# **Addressing disparities of care in non-ST-segment elevation myocardial infarction (NSTEMI) patients without standard modifiable risk factors: insights from a nationwide cohort study**

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No conflicts of interest

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### **Data Availability**

The authors do not have authorization to share the data, but it can be accessed through contacting the National Institute for Cardiovascular Outcomes Research (NICOR) upon approval.

### **Authorship**

SM and MM contributed to the conception and design of this work and drafted the first manuscript. MR, JN, KN, LYS, PV, SBW, ASV, and CPG critically revised and drafted the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

### **Ethics:**

Secondary use of anonymised MINAP dataset for research purposes is authorised under 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. Therefore, a formal ethical approval was not sought for this study.

**Abstract**

**Background:** The importance of standard modifiable cardiovascular risk factors (SMuRFs) in preventing non-ST segment myocardial infarction (NSTEMI) is established. However, NSTEMI may present in the absence of SMuRFs, and little is known about their outcomes.

**Methods & Results:** We analysed 176,083 adult (≥18 years) hospitalisations with NSTEMI using data from the United Kingdom (UK) Myocardial Infarction National Audit Project (MINAP). Clinical characteristics and all-cause in-hospital mortality were analysed according to SMuRF status, with 135,223 patients presenting with at least one of diabetes, hypertension, hypercholesterolemia or current smoking status and 40,860 patients without any SMuRFs. Those with a history of coronary artery disease were excluded. Patients without SMuRFs were more frequently older (median age 72 year vs. 71 years, P<0.001), male (62% vs. 61%, P<0.001) and Caucasian (95% vs. 92%, P<0.001). Those without SMuRFs less frequently received statins (71% vs. 81%, P<0.001), had their left ventricular function recorded (62% vs. 65%, P<0.001) or for those with moderate or severe left ventricular systolic dysfunction were prescribed angiotensin converting enzyme inhibitors/angiotensin receptor blockers (80% vs. 85%, P<0.001). Following propensity score matching the odds of all-cause mortality (OR: 0.85, 95% CI: 0.77-0.93), cardiac mortality (OR: 0.85, 95% CI: 0.76-0.94) and MACE (OR: 0.85, 95% CI: 0.77-0.93) were lower in patients without SMuRFs.

**Conclusion:** More than one in five patients presenting with NSTEMI had no SMuRFs, who were less frequently received guideline recommended management and had lower in-hospital (all-cause and cardiac) mortality and MACE than patients with SMuRFs.

**Key Words:** NSTEMI, SMuRF, Mortality, Care

**Graphical Abstract**

**Text

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SMuRF; standard modifiable cardiovascular risk factors, NSTEMI; non-ST-segment myocardial infarction, MACE; major adverse cardiovascular events, CVA; cerebrovascular accident ACEi/ARB; angiotensin converting enzyme inhibitor/angiotensin receptor blockers, LVSD; left ventricular systolic dysfunction, ICA; invasive coronary angiogram, CABG surgery; coronary artery bypass grafting surgery, PCI; percutaneous coronary intervention

\* MACE is defined as composite endpoint of in-patient mortality and reinfarction

**Introduction**

Primary and secondary prevention therapies for cardiovascular diseases (CVD) are targeted at treating the standard modifiable cardiovascular risk factors (SMuRFs) of diabetes, hypertension, hypercholesterolemia and smoking1, 2 as well as reducing subsequent ischaemic events.

Patients without standard modifiable risk factors, coined as SMuRF-less3 patients represent a clinically significant group that is often underrepresented in clinical trial publications. Whilst known risk factors are individually reported, often the proportion of patients with no risk factors are not. Data from the SWEDEHEART registry has shown that patients presenting with ST-segment elevation myocardial infarction (STEMI) in the absence of SMuRFs have a significantly increased risk of all-cause mortality compared to those with at least one SMuRF3. Whilst non-ST segment elevation myocardial infarction (NSTEMI) shares pathophysiological similarities with STEMI, has similar mortality outcomes4, and represents the majority of presentations of acute coronary syndrome (ACS)5, there are no studies looking at the outcomes of SMuRF-less patients presenting with NSTEMI, leaving a significant gap in knowledge of the outcomes of this large heterogenous group of patients.

Thus, using data derived from a nationwide registry of ACS from England and Wales, we investigated the characteristics, quality of care and outcomes of SMuRF-less patients presenting with NSTEMI.

## **Methods**

**Study design:**

We used the Myocardial Ischaemia National Audit Project (MINAP), a prospective national registry of patients admitted to hospitals in the UK with an acute coronary syndrome. The MINAP registry consists of over 130 variables including baseline demographics and clinical characteristics, comorbid conditions, management strategies, pharmacotherapy, place of care, in-hospital clinical outcomes and diagnoses on discharge6-8. Data are submitted by hospital clinical and clerical staff and approximately 90,000 pseudonymised records annually are uploaded to the National Institute for Cardiovascular Outcomes Research (NICOR).

**Study population:**

The sampling frame included patients admitted with NSTEMI to any of the 230 participating hospitals in England and Wales between 1st January 2010 to 31st March 2017. The discharge diagnosis of NSTEMI was determined by local clinicians according to 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 Cardiology9.

Patients with a known history of prior myocardial infarction, or coronary artery disease (previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery) were excluded from the analysis, allowing for comparisons with prior studies in this field. Missing records for baseline characteristics, mortality, and SMuRF status were excluded from the analysis (Supplementary Figure 1). The analytic cohort was dichotomised according to SMuRF status defined as one or more SMuRFs and SMuRF-less status including patients who did not have the risk factors of diabetes mellitus, hypercholesterolemia (patients with known elevation of serum cholesterol requiring dietary or drug treatment) , hypertension, or current smoking status (ex-smokers excluded).

**Quality indicators:**

We assessed care quality according to those European Society of Cardiology (ESC) quality indicators for acute myocardial infarction that were relevant to NSTEMI10. This included the use of invasive coronary angiography (ICA) within 72 hours of admission; the assessment of left ventricular (LV) function; the use of fondaparinux or low molecular weight heparin (LMWH); and the prescription of P2Y12 inhibition, dual antiplatelet therapy (DAPT) and statins on discharge. For patients with moderate and severe LV systolic dysfunction (LVSD), the use of angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) and beta blocker on discharge was also evaluated. The ESC QI for LVSD is defined as an ejection fraction (EF) less than or equal to 40%. The MINAP registry does not have the same cut off points for LVSD, thus moderate (EF<49%) and severe LVSD (EF<30%) were used as a surrogate. Furthermore, MINAP does not record the specific type or dose of statin prescribed so ‘statin prescription’ was used as a surrogate for high-intensity statin.

**Outcomes**

The primary outcomes were in-hospital all-cause mortality and in-hospital major adverse cardiovascular events (a composite endpoint of all-cause mortality and reinfarction). The secondary outcomes were in-hospital cardiac mortality (death attributable to myocardial ischaemia or infarction, heart failure and cardiac arrest of unknown cause), in-hospital reinfarction and in-hospital major bleeding (a composite of gastrointestinal, retroperitoneal and intracranial haemorrhage).

**Statistical Analysis:**

Baseline characteristics and management strategies were summarised according to the SMuRF status. Group wise comparisons were performed using Pearson’s chi squared, Student t-test or Mann-Whitney as appropriate. Gaussian continuous variables are expressed as mean ± standard deviation (SD); non-Gaussian continuous variables as median (IQR) and categorical variables as numbers and percentages.

Where data were missing, this was assumed to be at random and we applied multiple imputations using chained equations (MICE) with ten imputations of the dataset. For imputation, we applied linear regression models for continuous data, multinomial logistic regression for ordinal data and logistic regression for binary data. For each binary outcome of interest, multivariable logistic regression analysis was applied on imputed datasets to estimate the risk of adverse outcomes between groups. Estimates were combined using Rubin’s rules11. Propensity score matching (PSM) with the imputed data was used to estimate the average treatment effects (ATE) between the two cohorts. The groups were matched on age, sex, ethnicity, heart rate, blood pressure, serum creatinine concentration on admission (umol/L), Killip class, family history of coronary artery disease (CAD), ischaemic ECG changes, LVSD, comorbid conditions (history of cerebrovascular accident (CVA), peripheral vascular disease (PVD), asthma/chronic obstructive pulmonary disease (COPD, heart failure (HF), angina)), pharmacotherapy (prescription of LMWH warfarin, unfractionated heparin, GP IIb/IIIa inhibitor, intravenous nitrate, furosemide, aldosterone antagonist, fondaparinux, beta-blockers, ACEi/ARB's, aspirin, P2Y12 inhibitor, statins), cardiac arrest, procedures and investigations including ICA, PCI and CABG surgery during admission, type of admission ward, admission under cardiologist during first 24 hours, hospital, and year. One to one nearest-neighbour matching with replacement was applied, followed by logistic regression analysis (the sole predictor being group membership) to obtain the ATE over the multiple imputed datasets. Finally, the coefficients were converted to odds ratios.

Individual patient baseline risk was assessed using the Global Registry of Acute Coronary Events (GRACE) scoring systems. MINAP does not record GRACE score explicitly, so a validated method was utilised to calculate patients’ GRACE scores12.

**Factors associated with SMuRF-less status**

Multivariable logistic regression models were applied on the imputed dataset to identify independent predictors of SMuRF-less status

**Sensitivity Analysis:**

Using the imputed data, we fitted a series of hierarchical logistic regression models with patients nested within hospitals using maximum likelihood estimation, adjusting for (Model 1) age, sex, ethnicity, and year; (Model 2) Model 1 + heart rate, blood pressure, serum creatinine concentration on admission, Kilip class, cardiac arrest, family history of coronary artery disease (CAD), ischaemic ECG changes, LVSD, cerebrovascular accident, peripheral vascular disease, asthma/COPD, HF and history of angina), ICA, PCI and CABG surgery during admission; Model 3 (Model 2 + prescription of LMWH warfarin, un-fractionated heparin, GP IIb/IIIa inhibitor, intravenous nitrate, furosemide, aldosterone antagonist, fondaparinux, beta blockers, ACEi/ARB’s, aspirin, P2Y12 inhibitor, statins.

All statistical analyses were performed with Stata 14.2 (College Station, Texas, USA) with data anonymized. All statistical analyses were two-tailed, and an alpha of 5% was used throughout, without multiplicity adjustment

**Results**

**Baseline Characteristics:**

During the study period, there were 369,435 patients admitted to hospital in England and Wales with a diagnosis of NSTEMI. Applying the exclusion criteria of known history of AMI (128,320) and prior history of coronary revascularisation (22,292) (Supplementary Figure 1) left an analytical cohort of 176,083 patients. Of these, 40,860 (23%) had no SMuRFs.

The differences in clinical characteristics at admission between the two groups are presented in Table 1. Patients without SMuRFs more frequently were older (median age 72 years vs. 71 years, P<0.001), male (62% vs. 61%, P<0.001), Caucasian (95% vs. 92%, P<0.001), had moderate (16% vs. 13%, P<0.001) or severe (6% vs. 5%, P<0.001) LVSD, were prior smokers (43% vs. 32%, P<0.001) and more frequently were admitted under the care of a cardiologist in the first 24 following hospitalisation (53% vs. 51%, P<0.001). They were less likely to have chronic renal failure (4% vs. 8%, P<0.001), cerebrovascular disease (6% vs. 9%, P<0.001), peripheral vascular disease (2% vs. 5%, P<0.001) or have a family history of coronary artery disease (25% vs. 30%, P<0.001). There was a similar proportion presenting as a cardiac arrest (3.1% vs. 3.1%, P=0.69) and being stratified in the high-risk GRACE as defined by GRACE score >140 (75% vs. 75%, P=0.32) cohort between the two groups.

Pharmacotherapies, management strategies & unadjusted crude clinical outcomes for both cohorts are presented in Table 2. Patients without SMuRFs were less likely to receive furosemide (20% vs. 25%, P<0.001), calcium channel blockers (8% vs. 20%, P<0.001), ACEi/ARB (74% vs. 83%). They also less frequently received ICA (71% vs. 73%, P<0.001), PCI (45% vs. 47%, P<0.001) and CABG surgery (7% vs. 9%, P<0.001) compared with patients with SMuRFs.

**Quality indicators:**

With respect to the ESC QIs, of the patients who underwent ICA, SMuRF-less patients more frequently received this within a 72-hour time frame from admission (68% vs. 66%, P<0.001). There were lower proportions receiving statins on discharge (71% vs. 81%, P<0.001), having their LV function recorded (62% vs. 65%, P<0.001), or for those with moderate or severe LVSD, being prescribed ACEi/ARB’s (80% vs. 85%, P<0.001) on discharge (Table 3).

**Clinical Outcomes:**

Patients without SMuRFs had similar unadjusted in-hospital outcomes of mortality (5.0% vs. 4.8%, P=0.10), cardiac mortality (3.7% vs. 3.7%, P=0.42), reinfarction (0.7% vs. 0.8%, P=0.48) and MACE (5.5% vs. 5.4%, P=0.27) compared with those with one or more SMuRFs. After adjustment for differences in baseline clinical and treatment characteristics on propensity score matching, odds of all-cause mortality (OR: 0.85, 95% CI: 0.77-0.93), cardiac mortality (OR: 0.85, 95% CI: 0.76-0.94) and MACE (OR: 0.85, 95% CI: 0.77-0.93) were all lower in patients without SMuRFs (Table 4). Supplement Figure 4 shows the level of matching between the two cohorts in this analysis.

**Factors associated with “SMuRF-less” status:**

Independent factors associated with “SMuRF-less” status are presented in Supplementary Table 1. These patients were less likely to be female (OR: 0.88, 95% CI: 0.86-0.90), of Black (OR: 0.49, 95% CI: 0.43-0.56), Asian (OR: 0.53, 95% CI: 0.50-0.57) or other non-White ethnic minority groups (OR:0.69, 95% CI: 0.62-0.77), have a history of cerebrovascular accident (OR:0.59, 95% CI: 0.57-0.62), peripheral vascular disease (OR:0.38, 95% CI: 0.35-0.41) or family history of coronary artery disease (OR:0.80, 95% CI: 0.77-0.82). They were more likely to be older (OR: 1.01, 95% CI: 1.01-1.01).

Supplementary Figure 2 shows a forest plot of the primary outcomes of all-cause mortality and MACE utilising hierarchical logistic regression models with patients nested within hospitals. All 3 models demonstrated that odds of all-cause mortality and MACE were lower in patients without SMuRFs compared to those who had them.

There was no significant temporal variation with the proportion of SMuRF less patients varying from 21% to 23% in our study period (Supplementary Figure 3).

Supplementary Table 2 shows the unadjusted outcomes from the matched cohort. SMuRF-less patients had reduced overall mortality (4.4% vs 5.2%, P<0.001), cardiac mortality (3.3% vs 3.9%, P = 0.001), and MACE (4.9% vs 5.7%, P<0.001) compared to patients with one or more SMuRFs.

**Discussion:**

The results of this analysis of more than 175,000 patients hospitalised with NSTEMI reveal several important findings. After excluding patients with a known history of coronary artery disease, greater than one in five patients hospitalised with NSTEMI had no SMuRFs. Such SMuRF-less patients with NSTEMI typically were Caucasian, older and male, less co-morbid and were less likely to receive ICA, PCI and CABG surgery. They were less likely to be treated with optimal pharmacotherapy as stipulated by ESC quality indicators with lower proportions being discharged on a statin, and for those with moderate and severe LVSD being prescribed an ACEi/ARB on discharge. Following adjustment for baseline characteristics and management strategies, patients without SMuRFs had reduced in-hospital mortality (all-cause and cardiac) and in-hospital MACE.

SMuRF-less CAD patients represent a clinically significant group that present with ACS without any of the modifiable risk factors of hypertension, hypercholesterolemia, diabetes mellitus and smoking. A meta-analysis of 14 clinical trials utilising individual patient data for 122,458 patients reported that 17% of coronary heart disease patients had no SMuRFs13, 14, a proportion similar to that reported by *Figtree et al3*. In their multicentre analysis of 62,804 patients between 2005-2018, utilising the SWEDEHEART registry, they found no significant temporal variation in the proportion of SMuRF-less patients presenting with STEMI3. Whilst our study demonstrates no significant temporal variation of NSTEMI patients without SMuRFs, it suggests that greater than one fifth of patients presenting with NSTEMI have no “conventional” modifiable risk factors. SMuRF-less CAD patients represent an invisible group in both clinical trials and guidelines, with prior studies showing increased mortality in SMuRF-less STEMI patients compared to those with at least one SMuRF14.

Our analysis demonstrated that age was positively associated with SMuRF-less status, whilst female sex and race, with patients who were Black, Asian or of other non-white ethnic minorities (BAME) were identified as independent factors that were negatively associated with SMuRF-less status. BAME patients have previously been shown to have increased rates of diabetes mellitus, hypertension and hypercholesterolemia when presenting with NSTEMI compared to White British Caucasian patients8, whilst female sex has been associated with higher rates of hypertension and diabetes mellitus15. Patients with diagnoses of cerebrovascular accident and peripheral vascular disease were less likely to be associated with SMuRF-less status. This is not surprising, given they are conditions driven by atherosclerotic processes and the SMuRFs have been shown to be drivers of atherosclerosis16, 17.

We report significant differences in the use of guideline recommended pharmacotherapies according to SMuRF status. Patient who had no SMuRFs had less frequent use of ACEi/ARB both overall and for those with moderate and severe LVSD. The use of ACEi has been associated with improved survival and reduction of reinfarction with patients with myocardial infarction18. It is not clear why there are such differences in management based on SMuRF status as both American19 and European20 guidelines do not differ on the management of acute myocardial infarction based on cardiovascular risk factors. Similar discrepancies in the use of ACEi for SMuRF-less patients, albeit to a lesser degree, were also noted for STEMI patients3. It is likely that the use of ACEi/ARB is greater in patients with SMuRFs given the higher rates of hypertension in this group. Given the SMuRF-less cohort was older in our study, it is possible that they may have had other health issues that prelude the use of certain medications such as postural hypotension, frailty or interactions with other medications. Similarly, the use of statins on discharge for patients without SMuRFs was markedly less compared to those with SMuRFs. Whilst lower rates of hypercholesterolemia are the likely driver behind this, it is important to highlight that the use of statins has been shown to have an early and sustained survival benefit on patients with myocardial infarction and is a key secondary prevention strategy for patients with NSTEMI21, 22. Data from the *PROVE-IT-Trial*, have shown that an intensive lipid lowering statin regimen for patients with ACS has a prognostic benefit in reducing mortality and MACE, even in patients without raised cholesterol levels23.

Furthermore, we found patients without SMuRFs were less likely to receive ICA, PCI or have their LV function recorded in the notes than patients with SMuRFs. This is surprising as the median GRACE score between the two cohorts is similar and is often one of the main tools utilised to determine the use of an invasive strategy24. Whilst the SMuRF-less cohort were older at presentation, which may have resulted in a reduction in the use of invasive management, it is possible that the absence of conventional risk factors may have resulted in a perceived reduction in risk, thus resulting in less frequent use of an invasive strategy. Our analysis also showed that for both groups, over 30% of patients did not receive ICA within the 72-hour time frame as stipulated by the ESC guidelines. It is likely there are several institutional factors that account for this, as opposed to absolute differences between the cohorts based on SMuRF status. Our previous work with this registry has shown that logistic factors such as admission under a cardiologist25 or admission to a cardiac ward26 result in an increased proportion of patients obtaining optimal guideline-based therapies.

Following adjustment for baseline characteristics and management strategies, patients without SMuRFs had reduced odds of in-hospital mortality (all-cause and cardiac) and MACE. This is a key finding of our study, as prior literature has convincingly demonstrated an association between increased mortality and SMuRF-less status for patients presenting with STEMI3, 27, 28. Potential mechanisms to explain the increased mortality of SMuRF-less patients presenting with STEMI have included increased rates of life-threatening arrhythmias with greater frequency of presentation as a cardiac arrest 3. Our analysis demonstrates similar risk profiles between the groups with a similar median GRACE risk based on SMuRF status. Furthermore, the proportion of patients presenting with a cardiac arrest did not differ between the groups based on SMuRF-less status. It is possible that misclassification of NSTEMI and risk factor status in the MINAP registry would attribute in part to these findings. Furthermore, in our cohort of patients, SMuRF-less patients were more frequently older, Caucasian men, a normally hard-to-miss population for the diagnosis of CAD and related risk factors. It is likely that the lack of health seeking behaviour may have led to missed opportunities for identifying SMuRFs in this group, where this subset of patients is often well with few comorbidities until their first hospitalization29.

Our analysis has several clinical implications for practice. There is a misconception that coronary artery disease is an often-self-induced problem, with the main solution being the appropriate management of standard modifiable risk factors. Whilst population-based data such as the INTERHEART study have had an important societal effect and helped shape health policy, misunderstanding of the results may have led to reduced efforts to unravel new mechanisms, risk factors and biomarkers of disease30-32. The study concluded that nine conventional risk factors explained >90% of premature myocardial infarction, commonly misunderstood as saying that other cardiovascular risk factors can only account for a small remaining fraction of disease, at most 10%30-32. Our study is the first to identify that there are differences of in-hospital mortality of SMuRF-less patients between STEMI and NSTEMI patients. This is important, as whilst mechanisms are unlikely to be derived from observational data, investigation into subtle differences in the pathophysiology and differences in specific biomarkers between patients who present with STEMI vs. NSTEMI may provide further insight into aetiology and allow for better understanding of the characteristics of SMuRF-less patients. Furthermore, our study highlights that a large proportion of NSTEMI patients do not have any SMuRFs, and greater efforts should be made around the provision of guideline directed medical therapy (GDMT) in this patient group. This is particularly apparent in the use of ACEi for patients with impaired LV function. Data from the PROMETHEUS multicentre observation registry has shown use of GDMT is associated with significantly lower risk of 1-year MACE and mortality35. Crucially patients in the SMuRF-less group had higher rates of moderate and severe LVSD further highlighting the importance of optimal GDMT in this group.

There are a number of important limitations common to observational studies of this type. The MINAP data collection shares the weakness of other national registries, including self-reporting of adverse events where there is no external validation of these. Although the MINAP dataset included important clinical and demographic variables of interest, there are limitations to data collected. For instance, the database does not capture frailty score or index, severity of coronary artery disease, socioeconomic or psychosocial risk factors, access to use of health care, the rationale for specific medications or an exhaustive list of comorbid conditions. Furthermore, the database does not capture markers of inflammation, biomarkers, LDL-c levels, or less common risk factors such as malignancy, lipoprotein(a) or clonal haematopoiesis of indeterminate potential. Whilst the MINAP database does include ex-smoking history and family history of coronary artery disease (CAD) as variables, we chose not to change the definition of the SMuRF status to include this in order to make meaningful comparisons to previous literature with the standard definition not inclusive of this. The MINAP database only records in-hospital clinical outcomes and it is likely that long term follow-up data may reveal further differences in the crude clinical outcomes and management of patients by SMuRF status. Given our inclusion/exclusion criterion excluded patients with known coronary artery disease, a large proportion of patients were excluded from the analysis which may limit the generalizability of the results. In addition, given the size of our study, some statistically significant results do not represent a significant clinical difference between the groups. Finally, some cases of NSTEMI may have been misdiagnosed or misclassified as a type 2 myocardial infarction.

**Conclusion:**

Our study demonstrated that from 2010 to 2017, more than one fifth of NSTEMI presentations had no standard cardiovascular modifiable risk factors. Patients without SMuRFs had reduced in-hospital mortality (all-cause and cardiac) and MACE compared to those with SMuRFs. They were less likely to receive guideline directed medical therapy (particularly in the use of ACEi), optimal pharmacotherapy (statins) and less frequently treated invasively. Substantially more work is needed to raise the awareness of this group of patients, and further studies are required to look at differences in aetiology and pathophysiology between patients SMuRF-less patients and those presenting with known risk factors.

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**Table 1: Clinical characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **≥ 1 SMURF (n=135,223)** | **SMURF-less (n=40,860)** | **P-Value** |
| Age (years) | 71 (59-81) | 72 (60-82) | <0.001 |
| Women (%) | 59,194/135,223 (39%) | 15,406/40,860 (38%) | <0.001 |
| Caucasians (%) | 124,117/135,223 (92%) | 39,964/40,860 (95%) | <0.001 |
| BMI median [IQR] | 27 (24-31) | 26 (24-30) | <0.001 |
| **Killip class** |  |  |  |
| No Heart failure | 68,505/87,505 (78%) | 21,349/26,161 (82%) | <0.001 |
| Basal crepitations | 13,568/87,805 (16%) | 3,666/26,161 (14%) | <0.001 |
| Pulmonary oedema (%) | 5,250/87,805 (6%) | 1,030/26,161 (4%) | <0.001 |
| Cardiogenic shock (%) | 482/87,805 (0.6%) | 116/26,161 (0.4%) | <0.001 |
| GRACE score | 159 (139-190) | 158 (138-190) | 0.29 |
| **Other clinical characteristics** |  |  |  |
| ECG ST changes (%) | 103,408/131,847 (78%) | 30,946/39,901 (78%) | <0.001 |
| Previous smoker (%) | 39,832/130,013 (32%) | 17,378/40,860 (43%) | <0.001 |
| Chronic renal failure (%) | 10,397/134,556 (8%) | 1,493/40,733 (4%) | <0.001 |
| CCF (%) | 6,767/134,574 (5%) | 1,681/40,745 (4%) | <0.001 |
| Angina (%) | 22,791/134,580 (17%) | 4,255/40,780 (11%) | <0.001 |
| Cerebrovascular disease (%) | 12,591/134,726 (9%) | 2,426/40,788 (6%) | <0.001 |
| Peripheral vascular disease (%) | 6,373/134,349 (5%) | 747/40,696 (2%) | <0.001 |
| Asthma / COPD (%) | 22,734/134,723 (17%) | 6,440/40,771 (16%) | <0.001 |
| Family history of CAD (%) | 34,320/114,865 (30%) | 8,872/35,256 (25%) | <0.001 |
| Heart rate, bpm, median (IQR) | 80 (68-93) | 78 (66-91) | <0.001 |
| Systolic blood pressure, median (IQR) | 141 (124-160) | 140 (122-157) | <0.001 |
| Moderate LVSD (EF <49%) | 22,659/176,083 (13%) | 17,794/108,669 (16%) | <0.001 |
| Severe LVSD (EF<30%) | 8,580/176,083 (5%) | 6,730/108,669 (6%) | <0.001 |
| Admission under Cardiologist during first 24 hours (%) | 65,587/129,500 (51%) | 20,938/39,257 (53%) | <0.001 |
| Cardiac arrest (pre and in-hospital) (%) | 4,059/132,529 (3.1%) | 1,245/40,137 (3.1%) | 0.69 |

CABG surgery; coronary artery bypass grafting surgery, PCI; percutaneous coronary intervention, MI; myocardial infarction, BMI; body mass index, GRACE: global registry of acute coronary events, ECG; electrocardiograph, CCF; congestive cardiac failure, COPD; chronic obstructive pulmonary disease, CAD; coronary artery disease, IQR; interquartile range, LVSD; left ventricular systolic dysfunction, EF; ejection fraction

**Table 2: Management strategy & crude clinical outcome**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **≥ 1 SMURF**  **(n=135,223)** | **SMURF-less**  **(n=40,860)** | **P-Value** |
| **Pharmacotherapy** |  |  |  |
| Low molecular weight heparin (%) | 64,200/122,153 (53%) | 19,630/37,327 (53%) | 0.91 |
| Fondaparinux | 56,619/122,657 (46%) | 17,740/37,456 (47%) | <0.001 |
| Warfarin (%) | 6,620/121,598 (5%) | 1,761/37,080 (5%) | <0.001 |
| Unfractionated heparin | 17,837/121,285 (15%) | 4,616/36,996 (12%) | <0.001 |
| Glycoprotein 2b/3a inhibitor (%) | 3,982/123,358 (3%) | 1,194/37,723 (3%) | 0.55 |
| IV Nitrate | 15,694/1221,567 (13%) | 4,215/37,081 (11%) | <0.001 |
| Furosemide (%) | 30,856/121,811 (25%) | 7,443/37,123 (20%) | <0.001 |
| Calcium channel blockers (%) | 24,218/121,680 (20%) | 3,008/37,055 (8%) | <0.001 |
| IV beta blockers (%) | 1,531/122,199 (1.3%) | 369/37,323 (1%) | <0.001 |
| MRA (%) | 6,578/120,956 (5%) | 1,631/36,920 (4%) | <0.001 |
| Thiazide diuretics (%) | 7,248/121,476 (6%) | 568/37,041 (2%) | <0.001 |
| Aspirin (%) | 130,576/134,865 (97%) | 39,402/40,758 (97%) | 0.14 |
| P2Y12 inhibitor (%) | 123,837/134,741 (92%) | 37,113/40,703 (91%) | <0.001 |
| Statins (%) | 109,513/134,538 (81%) | 29,012/40,661 (71%) | <0.001 |
| ACE inhibitors/ARB (%) | 111,248/134,650 (83%) | 30,191/40,679 (74%) | <0.001 |
| Beta-Blockers (%) | 109,931/134,022 (82%) | 32,644/40,470 (81%) | <0.001 |
| **Management strategy** |  |  |  |
| Radionuclide Study (%) | 3,086/122,712 (2.5%) | 813/37,240 (2.2%) | <0.001 |
| Exercise test | 3,826/124,092 (3.1%) | 1,238/37,702 (3.3%) | 0.05 |
| Coronary angiogram (%) | 94,636/129,883 (73%) | 27,823/39,395 (71%) | <0.001 |
| Percutaneous coronary intervention (%) | 49,867/105,187 (47%) | 14,076/31,005 (45%) | <0.001 |
| CABG (%) | 9,431/105,187 (9%) | 2,205/31,005 (7%) | <0.001 |
| Revascularization (CABG/PCI) | 59,298/105,187 (56%) | 16,281/31,005 (53%) | <0.001 |
| **Crude in-hospital clinical outcomes** |  |  |  |
| Death (%) | 6,509/135,223 (4.8%) | 2,049/40,860 (5.0%) | 0.10 |
| Cardiac mortality (%) | 6,503/176,083 (3.7%) | 4,967/135,223 (3.7%) | 0.42 |
| Reinfarction (%) | 991/129,579 (0.8%) | 286/39,226 (0.7%) | 0.48 |
| Major bleeding (%) | 2,142/133,304 (1.6%) | 579/40,357 (1.4%) | 0.02 |
| MACE\* (%) | 7,292/135,223 (5.4%) | 2,261/40,860 (5.5%) | 0.27 |

CABG surgery; coronary artery bypass grafting surgery, IV; intravenous, MRA; mineralocorticoid receptor antagonist, ACE; angiotensin converting enzyme inhibitor, ARB; angiotensin receptor blockers, MACE; major adverse cardiovascular events

\* MACE is defined as composite endpoint of in-patient mortality and reinfarction

**Table 3: ESC ACVC Quality indicators**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **≥ 1 SMURF**  **(n=135,223)** | **SMURF-less (n=40,860)** | **P-Value** |
| Coronary Angiography received within 72 hours | 39,965/60,793 (66%) | 11,794/17,444 (68%) | <0.001 |
| LV Function recorded in notes | 70,822/108,669 (65%) | 20,247/32,877 (62%) | <0.001 |
| Adequate P2Y12 Inhibition on discharge | 123,837/134,741 (92%) | 37,113/40,703 (91%) | <0.001 |
| Fondaparinux or LMWH received | 107,012/124,058 (86%) | 33,167/37,905 (88%) | <0.001 |
| DAPT received on discharge | 121,098/134,606 (90%) | 36,350/40,658 (89%) | 0.001 |
| Statin on discharge\* | 109,513/134,538 (81%) | 29,012/40,661 (71%) | <0.001 |
| ACE inhibitor or ARB on discharge for those with moderate (EF<49%) and severe (EF<30%) LVSD (%) | 20,794/24,400 (85%) | 5,310/6,681 (80%) | <0.001 |
| B-blocker on discharge for those with moderate (EF<49%) and severe (EF<30%) LVSD (%) | 20,535/24,303 (85%) | 5,594/6,646 (84%) | <0.001 |

ESC; European society of cardiology, Association for Acute Cardiovascular Care (ACVC), LV; left ventricle, LMWH; low molecular weight heparin, DAPT; dual antiplatelet therapy, ACEi/ARB; angiotensin converting enzyme inhibitor/angiotensin receptor blockers, LVSD; left ventricular systolic dysfunction, EF; ejection fraction, N/A; not available

\*MINAP does not record the specific type of statins, so ‘statin prescription’ was used as a surrogate for high intensity statin

**Table 4: Propensity Score-Matched Analysis with Average Treatment Effects on imputed data**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcome** | **Group** | **Coefficient\* (95% CI)** | **Odds Ratio\* (95% CI)** | **P Value** |
| **In-hospital mortality (n=49,974)** | Group 1: ≥ 1 SMuRF | Reference |  | <0.001 |
| Group 2: SMuRF-less | -0.0068 (-0.01060 to -0.0031) | 0.85 (0.77-0.93) |
| **In-hospital cardiac death (n=49,974)** | Group 1: ≥ 1 SMuRF | Reference |  | 0.002 |
| Group 2: SMuRF-less | -0.0053 (-0.0087 to -0.0020) | 0.85 (0.76 – 0.94) |
| **In-hospital reinfarction (n=49,974)** | Group 1: ≥ 1 SMuRF | Reference |  | 0.16 |
| Group 2: SMuRF-less | -0.0012 (-0.0029 to 0.0005) | 0.99 (0.64 – 1.06) |
| **In-hospital major bleeding (n=49,974)** | Group 1: ≥ 1 SMuRF | Reference |  | 0.56 |
| Group 2: SMuRF-less | -0.0007 (-0.0032 to 0.0017) | 0.96 (0.78 – 1.10) |
| **In-hospital MACE (n=49,974)** | Group 1: ≥ 1 SMuRF | Reference |  | <0.001 |
| Group 2: SMuRF-less | -0.0078 (-0.0118 to -0.0037) | 0.85 (0.77 – 0.93) |

\*Adjusted for age, sex, ethnicity, heart rate, blood pressure, serum creatinine concentration on admission, kilip class, family history of coronary artery disease (CAD), ischaemic ECG changes, LVSD, co-morbid conditions (cerebrovascular accident, peripheral vascular disease, asthma/COPD, heart failure, history of angina), pharmacotherapy (prescription of LMWH warfarin, un-fractionated heparin, GP IIb/IIIa inhibitor, intravenous nitrate, furosemide, aldosterone antagonist, fondaparinux, beta blockers, ACEi/ARB’s, aspirin, P2Y12 inhibitor, statins), cardiac arrest, procedures and investigations including ICA, PCI and CABG surgery during admission, type of admission ward, admission under cardiologist during first 24 hours, hospital and year.

LMWH; low molecular weight heparin

COPD; chronic obstructive pulmonary disease

ICA; invasive coronary angiogram

PCI; percutaneous coronary intervention

ACEi/ARB; angiotensin converting enzyme inhibitor/angiotensin receptor blockers

CABG surgery; coronary artery bypass grafting surgery

MACE; major adverse cardiovascular events

# MACE is defined as composite endpoint of in-patient mortality and reinfarction

**Supplementary Table 1: Factors associated with SMuRF-less status**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Odds Ratio** | **95% CI** | **P-Value** |
| Age (Per year) | 1.01 | 1.01-1.01 | <0.001 |
| Sex (female) | 0.88 | 0.86-0.90 | <0.001 |
| **Ethnicity (White reference)** |  |  |  |
| Black | 0.49 | 0.43-0.56 | <0.001 |
| Asian | 0.53 | 0.50-0.57 | <0.001 |
| Other Non-White ethnicities | 0.69 | 0.62-0.77 | <0.001 |
| Ischemic ECG changes | 0.96 | 0.94-0.99 | 0.007 |
| **LV function (Normal – reference)** |  |  |  |
| Moderate impairment | 0.98 | 0.94-1.01 | 0.24 |
| Severe impairment | 1.04 | 0.98-1.10 | 0.20 |
| Heart Failure | 0.89 | 0.86-0.91 | <0.001 |
| **Kilip Class (No crepitation’s – reference)** |  |  |  |
| Basal crepetations | 0.82 | 0.79-0.86 | <0.001 |
| Pulmonary oedema | 0.63 | 0.58-0.68 | <0.001 |
| Cardiogenic shock | 0.77 | 0.60-0.99 | <0.001 |
| History of CVA | 0.59 | 0.57-0.62 | <0.001 |
| History of PVD | 0.38 | 0.35-0.41 | <0.001 |
| Family history of coronary heart disease | 0.80 | 0.77-0.82 | <0.001 |
| Asthma/COPD | 0.94 | 0.91-0.97 | <0.001 |
| Admissions as a cardiac arrest | 1.04 | 0.98-1.12 | 0.17 |
| Admitted under Cardiologist (first 24 hours of care) | 0.93 | 0.9-0.95 | <0.001 |
| Admitted to a cardiac ward | 0.96 | 0.99-0.99 | 0.007 |

SMuRF; standard modifiable cardiovascular risk factors PVD; peripheral vascular disease, CVA; cerebrovascular accident, COPD; chronic obstructive pulmonary disease, ECG; electrocardiograph

**Supplementary Table 2: Crude clinical Outcomes from the matched cohort**

|  |  |  |  |
| --- | --- | --- | --- |
| **Crude in-hospital clinical outcomes** | **≥ 1 SMURF**  **(n=24,987)** | **SMURF-less**  **(n=24,987)** | **P-Value** |
| Death (%) | 1,287/24,987 (5.2%) | 1,110/24,987 (4.4%) | <0.001 |
| Cardiac mortality (%) | 977/24,987 (3.9%) | 832/24,987 (3.3%) | 0.001 |
| Reinfarction (%) | 191/24,987 (0.8%) | 169/24,987 (0.7%) | 0.25 |
| Major bleeding (%) | 387/24,987 (1.6%) | 362/24,987 (1.5%) | 0.36 |
| MACE\* (%) | 1,430/24,987 (5.7%) | 1,234/24,987 (4.9%) | <0.001 |

SMuRF; standard modifiable cardiovascular risk factors, MACE; major adverse cardiovascular events

\* MACE is defined as composite endpoint of in-patient mortality and reinfarction

**Supplementary** **Figure 1: STROBE diagram to show all participant inclusion and exclusion**

Records excluded for history of myocardial infarction (n=128,320)

Total number of NSTEMI patients in MINAP data from 2010 – 2017

(n= 369,435)

Records excluded for known history of coronary artery disease (Prior PCI/CABG surgery) (n = 22,292)

Number of patients for Inclusion

(n= 176,083)

**≥ 1 SMURF**

**135,223**

**SMURF-less**

**40,860**

Records excluded for missing mortality data (n= 6,638)

Records excluded for missing data on SMURF characteristics (n=3,758)

Records excluded for subsequent admissions to primary admission (n=6,638)

Records excluded for missing baseline characteristics. Age (n=0), Sex (n=0), Ethnicity (n=16,809)

SMuRF; standard modifiable cardiovascular risk factors, NSTEMI; non-ST-segment myocardial infarction, MINAP; myocardial Infarction national audit project, CABG surgery; coronary artery bypass grafting surgery, PCI; percutaneous coronary intervention.

**Supplementary Figure 2: Risk of adjusted in-hospital primary outcomes by hierarchical multivariable logistic regression models**

**Model 1\***

**Model 2\*\***

**Model 3\*\*\***



\*Adjusted for age, sex, ethnicity, year

\*\* Adjusted for model 1 plus heart rate, heart rate, blood pressure, serum creatinine concentration on admission, Kilip class, cardiac arrest (pre + in-hospital), family history of coronary artery disease (CAD), ischaemic ECG changes, heart failure, history of angina, LVSD, cerebrovascular accident, peripheral vascular disease and asthma/COPD, ICA, PCI and CABG surgery during admission

\*\*\* Adjusted for model 2 plus prescription of LMWH warfarin, un-fractionated heparin, GP IIb/IIIa inhibitor, intravenous nitrate, furosemide, aldosterone antagonist, fondaparinux, beta blockers, ACEi/ARB’s, aspirin, P2Y12 inhibitor, statins

**Supplementary Figure 3: The proportion of NSTEMI patients between 2010-2017 stratified by SMuRF status**

SMuRF; standard modifiable cardiovascular risk factors, NSTEMI; non-ST-segment myocardial infarction

**Supplement Figure 4: A figure to show the propensity score-matched analysis on imputed data before and after matching**

Chart, bar chart

Description automatically generated

\*Adjusted for age, sex, ethnicity, heart rate, blood pressure, serum creatinine concentration on admission, kilip class, family history of coronary artery disease (CAD), ischaemic ECG changes, LVSD, co-morbid conditions (cerebrovascular accident, peripheral vascular disease, asthma/COPD, heart failure, history of angina), pharmacotherapy (prescription of LMWH warfarin, un-fractionated heparin, GP IIb/IIIa inhibitor, intravenous nitrate, furosemide, aldosterone antagonist, fondaparinux, beta blockers, ACEi/ARB’s, aspirin, P2Y12 inhibitor, statins), cardiac arrest, procedures and investigations including ICA, PCI and CABG surgery during admission, type of admission ward, admission under cardiologist during first 24 hours, hospital and year.

LMWH; low molecular weight heparin

COPD; chronic obstructive pulmonary disease

ICA; invasive coronary angiogram

PCI; percutaneous coronary intervention

ACEi/ARB; angiotensin converting enzyme inhibitor/angiotensin receptor blockers

CABG surgery; coronary artery bypass grafting surgery

MACE; major adverse cardiovascular events

# MACE is defined as composite endpoint of in-patient mortality and reinfarction