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ORIGINAL RESEARCH

Mortality and Cardiovascular Outcomes in Patients Presenting With Non–ST Elevation Myocardial Infarction Despite No Standard Modifiable Risk Factors: Results From the SWEDEHEART Registry

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BACKGROUND: A significant proportion of patients with ST-segment–elevation myocardial infarction (MI) have no standard modifiable cardiovascular risk factors (SMuRFs) and have unexpected worse 30-day outcomes compared with those with SMuRFs. The aim of this article is to examine outcomes of patients with non–ST-segment–elevation MI in the absence of SMuRFs.

METHODS AND RESULTS: Presenting features, management, and outcomes of patients with non–ST-segment–elevation MI without SmuRFs (hypertension, diabetes, hypercholesterolemia, smoking) were compared with those with SmuRFs in the Swedish MI registry SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies; 2005–2018). Cox proportional hazard models were used. Out of 99 718 patients with non–ST-segment–elevation MI, 11 131 (11.2%) had no SMuRFs. Patients without SMuRFs had higher all-cause and cardiovascular mortality at 30 days (hazard ratio [HR], 1.20 [95% CI, 1.10–1.30], $P<0.0001$; and HR, 1.25 [95% CI, 1.13–1.38]), a difference that remained after adjustment for age and sex. SMuRF-less patients were less likely to receive secondary prevention statins (76% versus 82%); angiotensin-converting enzyme inhibitors/angiotensin receptor blockade (54% versus 72%); or β-blockers (81% versus 87%, P for all <0.0001), with lowest rates observed in women without SMuRFs. In patients who survived to 30 days, rates of all-cause and cardiovascular death were lower in patients without SMuRFs compared with those with risk factors, over 12 years.

CONCLUSIONS: One in 10 patients presenting with non–ST-segment–elevation MI present without traditional risk factors. The excess 30-day mortality rate in this group emphasizes the need for both improved population-based strategies for prevention of MI, as well as the need for equitable evidence-based treatment at the time of an MI.

Key Words: atherosclerosis ■ coronary artery disease ■ myocardial infarction ■ risk factors

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CLINICAL PERSPECTIVE

What Is New?

- One in 10 patients presenting with non–ST-segment–elevation myocardial infarction present without standard modifiable cardiovascular risk factors.

What Are the Clinical Implications?

- The higher 30-day mortality rate in patients with non–ST-segment–elevation myocardial infarction without standard modifiable cardiovascular risk factors highlights the need for both improved population-based strategies for prevention of myocardial infarction, as well as the need for equitable evidence-based treatment at the time of a myocardial infarction.

Nonstandard Abbreviations and Acronyms

CONCORDANCE	Cooperative National Registry of Acute Coronary Syndrome Care Registry
SMuRF-less	no standard modifiable cardiovascular risk factors
SMuRFs	standard modifiable cardiovascular risk factors
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies Registry

Lifestyle modification and pharmacotherapy targeting the modifiable cardiovascular risk factors hypertension, diabetes, hypercholesterolemia, and smoking[1,2] have been key to advances in the prevention and treatment of coronary artery disease (CAD). However, the mechanisms involved in individual susceptibility to atherosclerosis in response to these risk factors are less well understood. An archetypal group that highlights this are those who present with myocardial infarction secondary to atherosclerosis without standard modifiable cardiovascular risk factors (SMuRFs), at least not at or above the threshold that would trigger guideline-driven therapy. This group comprise between 14% and 27% of the ST-segment–elevation myocardial infarction (STEMI) population.[3–5] We have recently reported that individuals without SMuRFs ("SMuRF-less") who present with a STEMI have substantially higher 30-day mortality than their counterparts whose events occur in the context of at least 1 traditional risk factor. This exacerbates the already known poor outcomes suffered by women post STEMI, with the highest 30-day mortality rate (18%) seen in women without SMuRFs, approximately 3-fold higher than men with at least 1 SMuRF (6%).[3]

Although non–ST-segment–elevation MI (NSTEMI) and STEMI share similarities in underlying mechanisms in regard to atherosclerosis, acute plaque features, and thrombus burden, clinical management pathways and outcomes in patients presenting with NSTEMI are well known to differ from STEMI,[6] and these groups should be considered and evaluated separately. The SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) national MI registry captures a large, unbiased population of patients presenting with acute coronary syndrome, providing an unparalleled opportunity to examine potential contributing factors and outcomes of patients who are SMuRF-less with NSTEMI.[7,8] In this analysis, we examined the proportion and characteristics of patients who are SMuRF-less with NSTEMI, as well as their short- and long-term outcomes versus their counterparts with SMuRFs in 99 718 first presentation patients with NSTEMI from the SWEDEHEART registry 2005 to 2018. Further exploratory analyses were performed to unravel potential contributing or confounding factors, with consideration of discharge guideline-based therapy.

METHODS

Study Sample

Details of the SWEDHEART national MI registry have been published previously.[7,8] Briefly, the registry enrolls all patients with suspected MI admitted to cardiac care units in Sweden. The registry includes data on patient characteristics, medications, and outcomes as well as data on acute coronary care, coronary interventions, and secondary prevention. Long-term outcomes were collected by linkage to mandatory National Board of Health and Welfare registries, which include the Swedish National Inpatient Register, the Swedish Cause of Death Register (based on *International Classification of Diseases* [*ICD*] codes), and the Swedish Prescribed Drug Register (containing data on all dispensed prescription drugs).[8] Patients included in the analysis were at least 18 years of age, presented with symptoms suggestive of an acute coronary syndrome, and had a discharge diagnosis of NSTEMI. Classification of MI into type 1 or type 2 was done by the treating physician according to the universal definitions of MI. Patients with a known history of CAD (percutaneous cardiovascular intervention, coronary artery bypass grafting, or MI) were excluded from

the current analysis. Laboratory analyses were performed at the treating hospital according to local practice, using standardized methods. This analysis was limited to those enrolled in the cohort between January 1, 2005 and May 25, 2018. The regional ethics committee in Stockholm, Sweden, approved the current study in accordance with the Declaration of Helsinki (approval numbers 2012/6013/2, 2018/1957–32, and 2019-04277) and subjects provided informed consent. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Definition of SMuRFs

The exposure variable was defined as having 1 or more of the following SmuRFs: hypertension, diabetes, hypercholesterolemia, and smoking. The definitions were based on previous clinical diagnoses, previous and current medication use, prior and current medical record data, and patient self-report (Figure S1). Hypertension was defined as having a prior diagnosis of hypertension or prior antihypertensive pharmacotherapy (calcium channel antagonist, beta blockers, angiotensin-converting enzyme inhibitors [ACEis] or angiotensin II receptor blockers [ARBs]), or a new diagnosis of hypertension during the index admission. Diabetes was defined as having a previous diagnosis of diabetes or prior glucose lowering pharmacotherapy or a clinical diagnosis of diabetes during the index admission. Admission levels of fasting glucose and blood pressure are both influenced by neurohormonal response secondary to acute MI and were therefore not incorporated in the definitions. Hypercholesterolemia was defined as having a previous diagnosis of hypercholesterolemia, previous or ongoing oral low-density lipid cholesterol lowering treatment, low-density lipid cholesterol ≥3.5 mmol/L, or a total cholesterol ≥5.5 mmol/L at time of hospitalization. A patient was defined as a current smoker if they had smoked daily within the past 1 month before hospitalization. Additional analyses were performed including obesity as a SMuRF (body mass index [BMI] >30 kg/m^2).

Outcomes

The primary outcome was all-cause mortality at 30 days. Secondary outcomes included an extended major adverse cardiovascular events end point defined as the composite of all-cause death, MI, stroke or heart failure; cardiovascular mortality; heart failure hospitalization; stroke; coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting); and major bleeding, during the index admission or at follow-up. All-cause mortality and the secondary outcomes were assessed at multiple time points: in hospital, at 30 days, at 3, 5 years, and for complete follow-up. The study index date was the admission date and full follow-up was until an event occurred or May 25, 2018. The completeness of ascertainment and accuracy of classification of diagnoses in the Swedish national registries and SWEDEHEART are high.[9] Further, data quality and accuracy in SWEDEHEART are assessed by a yearly formal monitoring process.

Statistical Analysis

Categorical variables are presented using frequencies and percentages and numerical variables using mean and SD, or median and interquartile range. Tests for normality were performed using Kolmogorov–Smirnov test and/or visual inspection of the Q-Q plot. Differences in patient characteristics, in-hospital findings, and treatments by sex and SMuRF-less status were for categorical variables compared with chi-square and for continuous variables by Mann–Whitney nonparametric test. With multivariable logistic regression analyses, odds ratios for in-hospital mortality were calculated by SMuRF status. The association between SMuRF-less status and outcomes after discharge were estimated with Cox proportional hazard regression models calculating hazard ratios (HR) and 95% CI, presented in tables and Forest plots. Unadjusted and adjusted (age, sex, BMI and preadmission aspirin, statin, ACEi/ARB and beta blocker treatment) logistic and Cox proportional hazard regression models were used. Further, a Cox proportional hazards model was performed including an interaction term for sex. Censoring was performed in patients who had a nonfatal outcome at the time of the outcome, for that specific outcome. These patients could be included in analyses for fatal and other nonfatal outcomes. Censoring was also performed at 2 different time points to ensure proportionality across all outcomes depending on model used: 1, in assessing outcomes from the time of index event, censoring was done after 9 months or end of the data capture, and 2, assessing outcomes from 30 days after index event, censoring was done at end of the data capture. The different censoring times were used based on inspection of the underlying proportional hazards assumptions of the Cox proportional hazard models in Kaplan–Meier graphs (Figure S2) and Schoenfeld residual plots (Figure S3) for all-cause mortality at 30 days and at 6 months.

Kaplan–Meier survival probability estimates were calculated from the admission date to 30 days for all-cause and cardiovascular mortality, and to the total available follow-up at 12 years for all outcomes. These analyses were stratified by sex and differences assessed by log-rank test. For variables used to define SMuRF categorization, missing data were minimal (<2% patients) and the respective risk factor was

assumed to be absent. The proportion of missing data was higher for smoking status and in a sensitivity analysis we assessed the HRs for all-cause mortality when smoking status was imputed with the assumption that the data were missing at random. Multiple imputation of missing values was performed (using the SAS function PROC MI and arbitrary missing pattern) with all variables in the covariate section used to produce the values for imputation. Five imputed data sets were combined (using SAS function PROC MIANALYZE).

All analyses were performed using SAS software (version 9.4) and R software (version 3.5.0). A 2-sided *P* value of less than 0.05 was considered to indicate statistical significance.

Role of the Funding Source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the article.

RESULTS

Patient Characteristics

A total of 99 718 NSTEMI patients without a known history of CAD were included in the study. Of these, 11 131 (11.2%) were SMuRF-less. The proportion of NSTEMI patients that were SMuRF-less remained stable throughout the study period (Figure S4). The rates of type 2 MI were similar at ~9% in both groups (data available from September 2010 onwards).

Baseline demographics, SMuRFs, and pre-admission medications of the cohort, are presented in Table 1. The mean age for patients with and without SMuRFs was 70.8±12 versus 69.7±14 years (*P*<0.0001), and a higher proportion of male patients had 0 SMuRFs compared with female patients (12.6% versus 8.8%, *P*<0.001; Table S1).

The most common SMuRF was hypertension, diagnosed in 80% of patients in the SMuRF group, followed by hypercholesterolemia (54%), diabetes (25%), and current smoking (22%). Women had higher rates of hypertension, and lower rates of smoking than men (Table S1). Rates of diabetes and hypercholesterolemia were similar between the sexes. The rate of aspirin use in the SMuRF-less patients before presentation was lower (9% versus 28%, *P*<0.0001) than in individuals with risk factors.

The BMI in the SMuRF-less patients was lower than in patients with SMuRFs (25.8±4 versus 27.1±5 kg/m^2; *P*<0.0001).

Plasma markers of cardiometabolic disease including lipids, HbA1c and creatinine are also presented in Table 1, with the recognized caveat that some of these may reflect the acute presentation, particularly fasting glucose and C-reactive protein (CRP), rather than pre-existing levels. Lipids were different between the groups, with a mean low-density lipid cholesterol of 2.6±0.6 mmol/L in the SMuRF-less patients versus 3.2±1.0 mmol/L in patients with SMuRFs (*P*<0.0001), noting this difference was likely attenuated as 22% of patients with SMuRFs were already on a statin at the time of their index event. SMuRF-less patients had higher HDL cholesterol, and lower triglycerides compared with their counterparts with SMuRFs (Table 1). The median HbA1c was higher in patients with SMuRFs, consistent with the known diagnosis of diabetes in 25% of this group (*P*<0.0001).

Presenting Characteristics and In-Hospital Clinical Course

NSTEMI patients without SMuRFs had significantly lower systolic and diastolic blood pressure measures at presentation, as well as a lower heart rate compared with those with at least 1 SMuRF (Table 2). The time taken from symptom onset until admission to a coronary care unit or emergency room was shorter for SMuRF-less compared with patients with SMuRFs (6.5 versus 6.8 hours, *P*=0.0012). Of the 3 troponin measurements available across the cohort (evolving over the period of recruitment), there was a significantly higher concentration observed for high-sensitivity troponin T and generation 4 troponin I in SMuRF-less compared with patients with SMuRFs (Table 2).

Where the culprit territory was identified and recorded (49%), SMuRF-less NSTEMI patients were slightly more likely to have left anterior descending artery (LAD) territory culprit (49 versus 45%; *P*<0.0001), and less likely to have multi-vessel disease than their counterparts with at least 1 risk factor (Table 2). The left ventricular systolic function grade was not different between the groups.

Rates of angiography were similar between the groups, at 74%, with slightly higher rates of coronary revascularization with percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG) in patients with SMuRFs and shorter symptom onset to PCI time in the SMuRF-less group (Table 2). Rates of aspirin and $P2Y_{12}$ inhibitor use at discharge were similar between the groups. However, despite higher troponin levels and similar requirement for PCI and CABG, discharge use of statins, ACEi/ARB, and beta blockers were significantly lower in the SMuRF-less group (Table 2) with the greatest discrepancy observed for ACEi/ARB use at discharge in only 52% of patients with NSTEMI who were SMuRF less versus 72% of patients with at least 1 SMuRF (*P*<0.0001). The rate of ACEi/ARB use at discharge was particularly low in the female subgroup, 46% in those who were SMuRF less and 69% in patients with SMuRFs (Table S2, *P*<0.0001).

Table 1. Summary of Demographic and Patient Characteristics

	Overall	SMuRF less	SMuRF >0	*P* value
No.	99718	11131	88587	
Demographics and risk factors				
Age, y				
Mean (SD)	70.7 (12.4)	69.7 (13.6)	70.8 (12.3)	<0.0001
Sex				
Male	60876 (61)	7700 (69)	53176 (60)	<0.0001
Female	38842 (39)	3431 (31)	35411 (40)	
Diabetes	22056 (22)		22056 (25)	<0.0001
Hypertension	71113 (71)		71113 (80)	<0.0001
Hypercholesterolemia	47973 (48)		47973 (54)	<0.0001
Smoking status				
Never smoked	41324 (42)	5890 (53)	35434 (40)	<0.0001
Former smoker	31235 (31)	4194 (38)	27041 (31)	
Current smoker	19538 (20)		19538 (22)	
Body mass index, kg/m^2				
n	81581	8853	72728	
Mean (SD)	26.9 (4.7)	25.8 (4.2)	27.1 (4.7)	<0.0001
Medical history				
Stroke/transient ischemic attack	10694 (11)	532 (5)	10162 (11)	<0.0001
Peripheral arterial disease	8649 (9)	342 (3)	8307 (9)	<0.0001
Atrial fibrillation	6837 (7)	605 (5)	6232 (7)	<0.0001
History of bleeding	5252 (5)	398 (4)	4854 (5)	<0.0001
Heart failure hospitalization	8340 (8)	176 (2)	8164 (9)	<0.0001
Cancer	2810 (3)	226 (2)	2584 (3)	<0.0001
Chronic obstructive pulmonary disease	7149 (7)	524 (5)	6625 (7)	<0.0001
Prehospital pharmacotherapy				
Statin	19348 (20)		19348 (22)	<0.0001
Aspirin	25953 (26)	978 (9)	24975 (28)	<0.0001
$P2Y_{12}$ inhibitor	3987 (4)	182 (2)	3805 (4)	<0.0001
Beta blocker	28644 (29)		28644 (33)	<0.0001
Angiotensin-converting enzyme inhibitor or angiotensin receptor II antagonist	30743 (31)		30743 (35)	<0.0001
Laboratory variables at baseline				
Total cholesterol, mmol/L				
n	72238	7099	65139	
Mean (SD)	5.14 (1.27)	4.45 (0.68)	5.22 (1.30)	<0.0001
Triglycerides, mmol/L				
n	68022	6790	61232	
Median (IQR)	1.4 (1.0–1.9)	1.1 (0.8–1.5)	1.4 (1.0–2.0)	<0.0001
High-density lipoprotein cholesterol, mmol/L				
n	69980	6945	63035	
Median (IQR)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	0.0005
Low-density lipoprotein cholesterol, mmol/L				
n	67865	6803	61062	
Mean (SD)	3.18 (1.11)	2.64 (0.58)	3.24 (1.14)	<0.0001
Hemoglobin A1c, mmol/mol				
n	10443	988	9455	
Median (IQR)	40.0 (36.0–47.0)	37.0 (35.0–40.0)	40.0 (37.0–49.0)	<0.0001

(*Continued*)

Table 1. (Continued)

	Overall	SMuRF less	SMuRF >0	*P* value
Glucose, mmol/L				
n	85601	9165	76436	
Median (IQR)	6.7 (5.8–8.6)	6.4 (5.6–7.5)	6.8 (5.8–8.8)	<0.0001
C-reactive protein, mg/L				
n	88491	9575	78916	
Median (IQR)	5.0 (3.0–14.0)	5.0 (2.4–15.0)	5.0 (3.0–13.0)	0.0977
Creatinine, μmol/L				
n	96031	10506	85525	
Median (IQR)	82 (69–99)	80 (69–94)	82 (69–100)	<0.0001

Values are means (SD) or medians (interquartile ranges) for continuous variables, and number (n, %) for categorical variables. Hemoglobin A1c normal: 31 to 46 mmol/mol. IQR indicates interquartile range; and SMuRF, standard modifiable cardiovascular risk factor.

Compared with patients with SMuRFs, patients who were SMuRF less had higher rates and unadjusted odds ratios of in-hospital death (4% versus 3%; *P*<0.0001) and cardiogenic shock (2% versus 1%; *P*<0.0001, Table 2, Table S3). Most of the excess death observed in patients without SMuRFs occurred in hospital. Rates of recurrent MI and stroke were similar between the groups (Table 2). A heart failure diagnosis during hospital admission was higher in the group with SMuRFs as compared with those without SMuRFs (24% versus 20%; *P*<0.0001). In a multivariable logistic regression model, having no risk-factors, female sex, and older age were all independently associated with a higher in-hospital mortality (Table S3).

30-Day Outcomes

Unadjusted and adjusted associations of SMuRF-less status with 30-day outcomes in patients with NSTEMI are shown in Figure 1. At 30 days, patients who were SMuRF less had 20% and 25% higher rates of unadjusted all-cause and cardiovascular mortality, respectively, compared with those with SMuRFs (HR, 1.20 [95% CI, 1.10–1.31] *P*<0.0001 and HR, 1.25 [95% CI, 1.13–1.38] *P*<0.0001, respectively). Mortality rates were highest in women who were SMuRF less, reaching 7% at 30 days, 17% higher than their female counterparts with at least 1 SMuRF, and 75% higher than men with at least 1 SMuRF (Figure 2, Table S2, Tables S4 through S6). The higher rates of all-cause and cardiovascular mortality in individuals who were SMuRF less remained significant after adjustment for age, sex, BMI, and preadmission cardiovascular medication (Figure 1B). No specific interaction between sex and SMuRF status was observed for all-cause (*P*=0.92) or cardiovascular death (*P*=0.86). Patients with NSTEMI who were SMuRF less had an 11% lower rate of recurrent MI and a 32% lower rate of revascularization compared with their counterparts who were SMuRF positive (*P*=0.03 and <0.0001 respectively; Figure 1, Table S4). Despite slightly higher troponin rises, clinical heart failure at 30 days was 40% less common in the SMuRF-less group compared with patients with NSTEMI with at least 1 SMuRF (*P*<0.0001; Figure 1). Kaplan–Meier survival curves stratified by SMuRF status and by sex for all-cause and cardiovascular mortality are presented in Figure 2 and are seen to separate from the initial day of presentation, remaining at a similar mortality rate from 4 to 30 days (Figure 2A and 2B). In a sensitivity analysis imputing missing data for those with missing smoking status in the definition of SMuRF status, the excess mortality in patients who were SMuRF less was attenuated but remained statistically significant (Table S7).

Because of the important role of obesity in the development of CAD, additional analyses were performed including BMI>30 kg/m^2 as a SMuRF examining outcomes by group. The 30-day outcome data (unadjusted and adjusted) are presented in Table S8. Similar findings were observed in the analyses without obesity included as a SMuRF, with higher all-cause and cardiovascular mortality in the SMuRF-less group.

Long-Term Outcomes

Individuals who were SMuRF less were observed to have a lower all-cause and cardiovascular mortality rate throughout 6 months of follow-up compared with their counterparts with at least 1 modifiable risk factor (Figure S5). This difference persisted at 6 months also after adjustment for age, sex, and ongoing prehospital aspirin treatment (Figure S5). The rates of recurrent MI, heart failure, major bleeding, and recurrent revascularization were lower in the SMuRF-less group throughout the 6 months (Figure S5 and Table S2), also after adjustment for age, sex, and ongoing prehospital aspirin treatment (Figure S5). Patients who were SMuRF less and alive at 30 days had a lower all-cause and cardiovascular mortality throughout the 12-year

Table 2. Presentation Characteristics and In-Hospital Findings/Management

	Overall	SMuRF less	SMuRF >0	*P* value
No.	99 718	11 131	88 587	
Presentation characteristics				
Systolic blood pressure, mm Hg				
n	96 166	10 760	85 406	
Mean (SD)	151.6 (28.7)	146.2 (27.4)	152.3 (28.8)	<0.0001
Diastolic blood pressure, mm Hg				
n	93 837	10 478	83 359	
Mean (SD)	85.7 (16.8)	84.3 (16.1)	85.8 (16.9)	<0.0001
Heart rate (per min)				
n	96 561	10 790	85 771	
Mean (SD)	83.1 (23.1)	81.4 (24.0)	83.3 (23.0)	<0.0001
Cardiac arrest at admission	2555 (2.6%)	417 (3.8%)	2138 (2.4%)	<0.0001
Left ventricular function grade				
Normal (≥50%)	50 298 (66)	5608 (66)	44 690 (66)	0.5981
Slightly lower than normal (40%–49%)	13 536 (18)	1496 (18)	12 040 (18)	
Moderately lower than normal (30%–39%)	7342 (10)	830 (10)	6512 (10)	
Severely lower than normal (<30%)	3697 (5)	441 (5)	3256 (5)	
Unknown	932 (1)	99 (1)	833 (1)	
Culprit lesion territory*				
Intermediate	1024/48518 (2)	139/5360 (3)	885/43158 (2)	<0.0001
Left anterior descending artery	22 137/48518 (46)	2641/5360 (49)	19 496/43158 (45)	
Left circumflex artery	11 920/48518 (25)	1222/5360 (23)	10 698/43158 (25)	
Left main coronary artery	872/48518 (2)	105/5360 (2)	767/43158 (2)	
Right coronary artery	12 565/48518 (26)	1253/5360 (23)	11 312/43158 (26)	
In-hospital management				
Percutaneous coronary intervention	51 394 (52)	5630 (51)	45 764 (52)	0.0316
Coronary artery bypass grafting	5755 (6)	538 (5)	5217 (6)	<0.0001
Angiography	73 901 (74)	8250 (74)	65 651 (74)	0.9850
Multivessel disease	30 022 (41)	2695 (33)	27 327 (42)	<0.0001
Infarction type				
Type 1	50 129 (89)	5525 (88)	44 604 (89)	0.3505
Type 2	5137 (9)	588 (9)	4549 (9)	
Length of stay, d				
n	99 717	11 131	88 586	
Median (IQR)	4.0 (3.0–7.0)	4.0 (3.0–6.0)	4.0 (3.0–7.0)	<0.0001
Troponin T (ng/L)				
n	20 838	2327	18 511	
Median (IQR)	0.6 (0.2–2.0)	0.6 (0.2–2.0)	0.6 (0.2–2.1)	0.7981
High sensitivity troponin T, ng/L				
n	37 928	4287	33 641	
Median (IQR)	290.0 (106.0–840.5)	335.0 (116.0–960.0)	283.0 (105.0–824.0)	<0.0001
Troponin I, ng/mL				
n	32 692	3339	29 353	
Median (IQR)	2.5 (0.6–9.6)	2.9 (0.7–10.0)	2.5 (0.6–9.5)	0.0115

(*Continued*)

Table 2. (Continued)

	Overall	SMuRF less	SMuRF >0	*P* value
In-hospital complications				
Death	3515 (4)	485 (4)	3030 (3)	<0.0001
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalization for heart failure)	26 177 (26)	2563 (23)	23 614 (27)	<0.0001
Recurrent myocardial infarction	3118 (3)	334 (3)	2784[3]	0.4170
Cardiogenic shock	1211 (1)	186 (2)	1025 (1)	<0.0001
Heart failure	22 793 (24)	2127 (20)	20 666 (24)	<0.0001
Major bleeding	1925 (2)	209 (2)	1716 (2)	0.6675
Stroke	902 (1)	86 (1)	816 (1)	0.1188
Symptom onset to coronary care or emergency room admission, h				
n	83 157	9180	73 977	
Median (IQR)	6.8 (3.8–14.8)	6.5 (3.7–14.5)	6.8 (3.8–14.8)	0.0012
Time from symptom onset to percutaneous coronary intervention start, h				
n	28 723	3415	25 308	
Median (IQR)	31.3 (15.5–62.7)	27.1 (11.3–55.0)	32.0 (16.1–63.5)	<0.0001
Discharge medication				
Statin	80 809 (82)	8452 (76)	72 357 (82)	<0.0001
Aspirin	87 893 (91)	9815 (92)	78 078 (91)	0.0005
$P2Y_{12}$ inhibitor	71 179 (74)	7899 (74)	63 280 (74)	0.6030
Beta blocker	82 877 (86)	8618 (81)	74 259 (87)	<0.0001
Angiotensin-converting enzyme inhibitor or angiotensin receptor II antagonist	67 052 (70)	5737 (54)	61 315 (72)	<0.0001

Values are mean (SD) or median (interquartile range) for continuous variables, and number (n, %) for categorical variables. IQR indicates interquartile range; and SMuRF, standard modifiable cardiovascular risk factor.

*Denominator represents available data, 48 158 (48%) patients had known, and 51 560 (52%) patients had unknown culprit lesion territory.

follow-up than their counterparts with at least 1 modifiable risk factor (Figure 3). The rates of recurrent MI, rehospitalization for heart failure, major bleeding, and coronary revascularization were lower in the SMuRF-less group up to 12 years in unadjusted (Table S5, Table S8, Figure S6A) and adjusted models (Table S8, Figure S6B).

DISCUSSION

This large, nationwide study highlights that more than 1 in 10 patients with NSTEMI have no standard modifiable cardiovascular risk factors and that individuals in this group suffer a higher early mortality than their counterparts with traditional risk factors. Patients who were SMuRF less were found to have an atherosclerotic burden almost as severe as patients with 1 or more risk factors but received lower rates of evidence-based pharmacotherapy at discharge.

Although the important finding of higher early mortality in patients who were SMuRF less versus patients with risk factors has recently been reported in at least 3 independent cohorts with STEMI,[3–5] differences in patient characteristics, comorbidities, underlying pathological mechanism, and incidence of complications between STEMI and NSTEMI make it inappropriate to extrapolate these conclusions to the group with NSTEMI . To our knowledge, this is the first study to specifically examine the hypothesis that early mortality after NSTEMI is different between those with no SMuRFs versus those with at least 1 traditional risk factor. Consistent with prior literature the rates of each traditional modifiable risk factor were higher in this cohort with NSTEMI, compared with the previously published cohort with STEMI, associated with a lower proportion of patients with NSTEMI who were SMuRF less (11%) compared with that seen in the SWEDEHEART STEMI (15%) population.[3,10]

We examined whether perceived “low risk” may have slowed patient presentation times, or influenced triage times, but this was not the case in this study, with patients who were SMuRF less receiving more rapid admission to heart intensive care or emergency room admission, identical rates of coronary angiography, and more rapid times to receiving percutaneous

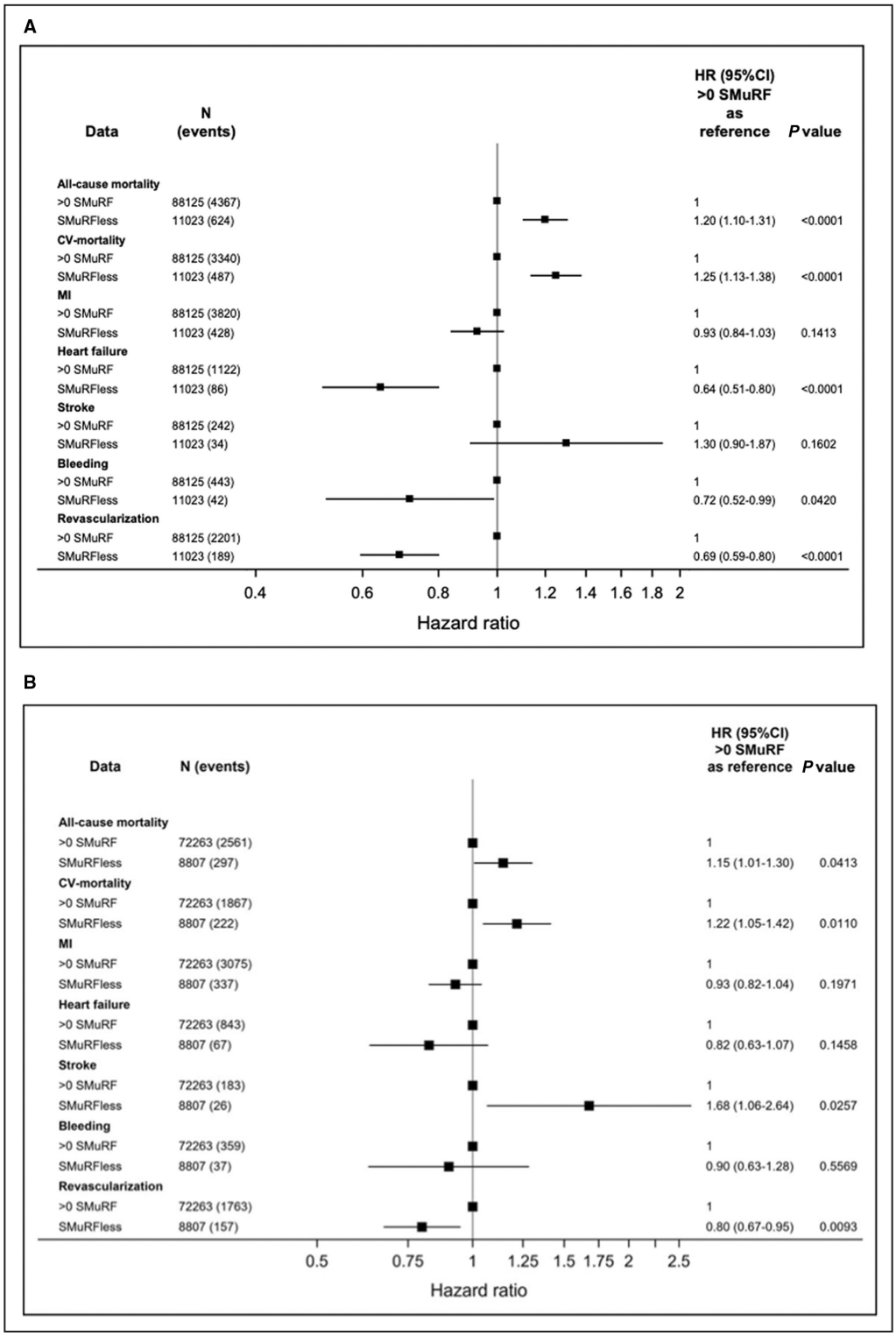

Figure 1. Hazard ratios (95% CI) for SMuRF-less versus >0 SMuRF status for 30-day all-cause mortality, cardiovascular mortality, recurrent myocardial infarction, heart failure, stroke, bleeding, and revascularization.

Point estimates and 95% CIs are presented. Unadjusted (**A**), and adjusted for sex, age, body mass index, and preadmission cardiovascular medications (**B**). CV indicates cardiovascular; HR, hazard ratio; MI, myocardial infarction; and SMuRF, standard modifiable cardiovascular risk factor.

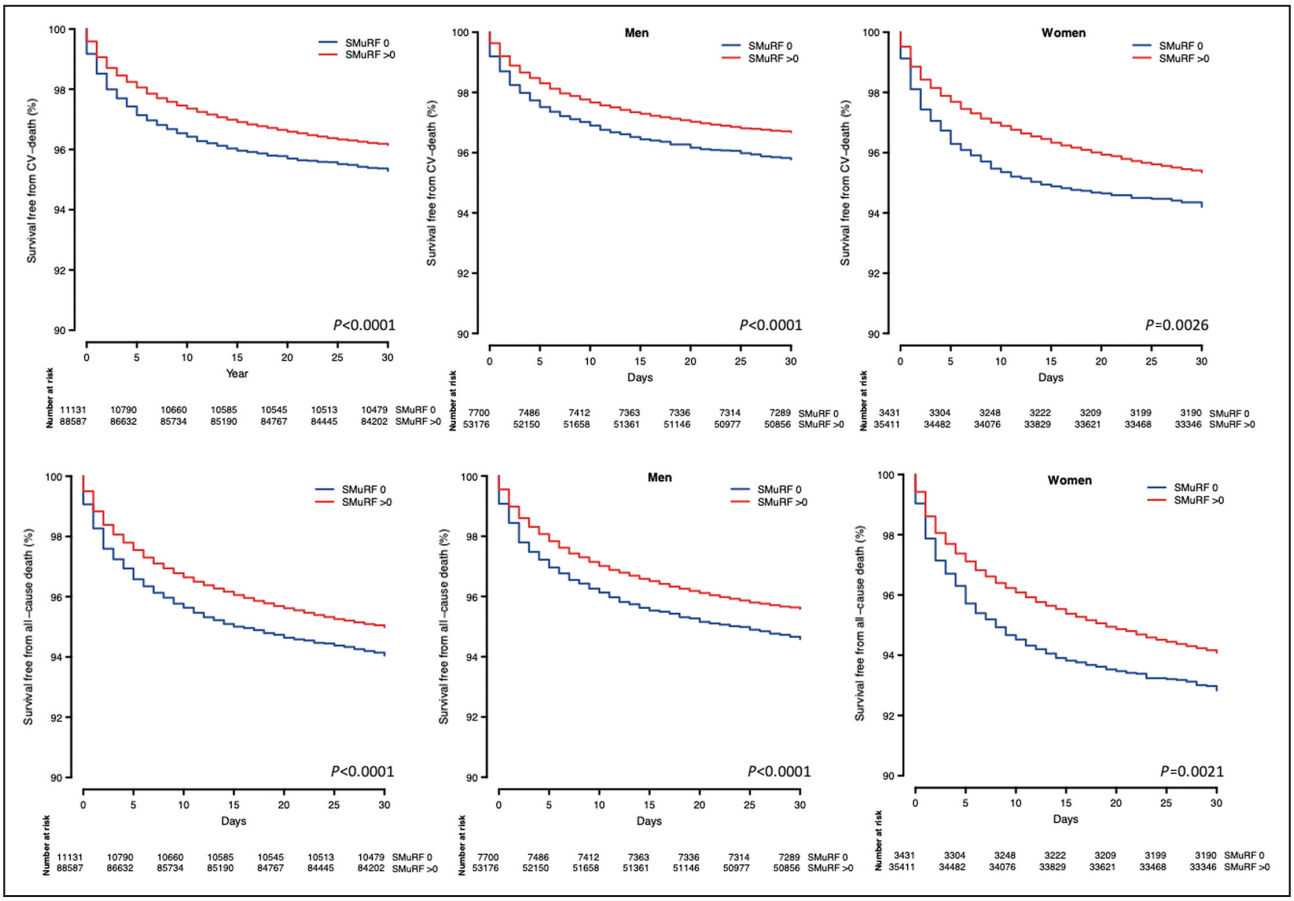

Figure 2. Kaplan-Meier survival curves for cardiovascular death (upper panels) and all-cause death (lower panels) to 30 days for 0 SMuRFs and >0 SMuRFs for all patients and by sex.
Difference assessed by log-rank test. CV indicates cardiovascular; and SMuRF, standard modifiable cardiovascular risk factor.

intervention. In contrast, similar to what we have reported for patients with STEMI,[3] patients who were SMuRF less less frequently received pharmacotherapeutic blockade of angiotensin and beta adrenergic neurohormonal signaling pathways than their counterparts with risk factors, as well as statin therapy.

Mechanisms explaining the early mortality of patients with MI who were SMuRF lessremain to be elucidated.[11,12] In the cohort with STEMI, the increased early mortality in patients who were SMuRF less was not explained by recurrent MI or heart failure but rather appeared to be due to fatal arrhythmia.[3] Here we show that the excess mortality for patients with NSTEMI who were SMuRF less occurred despite no differences in recurrent MI, type of MI, or stroke, and lower rates of heart failure, and revascularization, with arrhythmia or sudden death, again being the most likely explanation. In the case of STEMI, we were able to demonstrate that the lower rates of evidence-based ACEi/ARB and beta blockade prescription at least partially explained the increased susceptibility to early mortality in the SMuRF-less group in a mediation analysis performed on the subgroup who had survived to discharge and where pharmacotherapy was documented.[3] In this study, we observed similar lower rates of use of ACEi/ARB, beta blocker, and statins at discharge for patients with NSTEMI who were SMuRF less compared with those with at least 1 risk factor, that, again, was particularly poor for women. This may, in part, be related to lower rates of prior prescription of these therapies owing to the absence of hypertension and hypercholesterolemia in the SMuRF-less group. Although these differences may partially explain the observed differences in early mortality, a meaningful mediation analysis was not possible in the cohort with NSTEMI due to high proportion of 30-day deaths that occurred before discharge. In patients with NSTEMI who survived to discharge, mortality rates at 30 days were low, the power to observe the significant differences between the patients who were SMuRF less versus patients with risk-factors in regard to their discharge medications was lost.

Whether other mechanisms, independent of the lower rates of adherence to evidence-based pharmacotherapy, explains the heightened early mortality observed in individuals who were SMuRF less post MI remains to be determined. The higher rates of cardiac

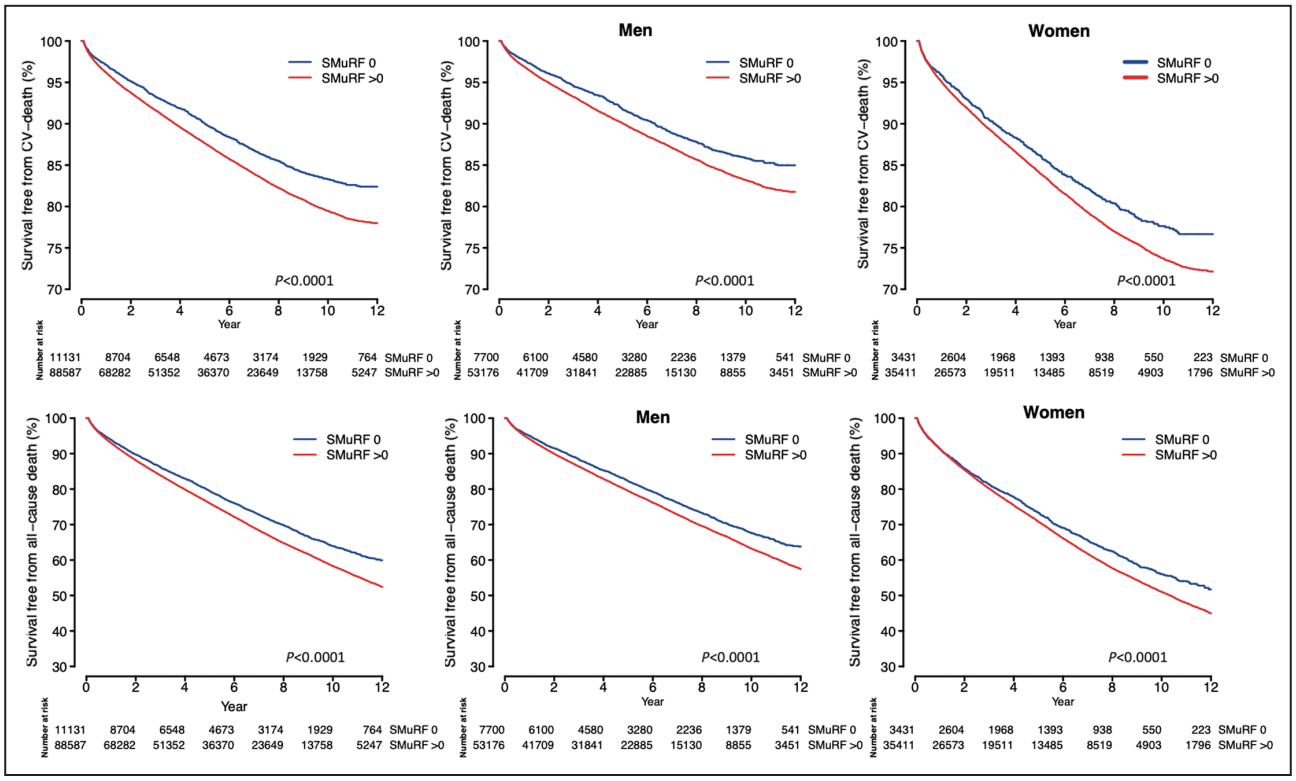

Figure 3. Kaplan-Meier survival curves for cardiovascular death (upper panels) and all-cause death (lower panels) for those who survived to 30 days with up to 12 years of follow-up for 0 SMuRFs and >0 SMuRFs for all patients and by sex.
Difference assessed by log-rank test. CV indicates cardiovascular; and SMuRF, standard modifiable cardiovascular risk factor.

arrest on admission are consistent with an associated arrhythmic susceptibility like that seen in patients with STEMI who were SMuRF less.[3] Another observation that we have made in this cohort with NSTEMI that is missing an obvious biological explanation was the higher proportion of patients with left anterior descending territory culprit lesions who were SMuRF less (Table 2; 49% versus 45%). Although most likely due to chance, this finding was also observed in the independent analysis of the cohort with STEMI from the SWEDEHEART registry and the CONCORDANCE Australian Cohort.[3,4] The group who were SMuRF less had slightly higher troponin levels. However, their left ventricular systolic function was similar to the patients with risk factors.

In this study, we also present the long-term outcomes in relation to patients who were SMuRF less or patients with risk-factors. Although event rates for mortality, repeat MI, heart failure hospitalization, stroke, and coronary revascularization were significantly lower in the group who were SMuRF less than their counterparts with at least 1 risk factor, they remained considerable. This highlights the importance of providing secondary prevention to all patients after an MI.

The findings we present in patients with NSTEMI further emphasize our current lack of understanding of biological mechanisms determining the differential susceptibility or resilience to established risk factors driving atherosclerosis.[13] Although the group who were SMuRF less may include individuals whose existing risk factors were missed, this potential for miscategorization is minimized by the detailed clinical phenotyping available and our inclusion of additional biochemistry and in-hospital diagnoses available that we incorporated into the categorization of SMuRF status. Such additional information is obviously not of benefit in identifying patients who are currently slipping "under the radar" and not receiving optimal primary and secondary prevention strategies to target subclinical disease. In addition to the efforts dedicated to identifying potential missing risk factors, the comprehensive nature of the SWEDEHEART data set allowed us to study less typical risk factors including BMI, triglycerides, and high-density lipoprotein. None of these differed to a degree that would be expected to have an impact on the atherosclerosis development or higher rates of early mortality in the group who were SMuRF less, and rates of malignancy and chronic obstructive pulmonary disease were lower.

This study has a number of strengths including the large number of participants, the follow-up, the completeness and comprehensiveness of the data set because of data linkage, and the universally used public health care system in Sweden. However, there were

also some limitations, including the observational nature of the data. Although we adjusted for confounders of short-term outcomes, there may be additional major confounders such as socioeconomic status, ethnicity, and other lifestyle factors beyond smoking. However, as the increased risk of CAD in patients with for example, low socioeconomic status, who have unhealthy lifestyles or a family history of CAD, are largely mediated by SMuRFs, this would most likely conservatively bias the results. We defined SMuRFs in a categorical manner based on accepted cutoffs. However, for those that are continuous we acknowledge that there is likely a gradient of risk.[14] Because of incomplete medical records at the time of death, there may be underreporting of SMuRFs in patients who die in hospital, particularly if they die within 24 hours of admission, compared with patients who are discharged alive. Family history of premature atherosclerotic disease, as well as less commonly used risk factors such as lipoprotein(a) and polygenic risk scores were not available in this analysis. The inclusion of antihypertensive medication use in the definition of hypertension may result in patients being falsely categorized if they were prescribed these (eg, ACEis) for other diseases such as diabetes or chronic kidney disease. Also, although the mean systolic blood pressure recorded at admission in the group who were SMuRF less exceeded 140 mm Hg, the commonly used cutoff for diagnosis of hypertension, heightened sympathetic state in the setting of acute MI made it unsuitable to be included in the diagnosis of hypertension. However, to minimize the possibility of miscategorization due to missed diagnosis of risk factors, discharge diagnosis of hypertension by the treating physician was included in the definition of patients with risk factors as outlined in Figure S1. Further, prevention guidelines and quality registry recommendations for secondary prevention medication in patients with NSTEMI, as well as cultural factors have slightly varied during the study period from 2005 to 2018. However, no significant change in the proportion of patients with NSTEMI who were SMuRF less occurred during this time (Figure S4).

What options do we have to improve the identification of individuals with subclinical atherosclerosis developing in the absence of risk factors reaching "threshold" to enable early intervention with effective pharmacotherapy? In addition to unraveling new mechanisms to help understand and prevent disease in these individuals, a marker of subclinical disease burden or activity, integrating the host's response to the variety of risk factors they had been exposed to, would be immensely valuable, and not only for the patient who is SMuRF less. Although coronary calcium scoring may seem like a logical solution given its noninvasive nature and ability to accurately quantify plaque burden and risk stratify individuals independently of their traditional risk factor profile, there is no current evidence or guideline that would recommend its use in the "low-risk" population. Improved incorporation of clinical and biochemical risk factors in algorithms made possible by machine learning may help. However, such algorithms will need to be tested prospectively in a rigorous manner and pragmatic considerations particularly around communication of emerging risk stratification tools to the patient will be paramount. Prospective studies examining the potential benefits of polygenic risk scores, have the potential to be of some assistance.[15–17] Currently, high-sensitivity CRP (C-reactive protein) is the closest serum biomarker we have that we believe reflects the degree of plaque activity or instability.[18,19] However, this is limited in its specificity and is not currently enough on its own to guide therapy in a patient with no SMuRFs who has not had an event. Specificity may be improved by combining high-sensitivity CRP along with high-sensitivity troponin measurements, with recent evidence expanding the potential prognostic utility for troponin good the general population without a history of cardiovascular disease.[20] Improved phenotyping of immune profiles may offer some hope for the future.[21]

CONCLUSIONS

More than 1 in 10 patients with NSTEMI present despite no traditional "warning" risk factors. The excess early mortality in this group who were SMuRF less, similar to that recently reported in STEMI, further highlight the need for both improved strategies for identifying early CAD and risk, as well as ensuring all patients with MI receive the best evidence-based treatment.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Table S1–S8
Figures S1–S6

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SUPPLEMENTAL MATERIAL

Table S1. Baseline clinical and demographic characteristics of patients with and without SMuRFs by sex.

		SMuRFs=0 (Men) N=7700	SMuRFs=0 (Women) N=3431	SMuRFs>0 (Men) N=53176	SMuRFs>0 (Women) N=35411	Overall N=99718
Demographics						
Age	n	7700	3431	53176	35411	99718
	Median (IQR)	69 (60, 79)	75 (63, 84)	69 (60, 77)	76 (67, 83)	71 (62, 80)
Sex	Male	7700 (100)		53176 (100)		60876 (61)
	Female		3431 (100)		35411 (100)	38842 (39)
SmuRF						
Diabetes mellitus				13155 (25)	8901 (25)	22056 (22)
Hypertension				40667 (76)	30446 (86)	71113 (71)
Hypercholesterolaemia				29368 (55)	18605 (53)	47973 (48)
Current smoker				12653 (24)	6885 (19)	19538 (20)
Smoking status	Never smoked	3842 (50)	2048 (60)	18227 (34)	17207 (49)	41324 (42)
	Former smoker	3254 (42)	940 (27)	19091 (36)	7950 (22)	31235 (31)
	Current smoker			12653 (24)	6885 (19)	19538 (20)
Body Mass Index (BMI), kg/m^2	n	6313	2540	44720	28008	81581
	Median (IQR)	26 (24, 28)	24 (22, 28)	27 (24, 30)	26 (23, 30)	26 (24, 29)
Medical history						
Previous stroke/transient ischemic attack		338 (4)	194 (6)	5737 (11)	4425 (12)	10694 (11)
Peripheral arterial disease		214 (3)	128 (4)	4918 (9)	3389 (10)	8649 (9)
Previous atrial fibrillation		439 (6)	166 (5)	3887 (7)	2345 (7)	6837 (7)
History of bleeding		255 (3)	143 (4)	2752 (5)	2102 (6)	5252 (5)
Heart failure hospitalization		102 (1)	74 (2)	3987 (7)	4177 (12)	8340 (8)
Cancer		171 (2)	55 (2)	1694 (3)	890 (3)	2810 (3)
Chronic obstructive pulmonary disease (COPD)		317 (4)	207 (6)	3315 (6)	3310 (9)	7149 (7)
Prehospital pharmacotherapy						
Statin				11550 (22)	7798 (22)	19348 (20)
Aspirin		604 (8)	374 (11)	13621 (26)	11354 (32)	25953 (26)
P2Y12 Inhibitor		121 (2)	61 (2)	2205 (4)	1600 (5)	3987 (4)
β -blocker				15051 (28)	13593 (39)	28644 (29)
ACEi or ARB				17782 (33)	12961 (37)	30743 (31)
Laboratory variables at baseline						
Plasma creatinine (µmol/L)	n	7296	3210	51431	34094	96031
	Median (IQR)	84 (74, 97)	69 (59, 81)	86 (75, 104)	74 (61, 92)	82 (69, 99)

Total cholesterol (mmol/L)	n	5220	1879	40954	24185	72238
	Median (IQR)	4.6 (4.0, 5.0)	4.6 (4.1, 5.0)	5.1 (4.2, 6.0)	5.3 (4.4, 6.2)	5.1 (4.3, 5.9)
Triglycerides (mmol/L)	n	4991	1799	38576	22656	68022
	Median (IQR)	1.1 (0.9, 1.5)	1.0 (0.8, 1.4)	1.4 (1.1, 2.0)	1.4 (1.0, 1.9)	1.4 (1.0, 1.9)
HDL-cholesterol (mmol/L)	n	5106	1839	39678	23357	69980
	Median (IQR)	1.1 (1.0, 1.4)	1.4 (1.2, 1.7)	1.1 (0.9, 1.3)	1.3 (1.1, 1.6)	1.2 (1.0, 1.5)
LDL-cholesterol (mmol/L)	n	4998	1805	38327	22735	67865
	Median (IQR)	2.8 (2.3, 3.1)	2.6 (2.2, 3.0)	3.2 (2.4, 4.0)	3.2 (2.4, 4.0)	3.1 (2.4, 3.9)
HbA1C (mmol(mol)	n	745	243	6062	3393	10443
	Median (IQR)	37.0 (35.0, 40.0)	37.0 (35.0, 40.0)	40.0 (36.0, 49.0)	40.0 (37.0, 48.0)	40.0 (36.0, 47.0)
Glucose (mmol/L)	n	6398	2767	46316	30120	85601
	Median (IQR)	6.3 (5.6, 7.4)	6.5 (5.6, 7.8)	6.7 (5.8, 8.6)	7.0 (5.9, 9.0)	6.7 (5.8, 8.6)
CRP (mg(L)	n	6647	2928	47432	31484	88491
	Median (IQR)	5.0 (2.0, 13.0)	6.0 (3.0, 19.4)	5.0 (2.8, 12.0)	6.0 (3.0, 16.0)	5.0 (3.0, 14.0)

Values are medians (interquartile ranges, IQR) and number (n, %) for categorical variables. ACEi, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor II antagonist, HbA1c, haemoglobin A1c (normal: 31–46 mmol/mol), LDL, low density lipoprotein cholesterol, HDL, high density lipoprotein cholesterol.
*The laboratory variables are taken from initial readings during the hospital admission and may be affected by the myocardial infarction.

Table S2. Presentation characteristics and in-hospital findings/management.

		SMuRFs=0 (Men) N=7700	SMuRFs=0 (Women) N=3431	SMuRFs>0 (Men) N=53176	SMuRFs>0 (Women) N=35411	Overall N=99718
Presentation characteristics						
Systolic blood pressure (mmHg)	n	7451	3309	51265	34141	96166
	Median (IQR)	147 (130, 164)	142 (125, 161)	150 (134, 170)	150 (130, 172)	150 (131, 170)
Diastolic blood pressure (mmHg)	n	7249	3229	50122	33237	93837
	Median (IQR)	85 (75, 95)	80 (70, 90)	87 (77, 99)	82 (70, 95)	85 (75, 97)
Heart rate (per min)	n	7467	3323	51487	34284	96561
	Median (IQR)	75 (64, 90)	82 (70, 100)	78 (66, 92)	82 (70, 100)	80 (68, 95)
Cardiac arrest on admission		316 (4.10%)	101 (2.95%)	1380 (2.60%)	758 (2.14%)	2555 (2.56%)
LV function grade	Normal (>=50%)	4050 (67)	1558 (64)	28046 (67)	16644 (65)	50298 (66)
	Slightly below normal (40-49%)	1058 (17)	438 (18)	7411 (18)	4629 (18)	13536 (18)
	Moderately below normal (30-39%)	546 (9)	284 (12)	3849 (9)	2663 (10)	7342 (10)
	Severely below normal (<30%)	319 (5)	122 (5)	2065 (5)	1191 (5)	3697 (5)
	Unknown	75 (1)	24 (1)	492 (1)	341 (1)	932 (1)
Culprit Lesion Territory	Intermediate	115 (1)	24 (1)	702 (1)	183 (1)	1024 (1)
	LAD	2168 (28)	473 (14)	13476 (25)	6020 (17)	22137 (22)
	LCx	1044 (14)	178 (5)	7650 (14)	3048 (9)	11920 (12)
	LMCA	84 (1)	21 (1)	500 (1)	267 (1)	872 (1)
	RCA	1034 (13)	219 (6)	7419 (14)	3893 (11)	12565 (13)
	Unknown	3251 (42)	2515 (73)	23395 (44)	21986 (62)	51147 (51)
In-hospital management						
PCI		625 (8)	147 (4)	3327 (6)	1474 (4)	5573 (6)
CABG		277 (4)	32 (1)	2154 (4)	712 (2)	3175 (3)
Angiography		6165 (80)	2085 (61)	42762 (80)	22889 (65)	73901 (74)
Multi vessel disease		2325 (38)	370 (18)	19761 (46)	7566 (33)	30022 (41)
Infarction type	Type 1	4070 (93)	1455 (83)	27796 (93)	16808 (87)	50129 (91)
	Type 2	283 (7)	305 (17)	1972 (7)	2577 (13)	5137 (9)
Length of stay	n	7700	3431	53175	35411	99717
	Median (IQR)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 6.0)	4.0 (3.0, 7.0)	4.0 (3.0, 7.0)
Troponin T (ng/L)	n	1588	739	10954	7557	20838
	Median (IQR)	0.7 (0.2, 2.2)	0.5 (0.2, 1.4)	0.6 (0.2, 2.3)	0.5 (0.2, 1.8)	0.6 (0.2, 2.0)
High-sensitivity troponin T (ng/L)	n	3070	1217	20538	13103	37928

	Median (IQR)	349.5 (115.0, 1040.0)	308.0 (118.0, 787.0)	301.0 (107.0, 911.0)	260.0 (102.0, 700.0)	290.0 (106.0, 840.5)
Troponin I (ng/mL)	n	2193	1146	17278	12075	32692
	Median (IQR)	3.4 (0.7, 12.0)	2.2 (0.6, 6.6)	2.9 (0.6, 10.9)	2.1 (0.5, 7.6)	2.5 (0.6, 9.6)
In-hospital complications						
All-cause death		303 (4)	182 (5)	1598 (3)	1432 (4)	3515 (4)
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalization for heart failure)		1576 (20)	987 (29)	12265 (23)	11349 (32)	26177 (26)
Myocardial infarction		227 (3)	107 (3)	1689 (3)	1095 (3)	3118 (3)
Cardiogenic shock		126 (2)	60 (2)	602 (1)	423 (1)	1211 (1)
Heart failure		1266 (17)	861 (26)	10469 (20)	10197 (30)	22793 (24)
Major bleeding		144 (2)	65 (2)	900 (2)	816 (2)	1925 (2)
Stroke		60 (1)	26 (1)	462 (1)	354 (1)	902 (1)
Symptom onset to coronary care or emergency room admission, hours	n	6373	2807	44608	29369	83157
	Median (IQR)	6.3 (3.5, 14.0)	7.1 (4.0, 15.3)	6.5 (3.7, 14.8)	7.0 (4.0, 14.8)	6.8 (3.8, 14.8)
Time from symptom onset to PCI start (hours)	n	2589	826	16516	8792	28723
	Median (IQR)	26.5 (10.3, 52.6)	30.7 (14.4, 63.6)	30.3 (15.2, 60.3)	36.1 (18.0, 69.8)	31.3 (15.5, 62.7)
Discharge medication						
Statin		6313 (83)	2139 (63)	45867 (87)	26490 (75)	80809 (82)
Aspirin		6931 (94)	2884 (89)	47937 (93)	30141 (89)	87893 (91)
$P2Y_{12}$ inhibitor		5764 (78)	2135 (66)	39625 (77)	23655 (70)	71179 (74)
β -blocker		6101 (83)	2517 (78)	45123 (88)	29136 (86)	82877 (86)
ACEi/ARB		4252 (58)	1485 (46)	37850 (73)	23465 (69)	67052 (70)

Values are medians (interquartile ranges) and number (n, %) for categorical variables. ACEi, angiotensin converting enzyme inhibitor, ARB, angiotensin receptor II antagonist, MI, myocardial infarction, PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting.

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Table S3. Associations between SMuRF status, sex, and all-cause death during hospitalization, analysed by logistic regression.

Model	No. of obs	Variable	Reference group	OR (95% CI)	P-value
Unadjusted	99718	SMuRF	SMuRF>0	1.287 (1.167 - 1.419)	<.0001
Unadjusted (complete dataset)	99148	SMuRF	SMuRF>0	1.233 (1.114 - 1.363)	<.0001
Adjusted	99148	SMuRF	SMuRF>0	1.284 (1.156 - 1.426)	<.0001
		Sex	Male	0.861 (0.801 - 0.925)	<.0001
		Age		2.399 (2.308 - 2.493)	<.0001
		Pre-hospital aspirin	No	1.185 (1.101 - 1.276)	<.0001

Logistic regression analyses, in the total population, in: 1, unadjusted model; 2, unadjusted model with complete dataset, 3, model adjusted for sex, pre-admission ongoing aspirin therapy, and age. Odds ratio (OR) for continuous variables based on 10-unit increase.

Table S4. Unadjusted outcomes, from hospital admission at different time points.

	Overall N=99718	SMuRFs=0 N=11131	SMuRFs>0 N=88587	P-value
All-cause death at full follow-up	34647 (35)	3508 (32)	31139 (35)	<.0001
All-cause death at full follow-up (from discharge)	31132 (32)	3023 (28)	28109 (33)	<.0001
All-cause death at 36 months	19585 (20)	2064 (19)	17521 (20)	0.0020
All-cause death at 24 months	16110 (16)	1745 (16)	14365 (16)	0.1455
All-cause death at 12 months	11810 (12)	1324 (12)	10486 (12)	0.8589
All-cause death at 1 month	5105 (5)	663 (6)	4442 (5)	<.0001
MI at full follow-up	14762 (15)	1311 (12)	13451 (15)	<.0001
Myocardial infarction at 36 months	11325 (11)	1002 (9)	10323 (12)	<.0001
Myocardial infarction at 24 months	10144 (10)	893 (8)	9251 (10)	<.0001
Myocardial infarction at 12 months	8337 (8)	743 (7)	7594 (9)	<.0001
Myocardial infarction at 1 month	4265 (4)	431 (4)	3834 (4)	0.0251
Stroke at full follow-up	5216 (5)	471 (4)	4745 (5)	<.0001
Stroke at 36 months	2864 (3)	250 (2)	2614 (3)	<.0001
Stroke at 24 months	2227 (2)	197 (2)	2030 (2)	0.0004
Stroke at 12 months	1431 (1)	137 (1)	1294 (1)	0.0546
Stroke at 1 month	277 (0)	34 (0)	243 (0)	0.5562
Major bleeding at full follow-up	5935 (6)	570 (5)	5365 (6)	<.0001
Major bleeding at 36 months	3681 (4)	356 (3)	3325 (4)	0.0034
Major bleeding at 24 months	3059 (3)	292 (3)	2767 (3)	0.0039
Major bleeding at 12 months	2242 (2)	215 (2)	2027 (2)	0.0168
Major bleeding at 1 month	485 (0)	42 (0)	443 (1)	0.0793
Cardiovascular death at full follow-up	17000 (17)	1726 (16)	15274 (17)	<.0001
Cardiovascular death at 36 months	11148 (11)	1178 (11)	9970 (11)	0.0341
Cardiovascular death at 24 months	9530 (10)	1022 (9)	8508 (10)	0.1529
Cardiovascular death at 12 months	7497 (8)	833 (7)	6664 (8)	0.8832
Cardiovascular death at 1 month	3920 (4)	522 (5)	3398 (4)	<.0001
Heart failure at full follow-up	9736 (10)	690 (6)	9046 (10)	<.0001
Heart failure at 36 months	6767 (7)	442 (4)	6325 (7)	<.0001
Heart failure at 24 months	5879 (6)	384 (3)	5495 (6)	<.0001
Heart failure at 12 months	4611 (5)	300 (3)	4311 (5)	<.0001
Heart failure at 1 month	1215 (1)	86 (1)	1129 (1)	<.0001
Recurrent revascularization at full follow-up	5629 (6)	401 (4)	5228 (6)	<.0001
Recurrent revascularization at 36 months	5007 (5)	359 (3)	4648 (5)	<.0001
Recurrent revascularization at 24 months	4811 (5)	346 (3)	4465 (5)	<.0001
Recurrent revascularization at 12 months	4492 (5)	329 (3)	4163 (5)	<.0001
Recurrent revascularization at 1 month	2401 (2)	190 (1.7)	2211 (2.5)	<.0001
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at full follow-up	45492 (46)	4553 (41)	40939 (46)	<.0001
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 36 months	31548 (32)	3079 (28)	28469 (32)	<.0001
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 24 months	27603 (28)	2697 (24)	24906 (28)	<.0001
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 12 months	22039 (22)	2194 (20)	19845 (22)	<.0001
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 1 month	10385 (10)	1174 (11)	9211 (10)	0.6266
All-cause death, myocardial infarction or heart failure at full follow-up	43970 (44)	4408 (40)	39562 (45)	<.0001
All-cause death, myocardial infarction or heart failure at 36 months	30196 (30)	2963 (27)	27233 (31)	<.0001
All-cause death, myocardial infarction or heart failure at 24 months	26424 (26)	2600 (23)	23824 (27)	<.0001

All-cause death, myocardial infarction or heart failure at 12 months	21223 (21)	2120 (19)	19103 (22)	<.0001
All-cause death, myocardial infarction or heart failure at 1 month	10179 (10)	1147 (10)	9032 (10)	0.7205
All-cause death or myocardial infarction at full follow-up	41854 (42)	4246 (38)	37608 (42)	<.0001
All-cause death or myocardial infarction at 24 months	23583 (24)	2417 (22)	21166 (24)	<.0001
All-cause death or myocardial infarction at 12 months	18558 (19)	1945 (17)	16613 (19)	0.0011
All-cause death or myocardial infarction at 1 month	9143 (9)	1077 (10)	8066 (9)	0.0493

Data are event number (%).

Table S5. Unadjusted outcomes, from hospital admission at different time points, by sex.

	SMuRFs=0 (MEN) N=7700	SMuRFs=0 (WOMEN) N=3431	SMuRFs>0 (MEN) N=53176	SMuRFs>0 (WOMEN) N=35411	Overall N=99718
All-cause death at full follow-up (from admission)	2133 (28)	1375 (40)	16287 (31)	14852 (42)	34647 (35)
All-cause death at full follow-up (from discharge)	1830 (25)	1193 (37)	14689 (28)	13420 (39)	31132 (32)
All-cause death at 36 months	1225 (16)	839 (24)	8965 (17)	8556 (24)	19585 (20)
All-cause death at 24 months	1037 (13)	708 (21)	7377 (14)	6988 (20)	16110 (16)
All-cause death at 12 months	792 (10)	532 (16)	5397 (10)	5089 (14)	11810 (12)
All-cause death at 1 month	417 (5)	246 (7)	2346 (4)	2096 (6)	5105 (5)
MI at full follow-up	902 (12)	409 (12)	7562 (14)	5889 (17)	14762 (15)
Myocardial infarction at 36 months	671 (9)	331 (10)	5708 (11)	4615 (13)	11325 (11)
Myocardial infarction at 24 months	598 (8)	295 (9)	5141 (10)	4110 (12)	10144 (10)
Myocardial infarction at 12 months	503 (7)	240 (7)	4289 (8)	3305 (9)	8337 (8)
Myocardial infarction at 1 month	306 (4)	125 (4)	2298 (4)	1536 (4)	4265 (4)
Stroke at full follow-up	290 (4)	181 (5)	2527 (5)	2218 (6)	5216 (5)
Stroke at 36 months	155 (2)	95 (3)	1346 (3)	1268 (4)	2864 (3)
Stroke at 24 months	123 (2)	74 (2)	1050 (2)	980 (3)	2227 (2)
Stroke at 12 months	88 (1)	49 (1)	650 (1)	644 (2)	1431 (1)
Stroke at 1 month	17 (0)	17 (0)	115 (0)	128 (0)	277 (0)
Major bleeding at full follow-up	416 (5)	154 (4)	3447 (6)	1918 (5)	5935 (6)
Major bleeding at 36 months	255 (3)	101 (3)	2122 (4)	1203 (3)	3681 (4)
Major bleeding at 24 months	213 (3)	79 (2)	1765 (3)	1002 (3)	3059 (3)
Major bleeding at 12 months	160 (2)	55 (2)	1288 (2)	739 (2)	2242 (2)
Major bleeding at 1 month	32 (0)	10 (0)	281 (1)	162 (0)	485 (0)
Cardiovascular death at full follow-up	1018 (13)	708 (21)	7607 (14)	7667 (22)	17000 (17)
Cardiovascular death at 36 months	688 (9)	490 (14)	4943 (9)	5027 (14)	11148 (11)
Cardiovascular death at 24 months	604 (8)	418 (12)	4237 (8)	4271 (12)	9530 (10)
Cardiovascular death at 12 months	497 (6)	336 (10)	3343 (6)	3321 (9)	7497 (8)
Cardiovascular death at 1 month	324 (4)	198 (6)	1759 (3)	1639 (5)	3920 (4)
Heart failure at full follow-up	451 (6)	239 (7)	4688 (9)	4358 (12)	9736 (10)
Heart failure at 36 months	273 (4)	169 (5)	3179 (6)	3146 (9)	6767 (7)
Heart failure at 24 months	233 (3)	151 (4)	2755 (5)	2740 (8)	5879 (6)
Heart failure at 12 months	185 (2)	115 (3)	2155 (4)	2156 (6)	4611 (5)
Heart failure at 1 month	48 (1)	38 (1)	550 (1)	579 (2)	1215 (1)
Revascularization at full follow-up	298 (4)	103 (3)	3498 (7)	1730 (5)	5629 (6)
Revascularization at 36 months	270 (4)	89 (3)	3155 (6)	1493 (4)	5007 (5)
Revascularization at 24 months	263 (3)	83 (2)	3041 (6)	1424 (4)	4811 (5)
Revascularization at 12 months	253 (3)	76 (2)	2862 (5)	1301 (4)	4492 (5)
Revascularization at 1 month	154 (2)	36 (1)	1623 (3)	588 (2)	2401 (2)
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at full follow-up	2902 (38)	1651 (48)	22261 (42)	18678 (53)	45492 (46)
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 36 months	1923 (25)	1156 (34)	15188 (29)	13281 (38)	31548 (32)
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 24 months	1681 (22)	1016 (30)	13309 (25)	11597 (33)	27603 (28)
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 12 months	1380 (18)	814 (24)	10633 (20)	9212 (26)	22039 (22)
Major adverse cardiovascular event (all-cause death, myocardial infarction, stroke, hospitalisation for heart failure) at 1 month	763 (10)	411 (12)	5092 (10)	4119 (12)	10385 (10)
All-cause death, myocardial infarction or heart failure at full follow-up	2808 (36)	1600 (47)	21425 (40)	18137 (51)	43970 (44)

All-cause death, myocardial infarction or heart failure at 36 months	1851 (24)	1112 (32)	14478 (27)	12755 (36)	30196 (30)
All-cause death, myocardial infarction or heart failure at 24 months	1620 (21)	980 (29)	12695 (24)	11129 (31)	26424 (26)
All-cause death, myocardial infarction or heart failure at 12 months	1330 (17)	790 (23)	10222 (19)	8881 (25)	21223 (21)
All-cause death, myocardial infarction or heart failure at 1 month	748 (10)	399 (12)	5007 (9)	4025 (11)	10179 (10)
All-cause death or myocardial infarction at full follow-up	2685 (35)	1561 (45)	20340 (38)	17268 (49)	41854 (42)
All-cause death or myocardial infarction at 24 months	1498 (19)	919 (27)	11302 (21)	9864 (28)	23583 (24)
All-cause death or myocardial infarction at 12 months	1217 (16)	728 (21)	8934 (17)	7679 (22)	18558 (19)
All-cause death or myocardial infarction at 1 month	711 (9)	366 (11)	4537 (9)	3529 (10)	9143 (9)

Table S6. Unadjusted and adjusted Cox proportional hazards analyses at 30 days by sex.

Outcome		Sex	Number of patients (events)	Unadjusted hazard ratio (95% CI)	p-value	Adjusted hazard ratio (95% CI)	p-value
All-cause mortality	>0 SMuRF	Men	53176 (2346)	1		1	
	SMuRFless	Men	7700 (417)	1.24 (1.11-1.37)	<.0001	1.16 (1.04-1.30)	0.0067
	>0 SMuRF	Women	35411 (2096)	1		1	
	SMuRFless	Women	3431 (246)	1.22 (1.07-1.40)	0.0027	1.26 (1.10-1.45)	0.0008
Cardiovascular death	>0 SMuRF	Men	53176 (1759)	1		1	
	SMuRFless	Men	7700 (324)	1.28 (1.14-1.44)	<.0001	1.22 (1.07-1.38)	0.0021
	>0 SMuRF	Women	35411 (1639)	1		1	
	SMuRFless	Women	3431 (198)	1.26 (1.09-1.46)	0.0021	1.30 (1.12-1.52)	0.0007
Myocardial infarction	>0 SMuRF	Men	53176 (2298)	1		1	
	SMuRFless	Men	7700 (306)	0.92 (0.82-1.04)	0.1708	0.95 (0.84-1.07)	0.4055
	>0 SMuRF	Women	35411 (1536)	1		1	
	SMuRFless	Women	3431 (125)	0.84 (0.70-1.01)	0.0607	0.88 (0.73-1.05)	0.1588
Heart failure hospitalisation	>0 SMuRF	Men	53176 (550)	1		1	
	SMuRFless	Men	7700 (48)	0.60 (0.45-0.81)	0.0007	0.59 (0.44-0.79)	0.0005
	>0 SMuRF	Women	35411 (579)	1		1	
	SMuRFless	Women	3431 (38)	0.68 (0.49-0.94)	0.0193	0.72 (0.52-1.01)	0.0550
Stroke	>0 SMuRF	Men	53176 (115)	1		1	
	SMuRFless	Men	7700 (17)	1.02 (0.61-1.70)	0.9364	1.10 (0.65-1.84)	0.7247
	>0 SMuRF	Women	35411 (128)	1		1	
	SMuRFless	Women	3431 (17)	1.37 (0.83-2.28)	0.2200	1.57 (0.94-2.63)	0.0847
Bleeding	>0 SMuRF	Men	53176 (281)	1		1	
	SMuRFless	Men	7700 (32)	0.79 (0.55-1.13)	0.1977	0.74 (0.51-1.07)	0.1089
	>0 SMuRF	Women	35411 (162)	1		1	
	SMuRFless	Women	3431 (10)	0.64 (0.34-1.21)	0.1658	0.63 (0.33-1.21)	0.1653
Revascularization	>0 SMuRF	Men	53176 (1623)	1		1	
	SMuRFless	Men	7700 (154)	0.65 (0.55-0.77)	<.0001	0.70 (0.59-0.83)	<.0001
	>0 SMuRF	Women	35411 (588)	1		1	
	SMuRFless	Women	3431 (36)	0.63 (0.45-0.88)	0.0071	0.63 (0.44-0.88)	0.0076

Cox proportional hazards analyses in: 1, unadjusted model; and 2 multivariable model adjusted for sex, pre-admission ongoing aspirin therapy, and age. Hazard ratios (HR) with 95% confidence intervals (CI) for continuous variables based on 10-unit increase.

Table S7. Unadjusted and adjusted cox proportional hazards models for all-cause mortality at 30 days in patients with unknown smoking status being imputed.

	Adjustment	Overall HR (95% CI)	p-value	Men HR (95% CI)	p-value	Women HR (95% CI)	p-value
Main manuscript results	Unadjusted Adjusted	1.20 (1.10-1.30) 1.20 (1.10-1.31)		1.24 (1.11-1.37) 1.16 (1.10-1.45)		1.22 (1.07-1.40) 1.26 (1.10-1.45)	
Imputed dataset	Unadjusted Adjusted	1.14 (1.05-1.24) 1.19 (1.09-1.29)	0.002 0.0001	1.17 (1.05-1.30) 1.14 (1.02-1.21)	0.006 0.019	1.19 (1.04-1.37) 1.27 (1.10-1.46)	0.0133 0.0008

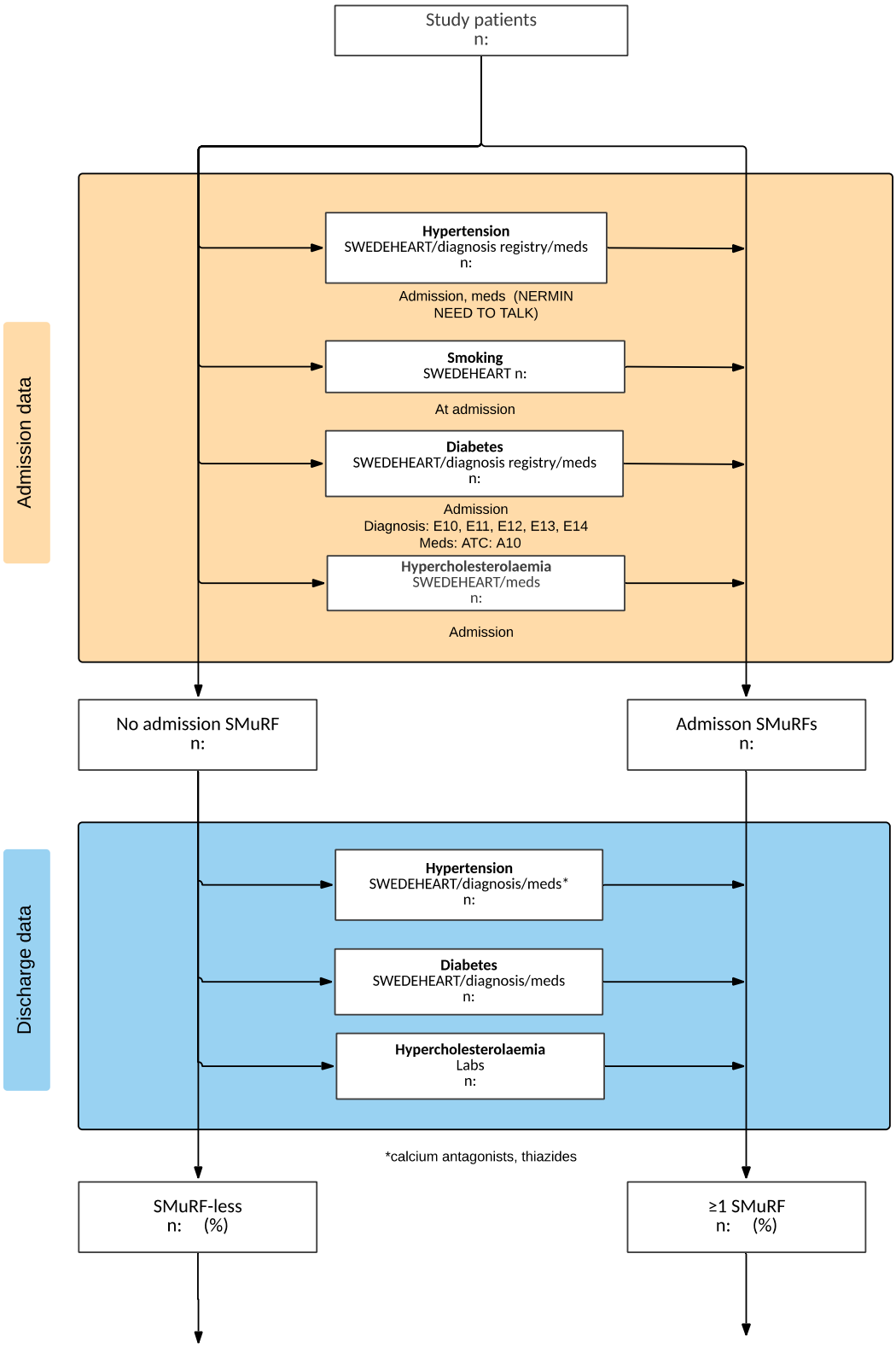
Cox proportional hazards analyses in: 1, unadjusted model; and 2 multivariable model adjusted for sex, pre-admission ongoing aspirin therapy, and age for main manuscript dataset and dataset imputed for smoking status (missing at random). Hazard ratios (HR) with 95% confidence intervals (CI) for continuous variables based on 10-unit increase.

Table S8. Association between SMuRF-less status and outcomes up to 12 years min patients surviving 30 days before and after adjustment for age, sex and pre- admission ongoing aspirin therapy.

	Outcome	Parameter	n	Reference group	Hazard ratio (95% CI)	p-value
Unadjusted	Bleeding	SMuRF	99718	>0 SMuRF	0.83 (0.76-0.91)	<.0001
	Cardiovascular death	SMuRF	99718	>0 SMuRF	0.79 (0.75-0.84)	<.0001
	Myocardial infarction	SMuRF	99718	>0 SMuRF	0.70 (0.65-0.75)	<.0001
	Stroke	SMuRF	99718	>0 SMuRF	0.75 (0.68-0.83)	<.0001
	All-cause mortality	SMuRF	99718	>0 SMuRF	0.83 (0.80-0.86)	<.0001
	Heart failure hospitalization	SMuRF	99718	>0 SMuRF	0.58 (0.54-0.63)	<.0001
	Revascularization	SMuRF	99718	>0 SMuRF	0.55 (0.48-0.63)	<.0001
Adjusted	Bleeding	SMuRF	99148	>0 SMuRF	0.84 (0.76-0.91)	0.0001
		Sex		Male	0.70 (0.66-0.75)	<.0001
		Pre-hospital aspirin		No	1.11 (1.04-1.18)	0.0007
		Age (in 10 years)			1.47 (1.43-1.50)	<.0001
	Cardiovascular death	SMuRF	99148	>0 SMuRF	0.84 (0.79-0.89)	<.0001
		Sex		Male	1.00 (0.97-1.04)	0.8281
		Pre-hospital aspirin		No	1.41 (1.36-1.46)	<.0001
		Age (in 10 years)			2.56 (2.51-2.61)	<.0001
	Myocardial infarction	SMuRF	99148	>0 SMuRF	0.78 (0.73-0.83)	<.0001
		Sex		Male	1.09 (1.05-1.13)	<.0001
		Pre-hospital aspirin		No	1.48 (1.42-1.54)	<.0001
		Age (in 10 years)			1.33 (1.31-1.35)	<.0001
	Stroke	SMuRF	99148	>0 SMuRF	0.84 (0.76-0.93)	0.0009
		Sex		Male	1.04 (0.98-1.10)	0.1697
		Pre-hospital aspirin		No	1.56 (1.47-1.65)	<.0001
		Age (in 10 years)			1.61 (1.57-1.66)	<.0001
	All-cause mortality	SMuRF	99148	>0 SMuRF	0.85 (0.82-0.89)	<.0001
		Sex		Male	0.97 (0.95-0.99)	0.0091
		Pre-hospital aspirin		No	1.25 (1.22-1.28)	<.0001
		Age (in 10 years)			2.20 (2.17-2.22)	<.0001
	Heart failure hospitalization	SMuRF	99148	>0 SMuRF	0.62 (0.57-0.68)	<.0001
		Sex		Male	1.01 (0.97-1.06)	0.5601
		Pre-hospital aspirin		No	1.33 (1.27-1.39)	<.0001
		Age (in 10 years)			1.88 (1.84-1.92)	<.0001
	Revascularization	SMuRF	99148	>0 SMuRF	0.60 (0.52-0.69)	<.0001
		Sex		Male	0.90 (0.83-0.97)	0.0039
		Pre-hospital aspirin		No	1.55 (1.43-1.67)	<.0001
		Age (in 10 years)			1.05 (1.01-1.08)	0.0037

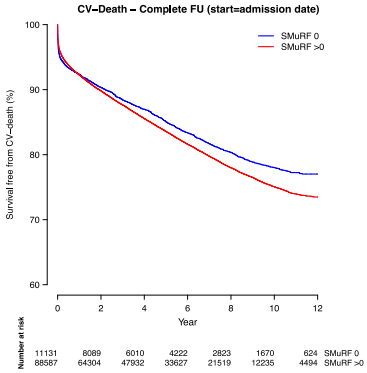
Cox proportional hazards analyses in: 1, unadjusted model; and 2 multivariable model adjusted for sex, pre-admission ongoing aspirin therapy, and age. Hazard ratios (HR) with 95% confidence intervals (CI) for continuous variables based on 10-unit increase.

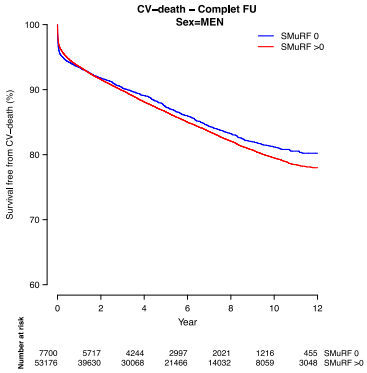
Figure S1. Flow chart.
(Numbers will be added to next iteration)

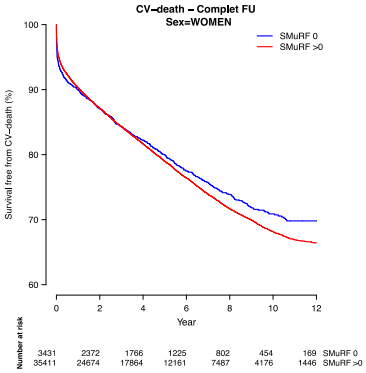


Flow-chart of patients included in the study and SMuRF definition. Current smoking is defined as having regularly smoked within the past 1month prior to hospitalization. Hypercholesterolaemia is defined as a prior diagnosis of hypercholesterolaemia, or prior cholesterol lowering treatment, or a fasting LDL-C ≥3.5 mmol/L, or a total cholesterol ≥5.5 mmol/L during admission. Diabetes mellitus is defined as a prior diagnosis of diabetes mellitus or ongoing or previous glucose lowering pharmacotherapy. Hypertension is defined as a prior diagnosis of hypertension or antihypertensive pharmacotherapy (calcium channel blocker, b-blocker, antihypertensive diuretic, angiotensin converting enzyme inhibitor, angiotensin receptor II antagonist).

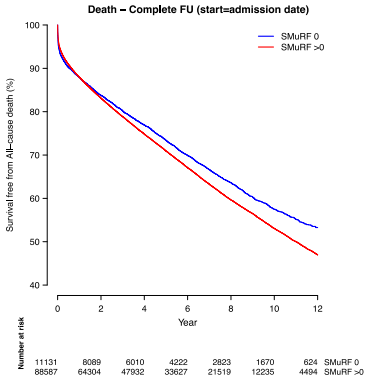
Figure S2. Kaplan Meier survival curves for cardiovascular death (upper panels) and all cause death (lower panels) up to 12 years of follow-up for 0 SMuRFs and >0 SMuRFs for all patients and by sex. (Log rank will be embedded in next version.)

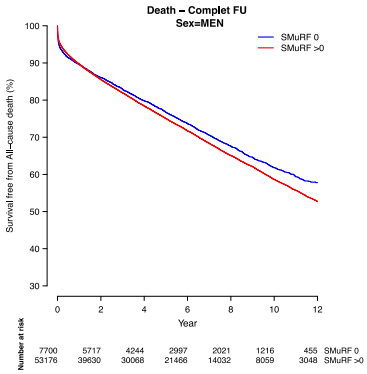


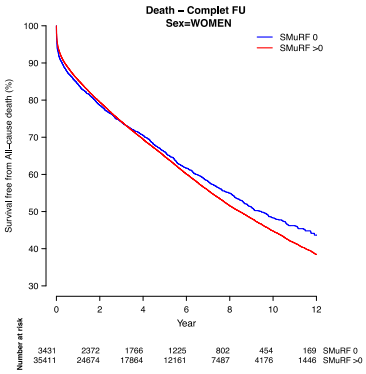




Log rank: P<0.0001 P=0.17 P<0.0001







Log rank: P<0.0001 P=0.035 P<0.0001

Figure S3. Schoenfeld residual plots at 30 days and 6 months for all-cause mortality.

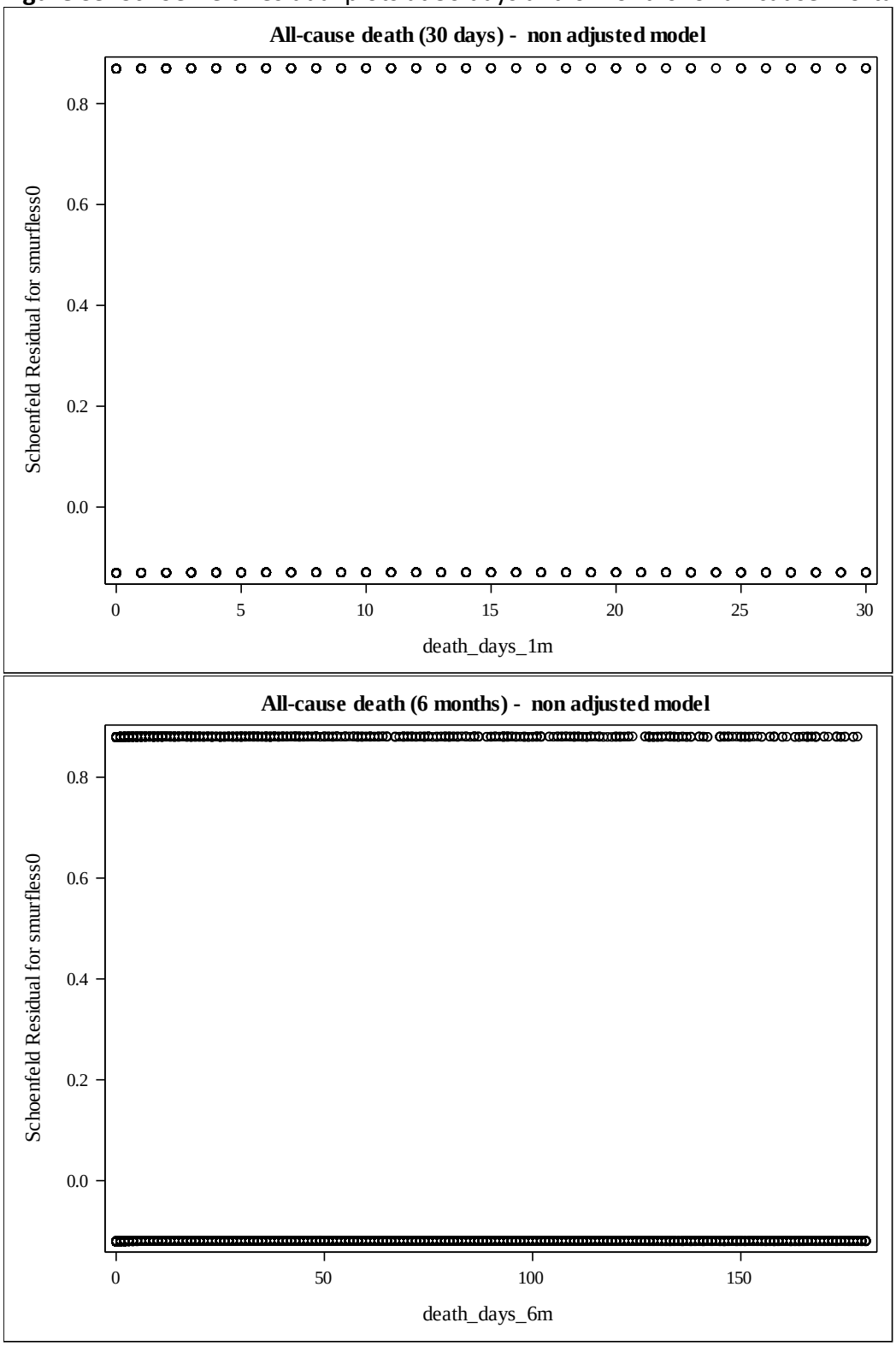


Figure S4. Proportion of SMuRF-less NSTEMI patients over the study period.

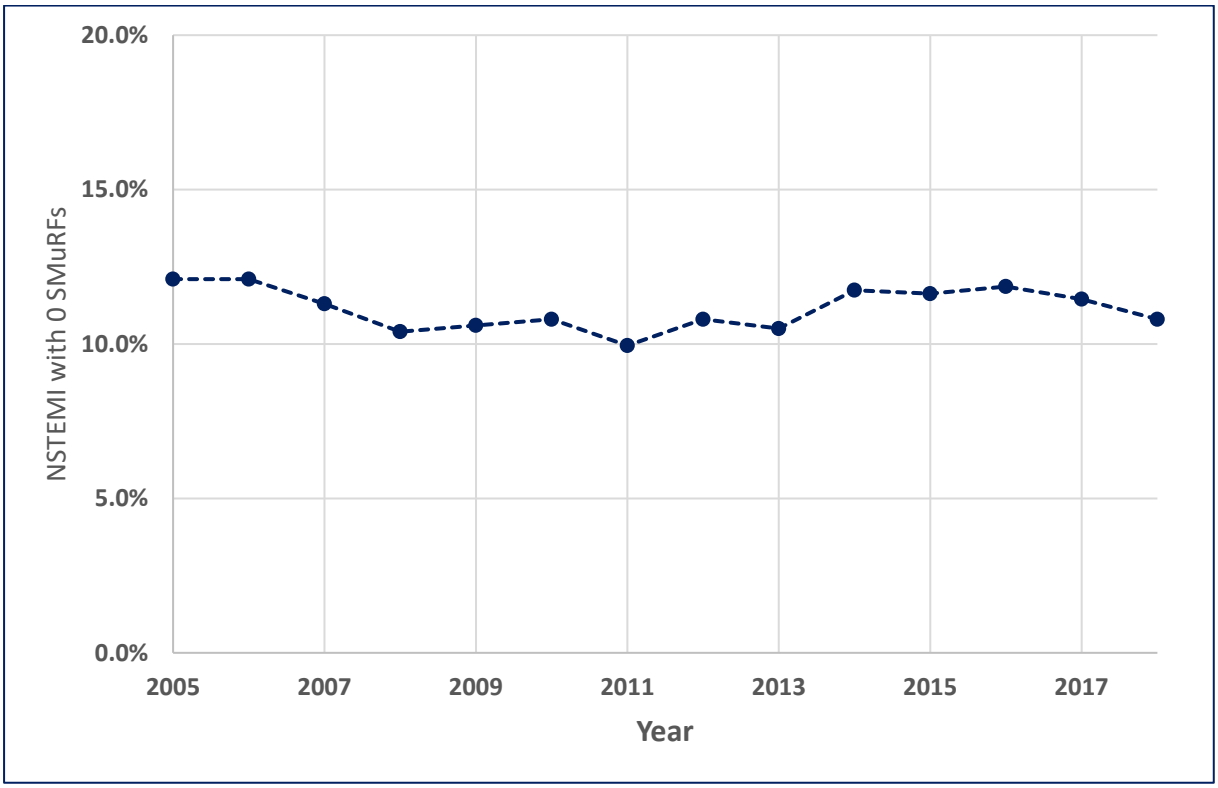


Figure S5. Adjusted hazard ratios (HR, 95% confidence intervals, CI) for SMuRF-less versus >0 SMuRF status for: all-cause mortality, cardiovascular (CV) mortality, recurrent myocardial infarction (MI), heart failure, stroke, bleeding, and revascularization at 6 months. Point estimates and 95% confidence intervals are presented from analyses adjusted for age, sex and pre-admission ongoing aspirin therapy.

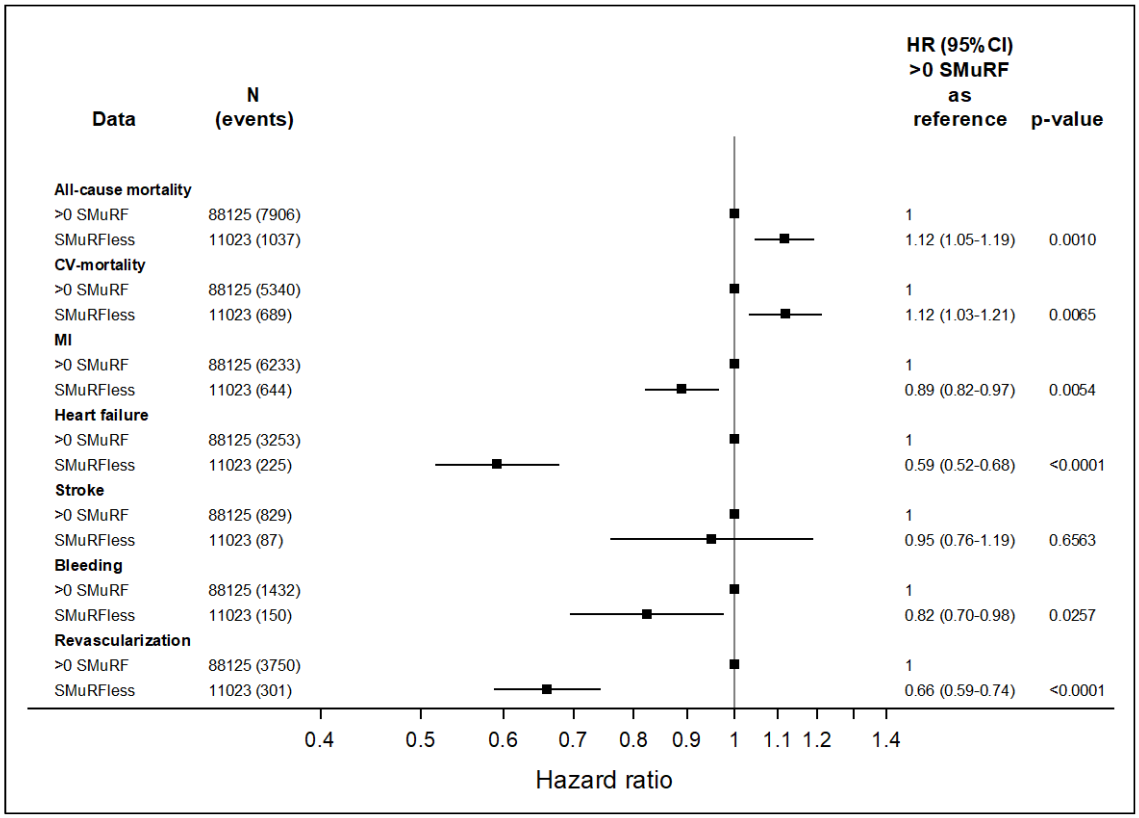
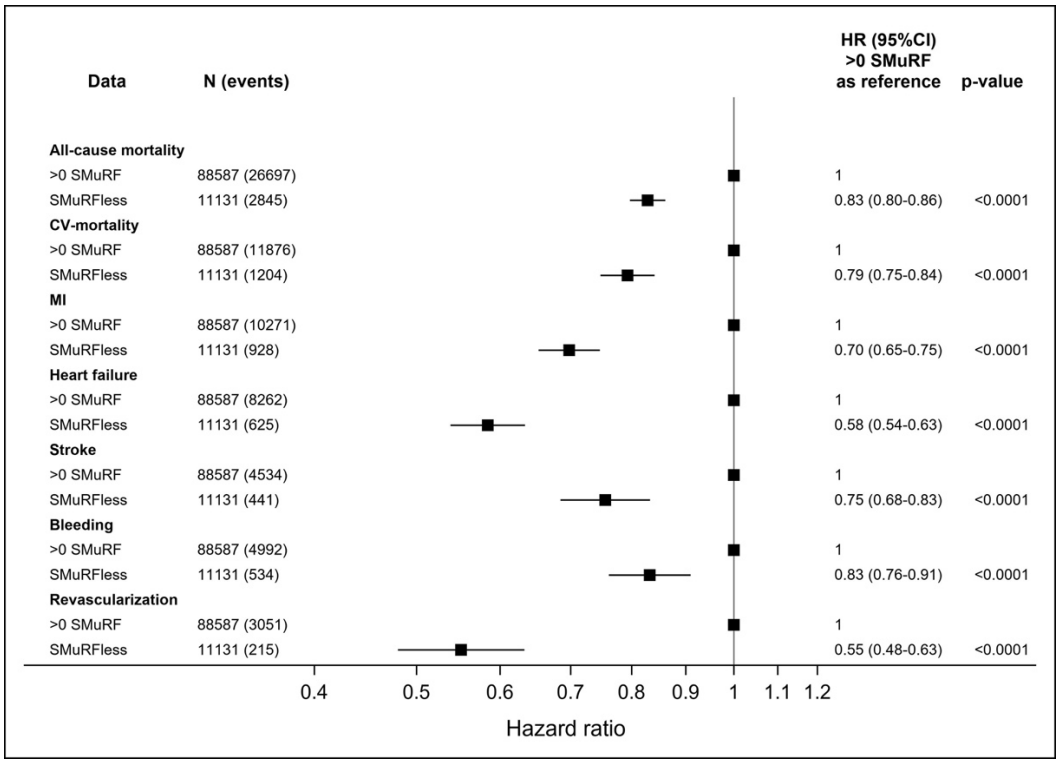


Figure S6. Adjusted hazard ratios (HR, 95% confidence intervals, CI) for SMuRF-less versus >0 SMuRF status for: all-cause mortality, cardiovascular (CV) mortality, recurrent myocardial infarction (MI), heart failure, stroke, bleeding, and revascularization up to 12 years in patients that survived 30 days after the index MI. Point estimates and 95% confidence intervals are presented from unadjusted analyses (A) and analyses adjusted (B) for age, sex and pre-admission ongoing aspirin therapy.

A



B