in combination with aspirin after coronary stenting : The clopidogrel aspirin stent international cooperative study (CLASSICS). *Circulation*. 2000;102(6):624-629.

20. Puymirat E, Simon T, Cayla G, et al. Acute myocardial infarction: Changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI program (french registry of acute ST-elevation or non-ST-elevation myocardial infarction) 1995 to 2015. *Circulation*. 2017;136(20):1908-1919.

21. Hall M, Dondo TB, Yan AT, et al. Association of clinical factors and therapeutic strategies with improvements in survival following non-ST-elevation myocardial infarction, 2003-2013. *JAMA*. 2016;316(10):1073-1082.

22. Gharacholou SM, Roger VL, Lennon RJ, et al. Comparison of frail patients versus nonfrail patients >/=65 years of age undergoing percutaneous coronary intervention. *Am J Cardiol*. 2012;109(11):1569-1575.

23. Birkhead JS, Weston CF, Chen R. Determinants and outcomes of coronary angiography after non-ST-segment elevation myocardial infarction. A cohort study of the myocardial ischaemia national audit project (MINAP). *Heart*. 2009;95(19):1593-1599.

24. Pilote L, Miller DP, Califf RM, Rao JS, Weaver WD, Topol EJ. Determinants of the use of coronary angiography and revascularization after thrombolysis for acute myocardial infarction. *N Engl J Med*. 1996;335(16):1198-1205.

25. Wilkinson C, Bebb O, Dondo TB, et al. Sex differences in quality indicator attainment for myocardial infarction: A nationwide cohort study. *Heart*. 2018.

26. Kim C, Redberg RF, Pavlic T, Eagle KA. A systematic review of gender differences in mortality after coronary artery bypass graft surgery and percutaneous coronary interventions. *Clin Cardiol*. 2007;30(10):491-495.

27. Bugiardini R, Ricci B, Cenko E, et al. Delayed care and mortality among women and men with myocardial infarction. *J Am Heart Assoc*. 2017;6(8):10.1161/JAHA.117.005968.

28. Jneid H, Fonarow GC, Cannon CP, et al. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118(25):2803-2810.

29. Ma Q, Wang J, Jin J, et al. Clinical characteristics and prognosis of acute coronary syndrome in young women and men: A systematic review and meta-analysis of prospective studies. *Int J Cardiol*. 2017;228:837-843.

30. O'Brien C, Valsdottir L, Wasfy JH, et al. Comparison of 30-day readmission rates after hospitalization for acute myocardial infarction in men versus women. *Am J Cardiol*. 2017;120(7):1070-1076.

31. Trzeciak P, Wozakowska-Kaplon B, Niedziela J, et al. Comparison of inhospital and 12- and 36-month outcomes after acute coronary syndrome in men versus women *Am J Cardiol*. 2016;118(9):1300-1305.

32. Canto JG, Rogers WJ, Goldberg RJ, et al. Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA*. 2012;307(8):813-822.

33. J Potts, CS Kwok, J Ensor, M Rashid, U Kadam, T Kinnaird, N Curzen, SB Pancholy, D Van der Windt, RD Riley, R Bagur, MA Mamas. **Temporal changes in comorbidity burden in patients having percutaneous coronary intervention and impact on prognosis**. *in press*. 2018.

34. Potts J, Sirker A, Martinez SC, et al. Persistent sex disparities in clinical outcomes with percutaneous coronary intervention: Insights from 6.6 million PCI procedures in the united states. *PLoS One*. 2018;13(9):e0203325.

35. Pepine CJ, Ferdinand KC, Shaw LJ, et al. Emergence of nonobstructive coronary artery disease: A woman's problem and need for change in definition on angiography. *J Am Coll Cardiol*. 2015;66(17):1918-1933.

36. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: Statistics from world health organisation and united nations. *Int J Cardiol*. 2013;168(2):934-945.

37. Alabas OA, Gale CP, Hall M, et al. Sex differences in treatments, relative survival, and excess mortality following acute myocardial infarction: National cohort study using the SWEDEHEART registry. *J Am Heart Assoc*. 2017;6(12):10.1161/JAHA.117.007123.

38. Mehta LS, Beckie TM, DeVon HA, et al. Acute myocardial infarction in women: A scientific statement from the american heart association. *Circulation*. 2016;133(9):916-947.

39. Armstrong PW, Gershlick AH, Goldstein P, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368(15):1379-1387.

40. Mehta RH, Kaul P, Lopes RD, et al. Variations in practice and outcomes in patients undergoing primary percutaneous coronary intervention in the united states and canada: Insights from the assessment of pexelizumab in acute myocardial infarction (APEX AMI) trial. *Am Heart J*. 2012;163(5):797-803.

41. Myocardial ischaemia national audit Project Annual public report april 2014 – march 2015. http://www.ucl.ac.uk/nicor/audits/minap/documents/annual_reports/08818-minap-2014-15-1.1. Updated 2016. Accessed June 22, 2017.

42. Every NR, Larson EB, Litwin PE, et al. The association between on-site cardiac catheterization facilities and the use of coronary angiography after acute myocardial infarction. myocardial infarction triage and intervention project investigators. *N Engl J Med*. 1993;329(8):546-551.

43. Alter DA, Naylor CD, Austin PC, Tu JV. Long-term MI outcomes at hospitals with or without on-site revascularization. *JAMA*. 2001;285(16):2101-2108.

44. Bassand JP. Improving the quality and dissemination of guidelines: The quest for the holy grail. *Eur Heart J*. 2000;21(16):1289-1290.

45. Schneider EC, Timbie JW, Fox DS, Van Busum KR, Caloyeras JP. Dissemination and adoption of comparative effectiveness research findings when findings challenge current practices. *Rand Health Q*. 2013;2(4):5.

46. Tilson EC. Dissemination and adoption of guidelines: The experience of community care of north carolina. *N C Med J*. 2015;76(4):251-255.

47. Noman A, Ahmed JM, Spyridopoulos I, Bagnall A, Egred M. Mortality outcome of out-of-hours primary percutaneous coronary intervention in the current era. *Eur Heart J*. 2012;33(24):3046-3053.

48. Casella G, Ottani F, Ortolani P, et al. Off-hour primary percutaneous coronary angioplasty does not affect outcome of patients with ST-segment elevation acute myocardial infarction treated within a regional network for reperfusion: The REAL (registro regionale angioplastiche dell'emilia-romagna) registry. *JACC Cardiovasc Interv*. 2011;4(3):270-278.

49. van 't Hof AW, de Vries ST, Dambrink JH, et al. A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: Results of the early or late intervention in unStable angina (ELISA) pilot study. 2b/3a upstream therapy and acute coronary syndromes. *Eur Heart J*. 2003;24(15):1401-1405.

50. Riezebos RK, Ronner E, Ter Bals E, et al. Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart*. 2009;95(10):807-812.

51. Thiele H, Rach J, Klein N, et al. Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: The leipzig immediate versus early and late PercutaneouS coronary intervention triAl in NSTEMI (LIPSIA-NSTEMI trial). *Eur Heart J*. 2012;33(16):2035-2043.

52. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: The british heart foundation RITA 3 randomised trial. randomized intervention trial of unstable angina. *Lancet*. 2002;360(9335):743-751.

53. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and fast revascularisation during InStability in coronary artery disease investigators. *Lancet*. 1999;354(9180):708-715.

54. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: The FRISC II invasive randomised trial. FRISC II investigators. fast

revascularisation during instability in coronary artery disease. *Lancet*. 2000;356(9223):9-16.

55. Schuhlen H, Kastrati A, Dirschinger J, et al. Intracoronary stenting and risk for major adverse cardiac events during the first month. *Circulation*. 1998;98(2):104-111.

56. Monroe VS, Kerensky RA, Rivera E, Smith KM, Pepine CJ. Pharmacologic plaque passivation for the reduction of recurrent cardiac events in acute coronary syndromes. *J Am Coll Cardiol*. 2003;41(4 Suppl S):23S-30S.

57. Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes: A meta-analysis of contemporary randomized clinical trials. *J Am Coll Cardiol*. 2006;48(7):1319-1325.

58. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med*. 2005;353(11):1095-1104.

59. Katritsis DG, Siontis GC, Kastrati A, et al. Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur Heart J*. 2011;32(1):32-40.

60. Bonello L, Laine M, Puymirat E, et al. Timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes and clinical outcomes: An updated meta-analysis. *JACC Cardiovasc Interv*. 2016;9(22):2267-2276.

61. Rao SV, Cohen MG, Kandzari DE, Bertrand OF, Gilchrist IC. The transradial approach to percutaneous coronary intervention: Historical perspective, current concepts, and future directions. *J Am Coll Cardiol*. 2010;55(20):2187-2195.

62. Baklanov DV, Kaltenbach LA, Marso SP, et al. The prevalence and outcomes of transradial percutaneous coronary intervention for ST-segment elevation myocardial infarction: Analysis from the national cardiovascular data registry (2007 to 2011). *J Am Coll Cardiol*. 2013;61(4):420-426.

63. Bertrand OF, Rao SV, Pancholy S, et al. Transradial approach for coronary angiography and interventions: Results of the first international transradial practice survey. *JACC Cardiovasc Interv*. 2010;3(10):1022-1031.

64. Ratib K, Mamas MA, Anderson SG, et al. Access site practice and procedural outcomes in relation to clinical presentation in 439,947 patients undergoing percutaneous coronary intervention in the united kingdom. *JACC Cardiovasc Interv*. 2015;8(1 Pt A):20-29.

65. Dobies DR, Barber KR, Cohoon AL. Analysis of safety outcomes for radial versus femoral access for percutaneous coronary intervention from a large clinical registry. *Open Heart*. 2016;3(2):e000397-2015-000397. eCollection 2016.

66. Mamas MA, Anderson SG, Ratib K, et al. Arterial access site utilization in cardiogenic shock in the united kingdom: Is radial access feasible? *Am Heart J*. 2014;167(6):900-8.e1.

67. Mamas MA, Anderson SG, Carr M, et al. Baseline bleeding risk and arterial access site practice in relation to procedural outcomes after percutaneous coronary intervention. *J Am Coll Cardiol*. 2014;64(15):1554-1564.

68. Mamas MA, Nolan J, de Belder MA, et al. Changes in arterial access site and association with mortality in the united kingdom: Observations from a national percutaneous coronary intervention database. *Circulation*. 2016;133(17):1655-1667.

69. Mamas MA, Tosh J, Hulme W, et al. Health economic analysis of access site practice in england during changes in practice: Insights from the british cardiovascular interventional society. *Circ Cardiovasc Qual Outcomes*. 2018;11(5):e004482.

70. Ando G, Capodanno D. Radial access reduces mortality in patients with acute coronary syndromes: Results from an updated trial sequential analysis of randomized trials. *JACC Cardiovasc Interv*. 2016;9(7):660-670.

71. Jolly SS, Cairns J, Yusuf S, et al. Procedural volume and outcomes with radial or femoral access for coronary angiography and intervention. *J Am Coll Cardiol*. 2014;63(10):954-963.

72. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. *Lancet*. 2011;377(9775):1409-1420.

73. Valgimigli M, Gagnor A, Calabro P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: A randomised multicentre trial. *Lancet*. 2015;385(9986):2465-2476.

74. Kwok CS, Rashid M, Fraser D, Nolan J, Mamas M. Intra-arterial vasodilators to prevent radial artery spasm: A systematic review and pooled analysis of clinical studies. *Cardiovasc Revasc Med*. 2015;16(8):484-490.

75. Rashid M, Kwok CS, Pancholy S, et al. Radial artery occlusion after transradial interventions: A systematic review and meta-analysis. *J Am Heart Assoc*. 2016;5(1):10.1161/JAHA.115.002686.

76. Abdennadher MM, Delarche N. Operator exposure in interventional cardiology (right vs. left radial access). *Ann Cardiol Angeiol (Paris)*. 2016;65(5):375-376.

77. Dominici M, Diletti R, Milici C, et al. Left radial versus right radial approach for coronary artery catheterization: A prospective comparison. *J Interv Cardiol*. 2012;25(2):203-209.

78. Dominici M, Diletti R, Milici C, et al. Operator exposure to x-ray in left and right radial access during percutaneous coronary procedures: OPERA randomised study. *Heart*. 2013;99(7):480-484.

79. Kado H, Patel AM, Suryadevara S, et al. Operator radiation exposure and physical discomfort during a right versus left radial approach for coronary interventions: A randomized evaluation. *JACC Cardiovasc Interv*. 2014;7(7):810-816.

80. Herrett E, Smeeth L, Walker L, Weston C, MINAP Academic Group. The myocardial ischaemia national audit project (MINAP). *Heart*. 2010;96(16):1264-1267.

81. Ludman PF, de Belder MA, Redwood S, Banning A. United kingdom: Coronary and structural heart interventions from 2010 to 2015. *EuroIntervention*. 2017;13(Z):Z83-Z88.

82. Ludman PF, British Cardiovascular Intervention Society. British cardiovascular intervention society registry for audit and quality assessment of percutaneous coronary interventions in the united kingdom. *Heart*. 2011;97(16):1293-1297.

83. Healthcare cost and utilization project, agency for healthcare research and quality. NIS database documentation archive. rockville, MD; june 2016. www.hcup-us.ahrq.gov/db/nation/nis/nisarchive . . Updated 201814 March 2018.

84. Thomas E. An introduction to medical statistics for health care professionals: Basic statistical tests. *Musculoskeletal Care*. 2005;3(4):201-212.

85. Farewell V, Johnson T. Woods and russell, hill, and the emergence of medical statistics. *Stat Med*. 2010;29(14):1459-1476.

86. Toh S, Platt R. Big data in epidemiology: Too big to fail? *Epidemiology*. 2013;24(6):939.

87. Rubin D. Multiple imputation for nonresponse in surveys 1987 wiley new york. . 1987.

88. Cattle BA, Baxter PD, Greenwood DC, Gale CP, West RM. Multiple imputation for completion of a national clinical audit dataset. *Stat Med*. 2011;30(22):2736-2753.

89. Kontopantelis E, White IR, Sperrin M, Buchan I. Outcome-sensitive multiple imputation: A simulation study. *BMC Med Res Methodol*. 2017;17(1):2-016-0281-5.

90. Ananth CV, Kleinbaum DG. Regression models for ordinal responses: A review of methods and applications. *Int J Epidemiol*. 1997;26(6):1323-1333.

91. Harrell Jr FE. *Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis*. Springer; 2015.

92. Fagerland MW, Hosmer DW. A goodness-of-fit test for the proportional odds regression model. *Stat Med*. 2013;32(13):2235-2249.

93. Rashid M, Fischman DL, Gulati M, et al. Temporal trends and inequalities in coronary angiography utilization in the management of non-ST-elevation acute coronary syndromes in the U.S. *Sci Rep*. 2019;9(1):240-018-36504-y.

94. Rogers WJ, Frederick PD, Stoehr E, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the national registry of myocardial infarction from 1990 to 2006. *Am Heart J*. 2008;156(6):1026-1034.

95. Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N Engl J Med*. 2010;362(23):2155-2165.

96. Jennings SM, Bennett K, Lonergan M, Shelley E. Trends in hospitalisation for acute myocardial infarction in ireland, 1997-2008. *Heart*. 2012;98(17):1285-1289.

97. De Luca L, Olivari Z, Bolognese L, et al. A decade of changes in clinical characteristics and management of elderly patients with non-ST elevation myocardial infarction admitted in italian cardiac care units. *Open Heart*. 2014;1(1):e000148-2014-000148. eCollection 2014.

98. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med*. 2011;124(1):40-47.

99. Fath-Ordoubadi F, Spaepen E, El-Omar M, et al. Outcomes in patients with acute and stable coronary syndromes; insights from the prospective NOBORI-2 study. *PLoS One*. 2014;9(2):e88577.

100. Ren L, Ye H, Wang P, Cui Y, Cao S, Lv S. Comparison of long-term mortality of acute ST-segment elevation myocardial infarction and non-ST-segment elevation acute coronary syndrome patients after percutaneous coronary intervention. *Int J Clin Exp Med*. 2014;7(12):5588-5592.

101. Dondo TB, Hall M, Timmis AD, et al. Excess mortality and guideline-indicated care following non-ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2017;6(5):412-420.

102. van Leeuwen MA, Daemen J, van Mieghem NM, et al. Comparison of long-term outcomes in STEMI and NSTE-ACS after coronary stent placement: An analysis in a real world BMS and DES population. *Int J Cardiol*. 2013;167(5):2082-2087.

103. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Circulation*. 2013;127(23):e663-828.

104. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: A collaborative meta-analysis of randomized trials. *JAMA*. 2005;293(23):2908-2917.

105. Milosevic A, Vasiljevic-Pokrajcic Z, Milasinovic D, et al. Immediate versus delayed invasive intervention for non-STEMI patients: The RIDDLE-NSTEMI study. *JACC Cardiovasc Interv*. 2016;9(6):541-549.

106. O'Donoghue M, Boden WE, Braunwald E, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: A meta-analysis. *JAMA*. 2008;300(1):71-80.

107. Williams MJ, Harding SA, Devlin G, et al. National variation in coronary angiography rates and timing after an acute coronary syndrome in new zealand (ANZACS-QI 6). *N Z Med J*. 2016;129(1428):66-78.

108. Dondo TB, Hall M, Timmis AD, et al. Geographic variation in the treatment of non-ST-segment myocardial infarction in the english national health service: A cohort study. *BMJ Open*. 2016;6(7):e011600-2016-011600.

109. Chatterjee K, Gupta T, Goyal A, et al. Association of obesity with in-hospital mortality of cardiogenic shock complicating acute myocardial infarction. *Am J Cardiol*. 2017;119(10):1548-1554.

110. Dhital R, Basnet S, Poudel DR. Impact of hypothyroidism on occurrence and outcome of acute coronary syndrome from the national inpatient sample. *Am J Cardiol*. 2017;120(12):2160-2163.

111. LaMori JC, Shoheiber O, Dudash K, Crivera C, Mody SH. The economic impact of acute coronary syndrome on length of stay: An analysis using the healthcare cost and utilization project (HCUP) databases. *J Med Econ*. 2014;17(3):191-197.

112. Mahmoud AN, Taduru SS, Mentias A, et al. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: A population-based analysis. *JACC Cardiovasc Interv*. 2018;11(1):80-90.

113. Ogunbayo GO, Misumida N, Olorunfemi O, et al. Comparison of outcomes in patients having acute myocardial infarction with versus without sickle-cell anemia. *Am J Cardiol*. 2017;120(10):1768-1771.

114. Goel K, Gupta T, Kolte D, et al. Outcomes and temporal trends of inpatient percutaneous coronary intervention at centers with and without on-site cardiac surgery in the united states. *JAMA Cardiol*. 2017;2(1):25-33.

115. Khera S, Kolte D, Gupta T, et al. Temporal trends and sex differences in revascularization and outcomes of ST-segment elevation myocardial infarction in younger adults in the united states. *J Am Coll Cardiol*. 2015;66(18):1961-1972.

116. Kolte D, Khera S, Dabhadkar KC, et al. Trends in coronary angiography, revascularization, and outcomes of cardiogenic shock complicating non-ST-elevation myocardial infarction. *Am J Cardiol*. 2016;117(1):1-9.

117. Patel B, Shah M, Dusaj R, Maynard S, Patel N. Percutaneous coronary intervention and inpatient mortality in patients with advanced chronic kidney disease presenting with acute coronary syndrome. *Proc (Bayl Univ Med Cent)*. 2017;30(4):400-403.

118. Smilowitz NR, Gupta N, Guo Y, Bangalore S. Comparison of outcomes of patients with sepsis with versus without acute myocardial infarction and comparison of invasive versus noninvasive management of the patients with infarction. *Am J Cardiol*. 2016;117(7):1065-1071.

119. Smilowitz NR, Gupta N, Guo Y, Mauricio R, Bangalore S. Management and outcomes of acute myocardial infarction in patients with chronic kidney disease. *Int J Cardiol*. 2017;227:1-7.

120. Varadarajulu S, Kilgore ML, Wilcox CM, Eloubeidi MA. Relationship among hospital ERCP volume, length of stay, and technical outcomes. *Gastrointest Endosc*. 2006;64(3):338-347.

121. Mahmoud AN, Taduru SS, Mentias A, et al. Trends of incidence, clinical presentation, and in-hospital mortality among women with acute myocardial infarction with or without spontaneous coronary artery dissection: A population-based analysis. *JACC Cardiovasc Interv*. 2018;11(1):80-90.

122. Recent hospitalization trends for acute myocardial infarction in beijing. *Eur Heart J*. 2016;37(42):3188-3189.

123. Agarwal M, Agrawal S, Garg L, et al. National trends in the incidence, management, and outcomes of heart failure complications in patients hospitalized for ST-segment elevation myocardial infarction. *Mayo Clin Proc Innov Qual Outcomes*. 2017;1(1):26-36.

124. Elgendy IY, Mahmoud AN, Mansoor H, Bavry AA. Early invasive versus initial conservative strategies for women with non-ST-elevation acute coronary syndromes: A nationwide analysis. *Am J Med*. 2017;130(9):1059-1067.

125. Patel B, Carson P, Shah M, et al. Acute kidney injury requiring dialysis and in-hospital mortality in patients with chronic kidney disease and non-ST-segment elevation acute coronary syndrome undergoing early vs delayed percutaneous coronary intervention: A nationwide analysis. *Clin Cardiol*. 2017;40(12):1303-1308.

126. Movahed MR, John J, Hashemzadeh M, Hashemzadeh M. Mortality trends for non-ST-segment elevation myocardial infarction (NSTEMI) in the united states from 1988 to 2004. *Clin Cardiol*. 2011;34(11):689-692.

127. Issa M, Alqahtani F, Ziada KM, et al. Incidence and outcomes of non-ST elevation myocardial infarction in patients hospitalized with decompensated diabetes. *Am J Cardiol*. 2018;122(8):1297-1302.

128. Bhatia S, Arora S, Bhatia SM, et al. Non-ST-segment-elevation myocardial infarction among patients with chronic kidney disease: A propensity score-matched comparison of percutaneous coronary intervention versus conservative management. *J Am Heart Assoc*. 2018;7(6):10.1161/JAHA.117.007920.

129. Thompson NR, Fan Y, Dalton JE, et al. A new elixhauser-based comorbidity summary measure to predict in-hospital mortality. *Med Care*. 2015;53(4):374-379.

130. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.

131. Ondeck NT, Bovonratwet P, Ibe IK, et al. Discriminative ability for adverse outcomes after surgical management of hip fractures: A comparison of the charlson comorbidity index, elixhauser comorbidity measure, and modified frailty index. *J Orthop Trauma*. 2018;32(5):231-237.

132. Hosseini SM, Moazzami K, Rozen G, et al. Utilization and in-hospital complications of cardiac resynchronization therapy: Trends in the united states from 2003 to 2013. *Eur Heart J*. 2017;38(27):2122-2128.

133. Kang HJ, Simon D, Wang TY, et al. The contemporary use of angiography and revascularization among patients with non-ST-segment elevation myocardial infarction in the united states compared with south korea. *Clin Cardiol*. 2015;38(12):708-714.

134. Horwitz JR, Nichols A, Nallamothu BK, Sasson C, Iwashyna TJ. Expansion of invasive cardiac services in the united states. *Circulation*. 2013;128(8):803-810.

135. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Impact of comorbidities and gender on the use of coronary interventions in patients with high-risk non-ST-segment elevation acute coronary syndrome. *Catheter Cardiovasc Interv*. 2016;87(4):E128-36.

136. Zaman MJ, Stirling S, Shepstone L, et al. The association between older age and receipt of care and outcomes in patients with acute coronary syndromes: A cohort study of the myocardial ischaemia national audit project (MINAP). *Eur Heart J*. 2014;35(23):1551-1558.

137. Chan MY, Sun JL, Newby LK, et al. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. *Circulation*. 2009;119(24):3110-3117.

138. Palau P, Nunez J, Sanchis J, et al. Differential prognostic effect of revascularization according to a simple comorbidity index in high-risk non-ST-segment elevation acute coronary syndrome. *Clin Cardiol*. 2012;35(4):237-243.

139. Bhatt DL, Roe MT, Peterson ED, et al. Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary

syndromes: Results from the CRUSADE quality improvement initiative. *JAMA*. 2004;292(17):2096-2104.

140. Gulati M. Improving the cardiovascular health of women in the nation: Moving beyond the bikini boundaries. *Circulation*. 2017;135(6):495-498.

141. Udell JA, Koh M, Qiu F, et al. Outcomes of women and men with acute coronary syndrome treated with and without percutaneous coronary revascularization. *J Am Heart Assoc*. 2017;6(1):10.1161/JAHA.116.004319.

142. Mamas MA, Ratib K, Routledge H, et al. Influence of access site selection on PCI-related adverse events in patients with STEMI: Meta-analysis of randomised controlled trials. *Heart*. 2012;98(4):303-311.

143. Ratib K, Mamas MA, Routledge HC, Ludman PF, Fraser D, Nolan J. Influence of access site choice on incidence of neurologic complications after percutaneous coronary intervention. *Am Heart J*. 2013;165(3):317-324.

144. Sirker A, Mamas M, Robinson D, et al. Bivalirudin, glycoprotein inhibitor, and heparin use and association with outcomes of primary percutaneous coronary intervention in the united kingdom. *Eur Heart J*. 2016;37(16):1312-1320.

145. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360(21):2165-2175.

146. Fox KA, Anderson FA, Dabbous OH, et al. Intervention in acute coronary syndromes: Do patients undergo intervention on the basis of their risk characteristics? the global registry of acute coronary events (GRACE). *Heart*. 2007;93(2):177-182.

147. Roe MT, Peterson ED, Newby LK, et al. The influence of risk status on guideline adherence for patients with non–ST-segment elevation acute coronary syndromes. *Am Heart J*. 2006;151(6):1205-1213.

148. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC), Steg PG, James SK, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569-2619.

149. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: A randomized controlled trial. *JAMA*. 2003;290(12):1593-1599.

150. Jobs A, Mehta SR, Montalescot G, et al. Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: A meta-analysis of randomised trials. *Lancet*. 2017;390(10096):737-746.

151. Montalescot G, Cayla G, Collet JP, et al. Immediate vs delayed intervention for acute coronary syndromes: A randomized clinical trial. *JAMA*. 2009;302(9):947-954.

152. Kwok CS, Potts J, Gulati M, et al. Effect of gender on unplanned readmissions after percutaneous coronary intervention (from the nationwide readmissions database). *Am J Cardiol*. 2018;121(7):810-817.

153. Daly C, Clemens F, Lopez Sendon JL, et al. Gender differences in the management and clinical outcome of stable angina. *Circulation*. 2006;113(4):490-498.

154. Kunadian V, Qiu W, Lagerqvist B, et al. Gender differences in outcomes and predictors of all-cause mortality after percutaneous coronary intervention (data from united kingdom and sweden). *Am J Cardiol*. 2017;119(2):210-216.

155. Sawant AC, Josey K, Plomondon ME, et al. Temporal trends, complications, and predictors of outcomes among nonagenarians undergoing percutaneous coronary intervention: Insights from the veterans affairs clinical assessment, reporting, and tracking program. *JACC Cardiovasc Interv*. 2017;10(13):1295-1303.

156. Calvin JE, Roe MT, Chen AY, et al. Insurance coverage and care of patients with non-ST-segment elevation acute coronary syndromes. *Ann Intern Med*. 2006;145(10):739-748.

157. Edmund Anstey D, Li S, Thomas L, Wang TY, Wiviott SD. Race and sex differences in management and outcomes of patients after ST-elevation and non-ST-elevation myocardial infarct: Results from the NCDR. *Clin Cardiol*. 2016;39(10):585-595.

158. Malta Hansen C, Wang TY, Chen AY, et al. Contemporary patterns of early coronary angiography use in patients with non-ST-segment elevation myocardial infarction in the united states: Insights from the national cardiovascular data registry acute coronary treatment and intervention outcomes network registry. *JACC Cardiovasc Interv*. 2018;11(4):369-380.

159. Rhudy JP,Jr, Alexandrov AW, Hyrkas KE, et al. Geographic access to interventional cardiology services in one rural state. *Heart Lung*. 2016;45(5):434-440.

160. Capers Q, Sharalaya Z. Racial disparities in cardiovascular care: A review of culprits and potential solutions. *Journal of Racial and Ethnic Health Disparities*. 2014;1(3):171-180.

161. Kwok CS, Al-Dokheal M, Aldaham S, et al. Weekend effect in acute coronary syndrome: A meta-analysis of observational studies. *Eur Heart J Acute Cardiovasc Care*. 2018:2048872618762634.

162. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): Double-blind, randomised controlled trial. *The Lancet*. 2009;373(9665):723-731.

163. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-1057.

164. Lindholm D, Alfredsson J, Angeras O, et al. Timing of percutaneous coronary intervention in patients with non-ST-elevation myocardial infarction: A SWEDEHEART study. *Eur Heart J Qual Care Clin Outcomes*. 2017;3(1):53-60.

165. Montalescot G, Dabbous OH, Lim MJ, Flather MD, Mehta RH, Global Registry of Acute Coronary Events Investigators. Relation of timing of cardiac catheterization to outcomes in patients with non-ST-segment elevation myocardial infarction or unstable angina pectoris enrolled in the multinational global registry of acute coronary events. *Am J Cardiol*. 2005;95(12):1397-1403.

166. Gale CP, Cattle BA, Woolston A, et al. Resolving inequalities in care? reduced mortality in the elderly after acute coronary syndromes. the myocardial ischaemia national audit project 2003-2010. *Eur Heart J*. 2012;33(5):630-639.

167. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined--a consensus document of the joint european society of cardiology/american college of cardiology committee for the redefinition of myocardial infarction. *J Am Coll Cardiol*. 2000;36(3):959-969.

168. Simms AD, Reynolds S, Pieper K, et al. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the myocardial ischaemia national audit project (MINAP) 2003-2009: National institute for cardiovascular outcomes research (NICOR). *Heart*. 2013;99(1):35-40.

169. Chapman AR, Fujisawa T, Lee KK, et al. Novel high-sensitivity cardiac troponin I assay in patients with suspected acute coronary syndrome. *Heart*. 2018.

170. Shah ASV, Sandoval Y, Noaman A, et al. Patient selection for high sensitivity cardiac troponin testing and diagnosis of myocardial infarction: Prospective cohort study. *BMJ*. 2017;359:j4788.

171. Welsh P, Preiss D, Shah ASV, et al. Comparison between high-sensitivity cardiac troponin T and cardiac troponin I in a large general population cohort. *Clin Chem*. 2018;64(11):1607-1616.

172. Mariathas M, Allan R, Ramamoorthy S, et al. True 99th centile of high sensitivity cardiac troponin for hospital patients: Prospective, observational cohort study. *BMJ*. 2019;364:l729.

173. Engel J, Damen NL, van der Wulp I, de Bruijne MC, Wagner C. Adherence to cardiac practice guidelines in the management of non-ST-elevation acute coronary syndromes: A systematic literature review. *Curr Cardiol Rev*. 2017;13(1):3-27.

174. Rashid M, Fischman DL, Martinez SC, et al. Temporal trends and predictors of time to coronary angiography following non-ST-elevation acute coronary syndrome in the USA. *Coron Artery Dis*. 2019.

175. Curran HJ, Hubacek J, Southern D, et al. The effect of a regional care model on cardiac catheterization rates in patients with acute coronary syndromes. *BMC Health Serv Res*. 2014;14:550-014-0550-0.

176. Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the united states: A report from the CathPCI registry of the national cardiovascular data registry, 2010 through june 2011. *J Am Coll Cardiol*. 2012;60(20):2017-2031.

177. Barnhart J, Lewis V, Houghton JL, Charney P. Physician knowledge levels and barriers to coronary risk prevention in women: Survey results from the women and heart disease physician education initiative. *Womens Health Issues*. 2007;17(2):93-100.

178. Mochari-Greenberger H, Mills T, Simpson SL, Mosca L. Knowledge, preventive action, and barriers to cardiovascular disease prevention by race and ethnicity in women: An american heart association national survey. *J Womens Health (Larchmt)*. 2010;19(7):1243-1249.

179. Dehmer GJ, Weaver D, Roe MT, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the united states: A report

from the CathPCI registry of the national cardiovascular data registry, 2010 through june 2011. *J Am Coll Cardiol*. 2012;60(20):2017-2031.

180. Roe MT, Chen AY, Delong ER, et al. Patterns of transfer for patients with non-ST-segment elevation acute coronary syndrome from community to tertiary care hospitals. *Am Heart J*. 2008;156(1):185-192.

181. Dondo TB, Hall M, Timmis AD, et al. Excess mortality and guideline-indicated care following non-ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2017;6(5):412-420.

182. O'Neill D, Nicholas O, Gale CP, et al. Total center percutaneous coronary intervention volume and 30-day mortality: A contemporary national cohort study of 427 467 elective, urgent, and emergency cases. *Circ Cardiovasc Qual Outcomes*. 2017;10(3):10.1161/CIRCOUTCOMES.116.003186.

183. Waldo SW, Gokhale M, O'Donnell CI, et al. Temporal trends in coronary angiography and percutaneous coronary intervention: Insights from the VA clinical assessment, reporting, and tracking program. *JACC Cardiovasc Interv*. 2018;11(9):879-888.

184. Behar S, Hod H, Benari B, et al. On-site catheterization laboratory and prognosis after acute myocardial infarction. israeli thrombolytic survey group. *Arch Intern Med*. 1995;155(8):813-817.

185. Every NR, Parsons LS, Fihn SD, et al. Long-term outcome in acute myocardial infarction patients admitted to hospitals with and without on-site cardiac catheterization

facilities. MITI investigators. myocardial infarction triage and intervention. *Circulation*. 1997;96(6):1770-1775.

186. Krumholz HM, Chen J, Murillo JE, Cohen DJ, Radford MJ. Admission to hospitals with on-site cardiac catheterization facilities :Impact on long-term costs and outcomes. *Circulation*. 1998;98(19):2010-2016.

187. Halabi AR, Beck CA, Eisenberg MJ, Richard H, Pilote L. Impact of on-site cardiac catheterization on resource utilization and fatal and non-fatal outcomes after acute myocardial infarction. *BMC Health Serv Res*. 2006;6:148-6963-6-148.

188. Van de Werf F, Gore JM, Avezum A, et al. Access to catheterisation facilities in patients admitted with acute coronary syndrome: Multinational registry study. *BMJ*. 2005;330(7489):441.

189. Chen J, Krumholz HM, Wang Y, et al. Differences in patient survival after acute myocardial infarction by hospital capability of performing percutaneous coronary intervention: Implications for regionalization. *Arch Intern Med*. 2010;170(5):433-439.

190. Birkhead JS, Walker L, Pearson M, et al. Improving care for patients with acute coronary syndromes: Initial results from the national audit of myocardial infarction project (MINAP). *Heart*. 2004;90(9):1004-1009.

191. Birkhead JS. Responding to the requirements of the national service framework for coronary disease: A core data set for myocardial infarction. *Heart*. 2000;84(2):116-117.

192. Khadour FH, Fu Y, Chang WC, et al. Impact of on-site cardiac interventional facilities on management and outcome of patients with acute coronary syndromes. *Can J Cardiol*. 2003;19(3):257-263.

193. Leslie SJ, Henriksen PA, Timlin H, Stanton T, Spratt JC, Denvir MA. Urgent in-patient coronary angiography: A comparison of centres with and without cardiac catheter facilities. *Scott Med J*. 2006;51(4):24-26.

194. Sinnaeve PR, Zeymer U, Bueno H, et al. Contemporary inter-hospital transfer patterns for the management of acute coronary syndrome patients: Findings from the EPICOR study. *Eur Heart J Acute Cardiovasc Care*. 2015;4(3):254-262.

195. Gabriel Steg P, Iung B, Feldman LJ, et al. Determinants of use and outcomes of invasive coronary procedures in acute coronary syndromes: Results from ENACT. *Eur Heart J*. 2003;24(7):613-622.

196. Rogers WJ, Canto JG, Barron HV, Boscarino JA, Shoultz DA, Every NR. Treatment and outcome of myocardial infarction in hospitals with and without invasive capability. investigators in the national registry of myocardial infarction. *J Am Coll Cardiol*. 2000;35(2):371-379.

197. Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA*. 2006;295(16):1912-1920.

198. Fox KA, Anderson FA,Jr, Dabbous OH, et al. Intervention in acute coronary syndromes: Do patients undergo intervention on the basis of their risk characteristics? the global registry of acute coronary events (GRACE). *Heart*. 2007;93(2):177-182.

199. Rashid M, Lawson C, Potts J, et al. Incidence, determinants, and outcomes of left and right radial access use in patients undergoing percutaneous coronary intervention in

the united kingdom: A national perspective using the BCIS dataset. *JACC Cardiovasc Interv*. 2018;11(11):1021-1033.

200. Caputo RP, Tremmel JA, Rao S, et al. Transradial arterial access for coronary and peripheral procedures: Executive summary by the transradial committee of the SCAI. *Catheter Cardiovasc Interv*. 2011;78(6):823-839.

201. Sachdeva S, Saha S. Transradial approach to cardiovascular interventions: An update. *Int J Angiol*. 2014;23(2):77-84.

202. Feldman DN, Swaminathan RV, Kaltenbach LA, et al. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention: An updated report from the national cardiovascular data registry (2007-2012). *Circulation*. 2013;127(23):2295-2306.

203. Yeh RW, Kirtane AJ, Rao SV. Incentivizing transradial access for primary percutaneous coronary intervention while maintaining timely reperfusion. *JAMA Cardiol*. 2017.

204. Https://Www.bcis.org.uk/education/bcis-audit-report-2017-18/. . Updated 2019. Accessed 03/04, 2019.

205. Amin AP, Pinto D, House JA, et al. Association of same-day discharge after elective percutaneous coronary intervention in the united states with costs and outcomes. *JAMA Cardiol*. 2018;3(11):1041-1049.

206. Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol*. 2012;60(24):2490-2499.

207. Amin AP, Patterson M, House JA, et al. Costs associated with access site and same-day discharge among medicare beneficiaries undergoing percutaneous coronary intervention: An evaluation of the current percutaneous coronary intervention care pathways in the united states. *JACC Cardiovasc Interv*. 2017;10(4):342-351.

208. Hess CN, Krucoff MW, Sheng S, et al. Comparison of quality-of-life measures after radial versus femoral artery access for cardiac catheterization in women: Results of the study of access site for enhancement of percutaneous coronary intervention for women quality-of-life substudy. *Am Heart J*. 2015;170(2):371-379.

209. Kawashima O, Endoh N, Terashima M, et al. Effectiveness of right or left radial approach for coronary angiography. *Catheter Cardiovasc Interv*. 2004;61(3):333-337.

210. Lo TS, Nolan J, Fountzopoulos E, et al. Radial artery anomaly and its influence on transradial coronary procedural outcome. *Heart*. 2009;95(5):410-415.

211. Hamon M, Gomes S, Clergeau MR, Fradin S, Morello R, Hamon M. Risk of acute brain injury related to cerebral microembolism during cardiac catheterization performed by right upper limb arterial access. *Stroke*. 2007;38(7):2176-2179.

212. Shah RM, Patel D, Abbate A, Cowley MJ, Jovin IS. Comparison of transradial coronary procedures via right radial versus left radial artery approach: A meta-analysis. *Catheter Cardiovasc Interv*. 2016;88(7):1027-1033.

213. Pacchioni A, Versaci F, Mugnolo A, et al. Risk of brain injury during diagnostic coronary angiography: Comparison between right and left radial approach. *Int J Cardiol*. 2013;167(6):3021-3026.

214. Biondi-Zoccai G, Sciahbasi A, Bodi V, et al. Right versus left radial artery access for coronary procedures: An international collaborative systematic review and meta-analysis including 5 randomized trials and 3210 patients. *Int J Cardiol*. 2013;166(3):621-626.

215. Sciahbasi A, Romagnoli E, Burzotta F, et al. Transradial approach (left vs right) and procedural times during percutaneous coronary procedures: TALENT study. *Am Heart J*. 2011;161(1):172-179.

216. Hulme W, Sperrin M, Rushton H, et al. Is there a relationship of operator and center volume with access site-related outcomes? an analysis from the british cardiovascular intervention society. *Circ Cardiovasc Interv*. 2016;9(5):e003333.

217. Rao SV, Tremmel JA, Gilchrist IC, et al. Best practices for transradial angiography and intervention: A consensus statement from the society for cardiovascular angiography and intervention's transradial working group. *Catheter Cardiovasc Interv*. 2014;83(2):228-236.

218. Naidu SS, Aronow HD, Box LC, et al. SCAI expert consensus statement: 2016 best practices in the cardiac catheterization laboratory: (Endorsed by the cardiological society of india, and sociedad latino americana de cardiologia intervencionista; affirmation of value by the canadian association of interventional cardiology-association canadienne de cardiologie d'intervention). *Catheter Cardiovasc Interv*. 2016;88(3):407-423.

219. Abdelaal E, Molin P, Plourde G, et al. Successive transradial access for coronary procedures: Experience of quebec heart-lung institute. *Am Heart J*. 2013;165(3):325-331.

220. Caputo RP, Simons A, Giambartolomei A, et al. Safety and efficacy of repeat transradial access for cardiac catheterization procedures. *Catheter Cardiovasc Interv*. 2001;54(2):188-190.

221. Sakai H, Ikeda S, Harada T, et al. Limitations of successive transradial approach in the same arm: The japanese experience. *Catheter Cardiovasc Interv*. 2001;54(2):204-208.

222. Mamas MA, Fraser DG, Ratib K, et al. Minimising radial injury: Prevention is better than cure. *EuroIntervention*. 2014;10(7):824-832.

223. Sciahbasi A, Rigattieri S, Sarandrea A, et al. Operator radiation exposure during right or left transradial coronary angiography: A phantom study. *Cardiovasc Revasc Med*. 2015;16(7):386-390.

224. Kwok CS, Kontopantelis E, Myint PK, et al. Stroke following percutaneous coronary intervention: Type-specific incidence, outcomes and determinants seen by the british cardiovascular intervention society 2007-12. *Eur Heart J*. 2015;36(25):1618-1628.

225. Myint PK, Kwok CS, Roffe C, et al. Determinants and outcomes of stroke following percutaneous coronary intervention by indication. *Stroke*. 2016;47(6):1500-1507.

226. Barbash IM, Minha S, Gallino R, et al. Operator learning curve for transradial percutaneous coronary interventions: Implications for the initiation of a transradial access program in contemporary US practice. *Cardiovasc Revasc Med*. 2014;15(4):195-199.

227. Sciahbasi A, Romagnoli E, Trani C, et al. Evaluation of the "learning curve" for left and right radial approach during percutaneous coronary procedures. *Am J Cardiol*. 2011;108(2):185-188.

Chapter 10

Appendices

10.1 Appendix I: Acronyms

Acronym	Full Text
ACE	Angiotensin-converting enzyme
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute coronary syndrome
AHA	American Heart Association
AIDS	Acquired immune deficiency syndromes
ATE	Average treatment effects
AHRQ	Agency for Healthcare Research and Quality
ACC	American College of Cardiology
AMI	Acute myocardial infarction
BCIS	British Cardiovascular Intervention Society
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CA	Coronary angiography
CCAD	Central Cardiac Audit Database
CHD	Coronary heart disease
CCI	Charlson Comorbidity Index
CI	Confidence interval
CVA	Cerebrovascular accident
CCF	Congestive cardiac failure
CCS	Clinical Classification of Software
ECG	Electrocardiogram
ESC	European Society of Cardiology
GRACE	Global Registry of Acute Coronary Events
HCUP	Healthcare Cost and Utilization Project
ICD- 9	International of the Classification of Diseases, Version 9
IABP	Intra-aortic balloon pump
IHD	Ischemic heart disease
IQR	Inter-quartile range
LVF	Left ventricular failure
LRA	Left radial access
MI	Myocardial infarction
MINAP	Myocardial Ischemia National Audit Project
MACCE	Major adverse cerebrovascular events

NICOR	National Institute for Cardiovascular Research Outcomes
NICE	National Institute of Health and Clinical Excellence.
NHS	National Health System
NIS	National Inpatient Sample
ONS	Office of National Statistics
PVD	Peripheral vascular disease
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
RCT	Randomised control trials
RRA	Right radial access
RA	Rheumatoid arthritis
SD	Standard deviation
STEMI	ST-elevation myocardial infarction
TIA	Transient ischaemic attack
UA	Unstable angina
TIMI	Thrombolysis In Myocardial Infarction
TRA	Transradial access

10.2 Appendix II: supplementary tables

Appendix Table 1: List of the international classification of disease, Ninth Edition, clinical modification (ICD-9-CM) and clinical classification software codes used for identifying additional comorbidities

Comorbidities	Source	Codes
Dyslipidaemias	CCS	53
Coronary artery disease	ICD-9-CM	414.00-414.07
Family history of IHD	ICD-9-CM	V17.3
Previous stroke or transient ischemic attack	ICD-9-CM	V12.54x
Previous CABG	ICD-9-CM	V45.81x
Previous PCI	ICD-9-CM	V45.82x
Cardiogenic shock	ICD-9-CM	785.51
Use of inotropic agents	ICD-9-CM	00.17
Use of inotropic assist device	ICD-9-CM	376, 97.44
Smoking	ICD-9-CM	V15.82, 305.1
Dementia	ICD-9-CM	290.xx,294.1x,294.2x,294.8,331.0,331.12,331.82,797

IHD= ischemic heart disease, CABG= coronary artery bypass graft, PCI= percutaneous coronary intervention

Appendix Table 2: Deyo's modification of Charlson's comorbidity index (CCI).

ICD-9 codes	Condition	Charlson score
412	Previous myocardial infarction	1
428 – 428.9	Congestive heart failure	1
433.9, 441 – 441.9, 785.4 V43.4	Peripheral vascular disease	1
V12.54, 438.x	Previous cerebrovascular disease	1
290 – 290.9	Dementia	1
490 – 496, 500 –505, 506.4	Chronic pulmonary disease	1
710.0, 710.1, 710.4, 714 – 714.2, 714.81, 725	Rheumatologic disease	1
531 – 534.9	Peptic ulcer	1
571.2, 571.5, 571.6, 571.4 –571.49	Mild liver disease	1
250 – 250.3, 250.7	Diabetes	1
250.4 – 250.6	Diabetes with chronic complications	2
344.1, 342 – 342.9	Hemiplegia or paraplegia	2
582 – 582.9, 583 – 583.7, 585, 586, 588 – 588.9	Renal Disease	2
140 – 172.9, 174 –195.8, 200 – 208.9	Any malignancy including leukaemia and lymphoma	2
572.2 – 572.8	Moderate or severe liver disease	3
196 – 199.1	Metastatic solid tumour	6
042 – 044.9	Acquired immune deficiency syndromes (AIDS)	6

Appendix Table 3: ICD-9-CM codes for in-hospital outcomes

Post-procedural Complication	ICD-9-CM or CCS codes
Bleeding complication	
Gastrointestinal	CCS 153
Unspecified haemorrhage	459.0
Retroperitoneal haemorrhage	568.81, 998.1
Intracranial haemorrhage	430-432x
Post-op haemorrhage requiring transfusion	99.0 (procedure)
Blood transfusion	V58.2
Vascular complications	
Vascular injury	900-904, 998.2, 447, 868.04, 999.7 (diagnosis) 39.31, 39.41, 39.49, 39.52, 39.53, 39.56 - 39.59 39.79 (procedure)
Cardiac complications	

Iatrogenic cardiac complication	997.1
Pericardial complication	423.0, 423.3 (diagnosis) 47.0 (procedure)
Requiring CABG surgery	36.1x, 36.2, 36.31, 36.32, 36.9x
Coronary artery dissection complication	414.12

CABG= coronary artery bypass graft surgery

Appendix Table 4: Missing information about each variable included in the study

Variables	Number (%)
Age (Years)	0 (0%)
Women (%)	0 (0%)
Caucasians (%)	0 (0%)
BMI median [IQR]	61,835 (45%)
Cardiogenic shock	0 (0%)
ECG ST changes	1,381 (1.0%)
Cardiac arrest	5,192 (3.8%)
Acute heart failure	0 (0%)
GRACE score High risk >140	53,477 (39.0%)
Troponin positive	3,097 (2.3%)
GRACE score Intermediate risk 109-140	53,477 (39.0%)
Chronic renal failure	6,560 (4.8%)
Percutaneous coronary intervention	6,072 (4.4%)
Coronary artery bypass graft	5,961 (4.3%)
Diabetes	2,233 (1.6%)
LVEF<40% or CCF	64,896 (47.3%)
Hypercholesterolemia	7,606 (5.5%)
Angina	6,941 (5.1%)
Cerebrovascular disease	6,391 (4.6%)
Peripheral vascular disease	7,070 (5.1%)
Hypertension	5,573 (4.1%)
Smoking status	4,938 (3.6%)
Asthma / COPD	6,458 (4.7%)
Seen by cardiologist	0 (0%)
Heart rate, bpm, median (IQR)	17,555 (12.8%)
Systolic blood pressure, median (IQR)	18,545 (13.5%)
Family history of CHD	20,905 (15.2%)
Hospital catheter lab status	0 (0%)
Low molecular weight heparin	17,137 (12.5%)
Warfarin	21,183 (15.4%)
Loop Diuretic	20,975 (15.3%)

Glycoprotein use	18,440 (13.4%)
Aspirin	15,892 (11.6%)
P2Y12 inhibitors	2,687 (2.0%)
Statins	16,980 (12.4%)
ACE inhibitors	19,825 (14.4%)
Beta-Blockers	18,066 (13.2%)
Death	0 (0%)
Cardiac mortality	0 (0%)
Reinfarction	7,254 (5.3%)
Major bleeding	3,195 (2.3%)

BMI= body mass index, CHD, coronary heart disease, CCF= congestive cardiac failure

Appendix Table 5: Missing information on each variable used in the analysis

Variables	Number	Percentage
Age	0	0%
Male (%)	0	0%
Caucasians (%)	0	0%
Body mass index median [IQR]	273,226	60%
Heart rate, bpm, median (IQR)	54,046	11.9%
Systolic blood pressure, median (IQR)	54,375	12.0%
ECG changes	10,812	2.4%
Troponin positive	12,840	2.8%
Out of hospital cardiac arrest	22,697	5.0%
Creatinine, median (IQR)	50,345	11.1%
Seen by cardiologist	26,891	6.0%
Left ventricular systolic function	271,650	60.1%
GRACE risk score	271,813	60.1%
Percutaneous coronary intervention	27,614	6.1%
Coronary artery bypass graft	26,656	5.9%
Heart failure	29,545	6.5%
Hypercholesterolemia	31,296	6.9%
Angina	26,891	6.0%
Cerebrovascular disease	28,454	6.3%
Peripheral vascular disease	34,518	7.6%
Chronic renal failure	29,335	6.5%
Diabetes	9,063	2.0%
Hypertension	23,115	5.1%
Smoking status	28,328	6.3%

Asthma / COPD	30,705	6.8%
Family history of CHD	98,104	21.7%
Low molecular weight heparin	49,885	11.0%
Warfarin	62,116	13.7%
Loop Diuretic	60,766	13.4%
Glycoprotein use	56,663	12.5%
Coronary angiography	59,381	13.1%
Receipt of PCI	94,256	20.8%
Aspirin	97,573	21.6%
P2Y12 inhibitors	110,989	24.5%
Statins	9,656	2.1%
ACE inhibitors	111,209	24.6%
Beta-Blockers	11,828	2.6%
In-hospital mortality	0	0%
Cardiac mortality	0	0%
Bleeding	10,395	2.3%

Appendix Table 6: Baseline characteristics of patients with GRACE risk score >140 stratified into different levels of hospital catheter laboratory facilities.

Variables	**No lab 21,226 (21.0%)**	**Diagnostic (offsite) 5,184 (5.8%)**	**Diagnostic (Onsite) 18,634 (18.5%)**	**PCI hospitals 55,224 (54.7%)**	**P value**
Age	80 [74-86]	76 [70.1-81]	82 [75-87]	73[73-85]	<0.001
Male (%)	12,136 (57.8%)	3,767 (64.8%)	10,012 (53.7%)	33,318 (56.3%)	<0.001
Caucasians (%)	18,287 (86.2%)	5,240 (90.1%)	16,647 (89.3%)	46,015 (83.3%)	<0.001
BMI median [IQR]	26.1 [23.1-30.1]	27.5 [24.4-30.8]	25.8 [22.6-29.5]	26.5 [23.5-30.1]	0.0001
Presenting Characteristics					
Heart rate, bpm, median (IQR)	82 [69-98]	79 [67-95]	83 [70-98]	80 [68-96]	<0.001
Systolic blood pressure, median (IQR)	137 [118-158]	140 [121-160]	136 [118-156]	137 [118-157]	0.001
ECG changes	17,432 (82.1%)	4,926 (84.7%)	15,303 [82.1%)	46,223 (83.7%)	0.001
Troponin positive	20,598 (97.0%)	5,737 (98.7%)	18,156 (97.4%)	53,532 (96.9%)	0.001
Out of hospital cardiac arrest	311 (1.5%)	76 (1.3%)	210 (1.1%)	1,003 (1.8%)	<0.001
Creatinine, median (IQR)	102 [84-133]	97 [83-120]	103 [84-136]	101 [83-133]	<0.001
Seen by cardiologist	18,448 (88.6%)	5,651 (98.4%)	1,791 (90.2%)	51,727 (94.6%)	<0.001
Left ventricular systolic function					<0.001

Good	5,087 (49.5%)	1,550 (58.2%)	4,783 (50.4%)	15,199 (51.5%)	
Moderate	3,375 (32.9%)	789 (29.6%)	3,015 (31.8%)	9,658 (32.7%)	
Poor	1,812 (17.6%)	322 (12.1%)	1,696 (17.8%)	4,658 (15.8%)	
Previous medical history					
Percutaneous coronary intervention	2,551 (12.3%)	862 (15.4%)	1,715 (9.8%)	8,798 (16.4%)	<0.001
Coronary artery bypass graft	2,142 (10.2%)	682 (12.2%)	1,820 (10.4%)	6,709 (12.5%)	<0.001
Heart failure	2,665 (12.8%)	368 (6.6%)	2,358 (13.5%)	6,211 (11.5%)	0.001
Hypercholesterolemia	6,459 (31.4%)	2,291 (14.3%)	5,917 (34.1%)	20,539 (38.8%)	<0.001
Angina	8,210 (39.4%)	2,292(41.0%)	7,438 (42.5%)	20,042 (37.3%)	0.001
Cerebrovascular disease	3,107 (14.9%)	533 (9.5%)	2,755 (15.7%)	7,384 (13.7%)	<0.001
Peripheral vascular disease	1,395 (6.7%)	328 (5.9%)	1,213 (7.0%)	4,156 (7.8%)	<0.001
Chronic renal failure	2,953 (14.2%)	503 (9.0%)	2,406 (13.8%)	7,957 (14.8%)	0.04
Diabetes	6,394 (30.4%)	1,741 (30.2%)	5,389 (29.2%)	17,111 (31.3%)	0.001
Hypertension	13,336 (63.8%)	3,658 (65.2%)	11,058 (62.9%)	35,278 (65.4%)	0.001
Smoking status					<0.001
Previous smoker	8,624 (43.5%)	2,477 (43.8%)	7,256 (40.9%)	22,465 (43.0%)	
Current smoker	2,357 (11.9%)	851 (15.0%)	1,941 (10.9%)	6,354 (12.2%)	
Asthma / COPD	4,270 (20.5%)	1,029 (18.4%)	3,832 (21.9%)	10,301 (19.1%)	0.001
Family history of CHD	2,678 (17.3%)	1,140 (25.5%)	2,081 (15.8%)	9,523 (20.7%)	<0.001
In-hospital Pharmacology					
Low molecular weight heparin	10,687 (53.8%)	2,444 (44.8%)	9,211 (52.8%)	25,957 (51.0%)	<0.001
Warfarin	1,799 (9.2%)	350 (6.5%)	1,885 (10.9%)	4,465 (8.9%)	<0.001
Loop Diuretic	8,199 (41.5%)	1,600 (29.6%)	7,781 (44.8%)	20,776 (41.2%)	<0.001
Glycoprotein use	367 (1.9%)	166 (3.1%)	125 (0.7%)	1,860 (3.6%)	<0.001
Coronary angiography use	9,368 (62.0%)	5,814 (100%)	5,217 (45.0%)	32,396 (72.0%)	<0.001
Receipt of PCI	3,440 (25.6%)	1,446 (49.9%)	1,175 (9.3%)	18,653 (38.9%)	<0.001
Discharge Medications					
Aspirin	13,077 (87.5%)	2,233 (96.2%)	12,709 (85.0%)	44,909 (92.7%)	<0.001
P2Y12 inhibitors	11,853 (83.0%)	2,106 (91.5%)	11,538 (79.8%)	41,334 (87.6%)	<0.001
Statins	13,095 (89.8%)	2,219 (95.6%)	13,336 (90.0%)	43,969 (92.0%)	<0.001
ACE inhibitors	11,041 (76.9%)	1,982 (86.7%)	10,630 (72.9%)	37,169 (79.5%)	<0.001
Beta-Blockers	11,563 (78.3%)	1,961 (85.2%)	11,785 (78.8%)	39,606 (82.7%)	<0.001

ECG changes= ST –depression, transient ST elevation, T wave inversion, GRACE = Global Registry of Acute Coronary Event, ACE= angiotensin converting enzyme PCI= Percutaneous coronary intervention, BMI= body mass index

Appendix Table 7: Missing information on each variable used in the analysis

Variable	Missing information
Age (y), mean (SD)	0
Male, n(%)	0
BMI mean, (SD)	132,067 (38.5%)

Hypercholesterolemia (%)	19,947 (5.8%)
Hypertension (%)	19,946 (5.8%)
Diabetes (%)	11,863 (3.46%)
Previous CABG (%)	103,843(30.3%)
Previous CVA (%)	19,946 (5.8%)
Peripheral vascular disease (%)	19,947 (5.8%)
Previous AMI (%)	21,484 (6.3%)
Previous PCI (%)	10,166 (3%)
LVSD (%)	157,073 (45.8%)
Smoking (%)	29,648 (8.6%)
Renal Failure (%)	20,933 (6.1%)
Indication for PCI	2,561 (0.75%)
Operator status	38,761(11.3%)
Multi vessel PCI (%)	4,467 (1.3%)
Cardiogenic Shock (%)	124,582 (36.3%)
Pharmacological Inotropes	18,163 (5.3%)
Intra-aortic balloon pump device (%)	18,163 (5.3%)
Left main stem PCI (%)	4,467 (1.3%)
Mechanical ventilation (%)	45,154 (13.2%)
PCI to Grafts	4,467 (1.3%)
Chronic total occlusion PCI	22,449(6.5%)
Stent Use	12,182(3.5%)
Bivalirudin (%)	28,913 (8.4%)
GP2b3a use (%)	28,913 (8.4%)
Ticagrelor (%)	28,912 (8.4%)
Prasugrel (%)	28,912 (8.4%)
Warfarin (%)	28,916 (8.4%)
In hospital death (%)	8,062 (2.3%)
MACE (%)	10,558 (3.0%)
Major Bleeding (%)	10,552 (3.0%)
In-hospital stroke	10,558 (3.0%)
30-day mortality (%)	62,282 (19.6%)

MACE=major adverse cardiovascular events defined as composite of in-hospital mortality, in-hospital myocardial infarction or re-infarction and revascularization- emergency PCI or CABG, HTN= hypertension, AMI= acute myocardial infarction, LVDS= left ventricular systolic dysfunction, PVD= peripheral vascular disease, PCI= percutaneous coronary intervention, CABG= coronary artery bypass graft, IABP= intra-aortic balloon pump,LMS= left main stem, BMS= bare metal stent, DES= drug-eluting stent.BMI=body mass index

Appendix Table 8: Baseline characteristics and procedural details of patients undergoing left and right radial percutaneous coronary intervention in the United Kingdom after excluding patients with a previous history of coronary artery bypass grafting.

	Right Radial access n=258,039	Left Radial access n=10,986	P value

Age (y), mean (SD)	64.0±11.8	66.4±11.0	<0.001
Male, n(%)	197,206 (76.4%)	8,143 (74.1%)	<0.001
BMI mean, (SD)	28.5±5.18	29.2±5.61	<0.001
Hypercholesterolemia (%)	137,880 (55.5%)	7,338 (68.9%)	<0.001
Hypertension (%)	134,098 (54%)	7,167 (67.2%)	<0.001
Diabetes (%)	46,339 (18.5%)	2,970 (27.7%)	<0.001
Previous CVA (%)	9,743 (3.9 %)	780 (7.3%)	<0.001
Peripheral vascular disease (%)	11,140 (4.5%)	1,351 (12.7%)	<0.001
Previous AMI (%)	57,040 (25.3%)	4,726 (45.6%)	<0.001
Previous PCI (%)	50,413 (19.9%)	4,149 (38.4 %%)	<0.001
LVSD (%)	35,858 (27.4%) (30.1%)	2,164 (34.0%)	<0.001
Smoking (%)			
Never smoked	82,779(35.0%)	3,383(33.3%)	
Current smoker	91,013(38.5%)	4,861(48%)	
Ex-smoker	62,475(26.4%)	1,891(18.7%)	
Renal Failure (%)	1,826 (0.7%)	165 (1.6%)	<0.001
Indication for PCI			
Stable Angina (%)	89,065 (34.7%)	5,031(46.4%)	
STEMI (%)	101,107 (39.4%)	4,684 (43.2%)	
UA/NSTEMI	66,095 (25.8%)	1,310 (10.4%)	
Operator status			
Consultant	169,662 (69.4%)	3,433 (67%)	<0.001
Trainee	74,789 (30.6%)	3,433 (33.0%)	<0.001
Multi vessel PCI (%)	34,605 (13.5%)	1,602 (14.8%)	<0.001
Cardiogenic Shock (%)	3,027 (1.8%)	125 (2.1%)	0.07
Pharmacological Inotropes	1.036 (0.4%)	59 (0.5%)	0.03
Intra-aortic balloon pump device (%)	1,559 (0.6%)	52 (0.5%)	0.07
Left main stem PCI (%)	7,070 (2.8%)	633 (5.8%)	<0.001
Mechanical ventilation (%)	2,036 (0.9%)	139 (1.4%)	<0.001
Chronic total occlusion PCI	13,848 (5.7%)	702 (6.7%)	<0.001
Stent Use			
No Stents (%)	16,268 (6.5%)	1,109 (10.4%)	
BMS only (%)	44,989 (18%)	1,709 (16.0%)	
DES only (%)	181,274 (72.4%)	7,531 (70.5%)	
BMS & DES (%)	7,836 (3.1%)	319 (3.0%)	
Bivalirudin (%)	11,738 (4.8%)	189 (1.8%)	<0.001
GP2b3a use (%)	77,681 (25.0%)	2,248 (16.7%)	<0.001
Ticagrelor (%)	19,087 (7.8%)	674 (6.4%)	<0.001
Prasugrel (%)	14,934 (6.1%)	408 (3.9%)	<0.001
Warfarin (%)	2,708(1.1%)	300 (2.9%)	<0.001
In hospital death (%)	1,821 (0.7%)	96 (0.9%)	0.04
MACE (%)	3,535 (1.4%)	179 (1.6%)	0.02
Major Bleeding (%)	1,305 (0.41%)	75 (0.54%)	0.02
In hospital Stroke	311 (0.12%)	9 (0.08%)	0.250
30-day mortality (%)	3,808 (1.5%)	202 (1.8%)	0.002

MACE=major adverse cardiovascular events defined as a composite of in-hospital mortality, in-hospital myocardial infarction or re-infarction and revascularization- emergency percutaneous coronary intervention or CABG, LVSD= left ventricular systolic dysfunction, CABG= coronary artery bypass grafting, AMI= acute myocardial infarction, PCI= percutaneous coronary intervention

Appendix Table 9: Adjusted outcomes following Left radial versus right radial access after excluding patients with a previous history of CABG

Clinical outcomes	Odds ratio (95%CI)	p-value
In hospital death	1.11 (0.85-1.44)	0.82
Major bleeding	1.01 (0.791.52)	0.56
In hospital stroke	0.43 (0.15-1.17)	0.10
MACE	1.03 (0.84-1.26)	0.74
30- day mortality	1.06 (0.85-1.32)	0.56

MACE=major adverse cardiovascular events defined as a composite of in-hospital mortality, in-hospital myocardial infarction or re-infarction and revascularization- emergency percutaneous coronary intervention or CABG

Appendix Table 10: Predictors of Left radial access after excluding patients with a previous history of CABG

Predictor	Odds ratio (95%CI)	p-value
Female	1.01 (1.00-1.01)	<0.001
Repeat Procedures	1.30(1.22-1.37)	<0.001
Previous AMI	1.77 (1.65-1.90)	<0.001
Peripheral vascular disease	2.02 (1.84-2.21)	<0.001
Mechanical ventilation	2.09 (1.71-2.56)	<0.001
Renal Failure	1.57(1.26-1.95)	<0.001

CABG= coronary artery bypass grafting, AMI= acute myocardial infarction, PCI= percutaneous coronary intervention

Clinical Lead or appropriate project scientific committee chairman *The clinical lead / chair of an appropriate audit or outcome review programme scientific committee confirms that the information included within this application would represent a clinically appropriate usage of the data requested*	Name: Clive Weston Position: Clinical Lead, MINAP Signature: 
Audit / Data Provider Releasing Data: *The provider confirms to the extent of its involvement that the information included within this application would represent a methodologically appropriate usage of the data requested. Where personal data has been requested, the provider confirms that an*	Name: Mr James Chal Position: NICOR Chief Operating Officer Signature: 

10.3 Appendix III: Thesis related publications

June 2018 CME:

Incidence, determinants and outcomes of left and right radial access use in patients undergoing percutaneous coronary intervention in the United Kingdom, a national perspective using the British Cardiovascular Intervention Society (BCIS) dataset

Muhammad Rashid[1,2], Mamas A Mamas[1,2]

1. Keele Cardiovascular Research Group, Centre for Prognosis Research, Institute of Primary Care and Health Sciences, Keele University, UK
2. Academic Department of Cardiology, Royal Stoke Hospital, University Hospital North Midlands, Stoke-On-Tent, UK

Learning Objectives:

- Appraise the risks and benefits associated with different vascular access sites for performing the percutaneous coronary intervention.
- Recognise the anatomical variations associated with left radial access and right radial access.
- Compare the procedural advantages between left and right radial access and their association with clinical benefits.

Questions:

1. **Radial access is associated with all of the following except:**
   - **a)** Reduced access-site related vascular complications
   - **b)** Increased risk of stroke
   - **c)** Reduced length of stay in hospital
   - **d)** Reduced bleeding complications.
   - **e)** Longer learning curve.

Radial artery is a smaller superficial artery which is easily compressible compared to the femoral artery. The most obvious benefits of radial access include the reduced access site related vascular complications, bleeding complications and early patient ambulation. Consequently, the length of stay in a patient managed via radial access is much shorter compared to those treated via femoral. RW.ERROR - Unable to find reference:575 In one the largest trials to date comparing TRA versus TFA, the MATRIX (Minimising Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX) trial reported a 28% reduction in mortality (1.6% vs. 2.2%; p = 0.045) with a reduction in net adverse clinically events (9.8% vs. 11.7%; p = 0.009) mainly driven by a marked reduction in Bleeding Academic Research Consortium3 or 5 major bleeding in the TRA group[73]. Shortly afterwards, an updated trial sequential analysis of randomized trials reported that radial access significantly reduces mortality by 27%, MACE by 14%, access site bleeding by 63% and major bleeding by 40%, with no significant effects on recurrent myocardial infarction and stroke in randomised trials of patients managed invasively[70]. Given the anatomical challenges such as small artery size, radial loops and tortuosity, radial access is associated with a slightly longer learning curve than femoral access particularly early in training[226]. Finally, we previously reported that the risk of stroke is actually quite comparable between transfemoral and trans-radial access[224].

2. **Potential benefits of left radial access include all except**
    a) Better access to LIMA graft
    b) Lesser tortuosity and radial loops in the arm
    c) Increase operator comfort
    d) Reduced contrast and fluoroscopy time
    e) Faster learning curve

Left radial access offers better access to LIMA graft compared to right radial access. Studies have shown that left radial access has a smaller incidence of radial loops and also offer favourable anatomy similar to femoral access particular in shorter patients[210]. Consequently, there is some evidence that left radial access may be quicker in the early stages of learning and reduces contrast and fluoroscopy time[76,212,215,223]. Sciahbasi at al randomised 1,547 patients to either left radial or right radial access whereby procedures were performed by training fellows or senior cardiologists. Six fellows performed 532 procedures, 260 through the RRA and 272 through the LRA. During the training period, fellows showed a progressive significant reduction in fluoroscopy time for the LRA over the 3 stages from 258 seconds in the first stage to 142 seconds in stage 3, whereas for the RRA, only a slight and non-significant reduction in fluoroscopy time was observed[227].

3. **In this study, which of the following was associated with the use of left radial access**
    a) Increase vascular complications
    b) Increased risk of stroke
    c) Increased MACE
    d) Increased mortality
    e) Reduced risk of stroke

Stroke is a very rare but serious complication associated with PCI. In this study, left radial access was associated with a significant reduction in in-hospital stroke ((OR 0.52 95%CI 0.37-0.82, p=0.005). This is likely due to the fact that in RRA access, the anatomical variations such as increased incidence of tortuosity and loops in the arm and subclavian artery may require extra catheter manipulation. Additionally, during RRA access the catheter needs to be passed from the innominate artery into the ascending aorta where the right carotid comes off resulting in a theoretically increased risk of embolization of plaque into the right carotid artery resulting in an embolic stroke. In contrast, LRA access offers very similar anatomy to the TFA approach as the left common carotid artery arises directly from the aortic arch.

4. **In the current study, switch from right radial access to femoral access was significantly higher in**
    a) Young men
    b) Men presenting with NSTEMI
    c) Women
    d) Chronic total occlusion procedures
    e) Taller patients

In this study, we found that when RRA is used at the first procedure, future use of the RRA for PCI drops by 28% overall, by 35% in females and 27% in patients aged >75 at a second procedure with a concomitant increase mainly in the use TFA access.

5. **Which of the following is not a predictor of left radial access?**

a) Repeat PCI procedure
b) Vein graft PCI
c) Renal failure
d) Previous CABG
e) Male sex

In this study, we found that independent predictors of left radial access use repeated PCI procedure, vein graft PCI, Previous AMI, peripheral vascular disease, mechanical ventilation, renal failure, previous CABG and female gender.

Accompanying editorial

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EDITORIAL COMMENT

Who's a-Gonna Hold Your Hard Luck Hand and Who's a-Gonna Be Your Man

Bob Dylan, "Kingsport Town"*

Ferdinand Kiemeneij, MD, PhD, Ahmed A. Hassan, MD

In this issue of *JACC: Cardiovascular Interventions*, Rashid et al. (1), in their analysis of left radial approach (LRA) and right radial approach (RRA) for percutaneous coronary intervention, have found the answer to Bob Dylan's question in his song "Kingsport Town."

Since the first transradial coronary intervention (TRI) in 1992 (2), the right radial artery is used as default, despite the fact that most patients are right handed and despite the fact that, as a consequence, LRA is more patient friendly. The only explanation for this preference for RRA is quite trivial and banal—it is easier for the operator who works on the right side of the table.

Since the early years of TRI, many studies have questioned the clinical superiority of one or both approaches. There is evidence that LRA carries procedural advantages in terms of fewer catheters used and less catheter manipulation, fluoroscopy time, and contrast used (3–5), especially in cases in which coronary bypasses and left internal mammary artery grafts are present and in case of tortuosity and calcification of the right subclavian artery (6).

The study of Rashid et al. is interesting, as it provides insights at a national level with a considerable sample size of 342,806 patients. The study has a high quality of performance, despite the obvious limitations as pointed out by the authors. The results demonstrate, despite slight positive outcomes for LRA in previous studies, the infrequent use of LRA (4%) for percutaneous coronary intervention compared with RRA (96%). Those results resonate with the common practice in different countries in which RRA is the method of choice when performing TRI. The results of this large national analysis show no significant difference in major clinical outcomes between LRA and RRA when utilizing multivariable logistic regression analysis.

The use of propensity score matching demonstrated a significant difference in rates of in-hospital stroke incidence in favor of LRA, a very important message of this analysis. With the necessary caution interpreting registry data lacking the active follow-up approach to track endpoints in contrast to prospective randomized controlled trials, the large number of patients in this study provides reliable results. The positive outcome concerning in-hospital stroke incidence is remarkable considering the unfavorable cardiovascular characteristics in the group undergoing LRA such as peripheral vascular disease, previous myocardial infarction, renal failure, older age, increased incidence of diabetes, and previous cerebrovascular events. The advantageous outcome for LRA is probably due to less catheter manipulation as well as the direct origin of left common carotid artery from the aortic arch, as the authors have justly stated.

A disturbing finding is that about one-third of patients who had previous percutaneous coronary intervention via RRA had a next procedure via femoral approach. This was especially the case among women and elderly patients. Information about right radial artery patency is lacking in this analysis, as well as data concerning previous diagnostic coronary angiography. Such information would provide significant insights regarding the decision of access

*Editorials published in the *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the Department of Cardiology, MC Zuiderzee Hospital, Lelystad, the Netherlands. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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10.4 Application for data approval confirmation

The data approval from HQIP is provided below.

Data Access Request Form (DARF)

Applicants should ensure that they have reviewed the accompanying HQIP guidance *Accessing National Clinical Audit and Patient Outcomes Programme Data: Guidance for Applicants and Data Providers* and have discussed this request with the organisation(s) commissioned by HQIP to deliver the relevant clinical audit or clinical outcome review programme. The audit or outcome review programme acts as data processor to HQIP and is referred to below as the 'data provider' for the purpose of this data access request.

All sections within this form are mandatory unless specifically stated otherwise. Unless this form is completed in full, it will be returned to the applicant which will extend the time to data receipt

For HQIP use only			
HQIP Application number:	**16-MNP-02** **Amendment**	**Date of original submission to HQIP (dd/mm/yy):**	**08/02/2017**
Summary of submission history ***(if applicable)***	08/02/17 Application received - incomplete 27/02/17 Received complete application 16/3/17 Tabled at DARG 29/03/17 Requested clarifications from applicant (not anonymised data, need ethics approval/clinical lead signature/signed DSA) 27/04/17 Tabled at DARG and approved 03/05/17 Emailed to inform them the DARF is approved & requested signed DSA 04/05/17 Signed DSA received 29/11/18 Amendment application received. Some clarifications required. Section 1 – I see a comment but the application doesn't look like this has been updated and Kathleen removed Section 2 – Is it and extension or amendment? Both boxes are ticked. Can you provide further info in the box at the bottom? Section 8 – again comments need updating?		

SSECTION 1	APPLICANT INFORMATION
Title of project	Impact of timing of coronary angiography in patients admitted following non-ST elevation acute coronary syndromes.
Name of applicant	Keele Cardiovascular Research Group, Keele University
	Guy Hilton Research Centre

Address of applicant organisation(s):	Thornburrow Drive, Hartshill Stoke-on-Trent ST4 7QB UK			
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Telephone:	**01782671621**	**Email:**	**Doctorrashid7@gmail.com**	
Organisation type	**NHS**	**Academic**	**Healthcare**	**Other**
	☐	☒	☐	☐
	Local Authority	**Individual Citizen(s)**	**Commercial body**	**Other** *(please state)*
	☐	☐	☐	
HQIP data provider(s)	*Please list below the names(s) of each of the NCAPOP projects(s) from which you are requesting data. For reference, a list of NCAPOP projects and their Project Managers are listed on*			
	MINAP Name: **Akosua Donkor** Org: NICOR HQIP contact Tasnoom Hossain			

Section 23	**Authorised Signatories**
Please note that this agreement is not valid until all parties have signed and agreed this document, and (if applicable) the HQIP Data Sharing has also been	
Applicant *The applicant confirms that the above is accurate, valid and true. HQIP reserves the right at all times to confirm that is so. The applicant will give HQIP all reasonable assistance and access in*	Name: Prof. Mamas A Mamas Position: Professor of Cardiology Address: ISTM, Guy Hilton Research Centre, Keele University, Thornburrow Drive, Hartshill, Stoke-on-Trent, ST4 7QB Email: mamasmamas1@yahoo.co.uk