

ST-Segment–Elevation Myocardial Infarction (STEMI) Patients Without Standard Modifiable Cardiovascular Risk Factors—How Common Are They, and What Are Their Outcomes?

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Background—Programs targeting the standard modifiable cardiovascular risk factors (SMuRFs: hypertension, diabetes mellitus, hypercholesterolemia, smoking) are critical to tackling coronary heart disease at a community level. However, myocardial infarction in SMuRF-less individuals is not uncommon. This study uses 2 sequential large, multicenter registries to examine the proportion and outcomes of SMuRF-less ST-segment–elevation myocardial infarction (STEMI) patients.

Methods and Results—We identified 3081 STEMI patients without a prior history of cardiovascular disease in the Australian GRACE (Global Registry of Acute Coronary Events) and CONCORDANCE (Cooperative National Registry of Acute Coronary Syndrome Care) registries, encompassing 42 hospitals, between 1999 and 2017. We examined the proportion that were SMuRF-less as well as outcomes. The primary outcome was in-hospital mortality, and the secondary outcome was major adverse cardiovascular events (death, myocardial infarction, or heart failure, during the index admission). Multivariate regression models were used to identify predictors of major adverse cardiovascular events. Of STEMI patients without a prior history of cardiovascular disease 19% also had no history of SMuRFs. This proportion increased from 14% to 23% during the study period ($P=0.0067$). SMuRF-less individuals had a higher in-hospital mortality rate than individuals with 1 or more SMuRFs. There were no clinically significant differences in major adverse cardiovascular events at 6 months between the 2 groups.

Conclusions—A substantial and increasing proportion of STEMI presentations occur independently of SMuRFs. Discovery of new markers and mechanisms of disease beyond standard risk factors may facilitate novel preventative strategies. Studies to assess longer-term outcomes of SMuRF-less STEMI patients are warranted. (*J Am Heart Assoc.* 2019;8:e013296. DOI: 10.1161/JAHA.119.013296.)

Key Words: atherosclerosis • mortality • risk factor • ST-segment–elevation myocardial infarction

The standard modifiable cardiovascular risk factors (SMuRFs) of diabetes mellitus, hyperlipidemia, hypertension, and cigarette smoking are central elements of the well-established Framingham cardiovascular risk score and many subsequent validated risk scores.^{1–4} Primary and secondary

prevention programs that utilize and target susceptible individuals' modifiable risk factors for coronary heart disease (CHD) have resulted in a substantial reduction in morbidity and mortality due to CHD, particularly in high-income and some middle-income countries.⁵ However, CHD remains a leading

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Clinical Perspective

What Is New?

- The proportion of ST-segment–elevation myocardial infarction patients without standard modifiable cardiovascular risk factors is not insubstantial and has been increasing in recent years.
- ST-segment–elevation myocardial infarction patients without standard modifiable cardiovascular risk factors have a higher in-hospital mortality rate than ST-segment–elevation myocardial infarction patients with 1 or more standard modifiable cardiovascular risk factors.

What Are the Clinical Implications?

- Discovery of new markers and mechanisms of coronary artery disease beyond standard risk factors may facilitate new preventative strategies.

cause of death in all regions of the world.⁶⁻⁸ ST-segment–elevation myocardial infarction (STEMI) has a higher in-hospital mortality rate than non–ST-segment–elevation acute coronary syndromes.^{9,10} In a recent large, single-center cohort study, we reported that 25% of first-presentation STEMI patients, confirmed to be a result of atherosclerosis, had no known SMuRFs at the time of their event. Furthermore, the proportion of the STEMI cohort that was SMuRF-less increased significantly during the study period (2006-2014).¹¹

To date, in the fields of clinical and biomedical research, there has been a lack of attention paid to the SMuRF-less subgroup of STEMI patients. An example of this lack of attention is the traditional means of reporting risk factor profiles in STEMI clinical trials. Frequently the proportion of patients with diabetes mellitus, hypertension, smoking, and hypercholesterolemia are reported, but it is often difficult to extract information regarding the proportion without any traditional risk factors. For those that do report this, the proportion of SMuRF-lessness is similar to what we observed.¹² Given the absolute number of individuals that this proportion represents, and the mortality and morbidity of myocardial infarction, it is critical to determine any changing patterns on a broader scale than our single center and to formally study patterns of management and specific outcomes of SMuRF-less STEMI patients.

The Australian GRACE (Global Registry of Acute Coronary Events) and CONCORDANCE (Cooperative National Registry of Acute Coronary Syndrome Care) registries capture a large, unbiased population of patients presenting with acute coronary syndrome (ACS) to 42 hospitals across Australia, from 1999 to 2017 and provide us with an opportunity to examine our 3 key questions: (1) What is the proportion of STEMI patients who are SMuRF-less? (2) Is this changing over time?

(3) What are the short- and longer-term cardiovascular outcomes of SMuRF-less STEMI patients versus those with traditional risk factors, in a broad, representative, contemporary Australian context?

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Populations

Full details of the GRACE and CONCORDANCE registry methods have been published previously.^{13,14} GRACE and CONCORDANCE employed closely aligned inclusion and exclusion criteria designed to reflect an unbiased population of patients with ACS.^{13,14} In addition to symptoms consistent with myocardial ischemia, patients were required to have either ECG changes consistent with ACS, elevation of serum cardiac biomarkers of myocardial necrosis or documented coronary artery disease including STEMI, non–ST-segment–elevation myocardial infarction, and unstable angina. To enroll an unselected population, the first 10-20 consecutive eligible patients were recruited from each site per month. Hospitals in both registries were selected to represent regional and metropolitan acute-care facilities with and without catheterization laboratory facilities.

Inclusion Criteria

Patients included in this analysis were at least 18 years of age, presented with symptoms suggestive of coronary ischemia, and had a final diagnosis of STEMI. For this analysis, we limited our study to the Australian population enrolled in the GRACE registry between 1999 and 2007 and the CONCORDANCE registry between 2009 and 2017. No equivalent ACS registry data were available from the participating hospitals in 2008. An opt-out informed consent process was applied with a waiver of consent for patients who were too ill to provide informed consent. All participating hospitals received human research ethics approval to participate in the registries. Approval for this analysis was granted by the lead ethics committee, Concord Hospital, Sydney Local Health District.

Exclusion Criteria

ACSs precipitated by a significant noncardiovascular comorbidity such as anemia or trauma were excluded.¹³ For the purposes of this study, only patients presenting with their first cardiovascular event were included in the analysis. Therefore, patients with a known history of CHD (percutaneous

cardiovascular intervention, coronary artery bypass graft, ACS, or history of angina pectoris), cerebrovascular disease, or peripheral vascular disease or a final diagnosis other than STEMI, were excluded.

Data Sources

Data were collected by trained coordinators using standardized case report forms. Demographic characteristics, medical history, presenting symptoms, biochemical and electrocardiographic findings, treatment practices, and a variety of hospital outcome data were collected from the medical record. If a patient was transferred to an additional facility, data were collected from each facility. Patients were recontacted at 6, 12, and 24 months postdischarge for collection of data on unscheduled readmissions, unscheduled procedures (coronary angiography, percutaneous coronary intervention, coronary artery bypass graft surgery), and complications. To ensure data quality, a random sample of submitted case report forms were audited. In this analysis we report outcomes at 6 months only because of lower follow-up rates at later time points. Standardized definitions for all patient-related variables and clinical diagnoses were used across the 2 registries. We refer to a known history of hypertension, hyperlipidemia, diabetes mellitus, and current smoking as the 4 SMuRFs for cardiovascular disease (CVD). A patient was considered to be a current smoker if he or she had regularly smoked within the past 12 months. A patient was considered to have a known history of hyperlipidemia, diabetes mellitus, or hypertension if he or she identified as having a history of the same or was on pharmacological treatment for these conditions at the time of presentation. For the purposes of the study, primary analysis was focused on patients with a final diagnosis of STEMI presenting for the first time with CVD. A secondary analysis examined the proportion of SMuRF-less patients in the registry over the same study period as the primary analysis with a final diagnosis non-ST-segment–elevation acute coronary syndrome in the absence of a prior history of CVD as defined above.

Outcomes

The primary outcome was in-hospital mortality, and the secondary outcome was major adverse cardiovascular events (MACE) defined as death, myocardial infarction, or heart failure during the index admission and at 6 months. The study index date for both in-hospital and 6-month outcomes was the admission date. The 6-month MACE was based on postdischarge events only because not all subjects were able to be followed to 6 months.

Statistical Analyses

Categorical variables are summarized using frequencies and percentages, whereas numerical variables are summarized

using mean, SD, median, and quartiles. Multivariable logistic regression analyses were performed to estimate the adjusted odds ratio and 95% CI for the binary outcomes in-hospital mortality, in-hospital MACE, and 6-month MACE. The predictor variables were the components of the GRACE risk score (age, heart rate, systolic blood pressure, creatinine, Killip class, cardiac arrest, ST deviation, and initial positive biomarkers). These analyses were done within the framework of a generalized estimating equation. The Cochrane–Armitage trend test was used to determine if there was a trend across the study period for the proportion of ACS subjects who were SMuRF-less. All statistical tests were 2-tailed with the significance level set at 0.05. All statistical analyses are conducted using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Of the 13 911 patients enrolled in the GRACE Australia and CONCORDANCE ACS registry between 1999 and 2017, 3081 patients presented with their first cardiovascular event, had a final diagnosis of STEMI, and were included in the current analysis. The median age was 61 years (interquartile range 52 to 69 years), and 2310 (75%) were male. Of the total 3081 patients, 591 (19%) had 0 SMuRFs. The most common SMuRF was hypertension (44%), followed by current smoking (40%), dyslipidemia (37%), and diabetes mellitus (18%) (Table 1). The proportion of SMuRF-less STEMI patients was substantially higher in men than women (20% versus 15%; Table 1). In STEMI patients with and without SMuRFs there were small differences in the mean age (60.4 years [SD 12.9] versus 61.7 years [SD 12.4]), the proportion female (26% versus 19%), mean body mass index (28.5 [SD 5.43] versus 27.0 [SD 4.37]), history of atrial fibrillation (3% versus 1%), and the proportion of patients with a family history of CHD (36% versus 33%).

Presenting Characteristics and In-Hospital Management

In patients with and without SMuRFs, there were no significant differences in hemodynamic observations, Killip Class, cardiac arrest on admission, and GRACE risk score. There was also no significant difference in the incidence of significant multivessel disease (Table 2). A higher proportion of SMuRF-less patients received primary percutaneous coronary intervention than patients with 1 or more SMuRF (49% versus 45%), and a smaller proportion received thrombolysis (32% versus 37%). The proportion of SMuRF-less patients who were transferred to another hospital was lower than those with 1 or more SMuRFs (37% versus 44%). There was no

Table 1. Baseline (Preadmission) Characteristics

Variable	Statistic (Level)	0 SMuRFs (N=591)	>0 SMuRFs (N=2490)	Overall (N=3081)
Age	Mean (SD)	61.7 (12.39)	60.4 (12.88)	60.6 (12.80)
	Median (IQR)	62 (53-70)	60 (51-69)	60 (52-69)
Sex	Female (%)	115 (19)	656 (26)	771 (25)
	Male (%)	476 (81)	1834 (74)	2310 (75)
SMuRFs, n (%)				
Diabetes mellitus		0 (0)	554 (22)	554 (18)
Hypertension		0 (0)	1363 (55)	1363 (44)
Dyslipidemia		0 (0)	1126 (45)	1126 (37)
Current smoking		0 (0)	1243 (50)	1243 (40)
BMI	Mean (SD)	27.0 (4.37)	28.5 (5.43)	28.2 (5.28)
	Median (IQR)	26.8 (24.2-30.0)	27.8 (24.8-31.4)	27.8 (24.8-31.6)
Family history CHD, n (%)		180 (33)	790 (36)	970 (35)
Previous atrial fibrillation, n (%)		6 (1)	86 (3)	92 (3)
Prehospitalization medications, n (%)				
Statin		0 (0)	489 (20)	489 (16)
Aspirin		33 (6)	339 (14)	372 (12)
P ₂ Y ₁₂ inhibitor		7 (1)	45 (2)	52 (2)
β-blocker		0 (0)	219 (9)	219 (7)
ACE inhibitor		0 (0)	344 (14)	344 (11)
ARB		0 (0)	429 (17)	429 (14)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist blocker; BMI, body mass index; CHD, coronary heart disease; IQR, interquartile range; SMuRFs, standard modifiable cardiovascular risk factors.

clinically significant difference in evidence-based secondary prevention medications prescribed at time of discharge between those with and without SMuRFs (Table 3). We observed higher in-hospital and discharge use of angiotensin receptor blocker therapy use in patients with 1 or more SMuRFs. In secondary prevention angiotensin receptor blockers are second-line therapy generally reserved for patients unable to tolerate angiotensin-converting enzyme inhibitors. The higher rate of use of angiotensin receptor blockers in those with 1 or more SMuRFs may reflect a known intolerance to angiotensin-converting enzyme inhibitor administration.

Changing Proportion of SMuRF-Less STEMI

During the study period from 1999 to 2017, the proportion of STEMI patients with 0 SMuRFs increased from 14% to 23% (Cochrane-Armitage trend test, $P=0.0067$; Figure 1). Although this current study is focused on the STEMI cohort, we also performed a simple analysis of the SMuRF-less proportion in the 3773-subject subgroup of non-ST-segment-elevation acute coronary syndrome GRACE/CONCORDANCE subjects without prior CVD. It is important to note that this group is not

broadly representative of all non-ST-segment-elevation acute coronary syndromes, as it was intentionally enriched for patients with high-risk features based on their clinical presentation. Although the overall proportion (18%) was similar to that in the STEMI cohort, there was no statistically significant change in the SMuRF-less proportion during the study period.

In-Hospital Outcomes

The unadjusted in-hospital mortality rate for SMuRF-less STEMI patients was higher than that in patients with 1 or more SMuRFs (6% versus 4%). However, the rates of recurrent ischemic symptoms (12% versus 16%) and clinical heart failure (7% versus 11%) were lower in SMuRF-less patients compared with patients with 1 or more SMuRFs. There were no differences in the rates of recurrent in-hospital myocardial infarction, cardiogenic shock, or major bleeding between the groups (Table 4). In a multivariable analysis SMuRF-less status, cardiac arrest on admission, age greater than 70 years, heart rate greater than 90 beats/min, systolic blood pressure less than 155 mm Hg, and creatinine greater than 100 mmol/L predicted in-hospital mortality (Figure 2A).

Table 2. Patient Characteristics on Presentation

Variable	Statistic (Level)	0 SMuRFs (N=591)	>0 SMuRFs (N=2490)	Overall (N=3081)
Systolic blood pressure at time of presentation, mm Hg	Mean (SD)	137.6 (27.39)	137.6 (27.76)	137.6 (27.68)
	Median (IQR)	136 (119-154)	135 (119-155)	136 (119-155)
Diastolic blood pressure at time of presentation, mm Hg	Mean (SD)	82.8 (17.33)	82.1 (17.44)	82.2 (17.42)
	Median (IQR)	81 (70-93)	80 (70-93)	80 (70-93)
Heart rate, beats/min	Mean (SD)	77.4 (21.26)	78.9 (19.54)	78.6 (19.89)
	Median (IQR)	73 (63-88)	77 (65-90)	76 (65-90)
Killip class, n (%)				
1		542 (92)	2234 (90)	2776 (91)
2		31 (5)	174 (7)	205 (7)
3		9 (2)	45 (2)	54 (2)
4		6 (1)	21 (1)	27 (1)
Cardiac arrest on admission, n (%)		44 (7)	184 (7)	228 (7)
Serum creatinine, $\mu\text{mol/L}$	Mean (SD)	89.7 (24.77)	91.0 (40.80)	90.7 (38.24)
	Median (IQR)	87 (74-100)	84 (72-100)	85 (72-100)
Grace risk score	Mean (SD)	110.5 (29.67)	108.8 (30.02)	109.15 (29.59)
	Median (IQR)	108.2 (90.04-127.4)	106.0 (87.90-126.53)	106.5 (88.58-126.81)
Culprit lesion territory, n (%)				
Left main		0 (0)	5 (1)	5 (1)
Left anterior descending		34 (46)	144 (37)	178 (38)
Circumflex artery		8 (11)	47 (12)	55 (12)
Right coronary		22 (30)	151 (39)	173 (37)
Unknown		10 (14)	42 (11)	52 (11)
Multivessel disease, >50% stenosis		216 (38)	1025 (42)	1241 (41)
Left ventricular function	Normal, n (%)	117 (36)	509 (36)	626 (36)
	Mild impairment, n (%)	116 (36)	493 (34)	609 (35)
	Moderate impairment, n (%)	65 (20)	353 (25)	418 (24)
	Severe impairment, n (%)	25 (8)	76 (5)	101 (6)

IQR indicates interquartile range; SMuRFs, standard modifiable cardiovascular risk factors.

In a separate multivariable analysis, age greater than 70 years, heart rate greater than 90 beats/min, systolic blood pressure less than 155 mm Hg, cardiac arrest on admission, Killip class greater than 1, and negative cardiac biomarkers, but not SMuRF-less status, were all predictors of MACE, defined as death, myocardial infarction, or heart failure during the index admission (Figure 2B).

Posthospital Outcomes

Six-month follow-up data were available for 2487 of the original 3081 cohort (Table 5). There were no clinically significant differences in the unadjusted rates of recurrent

myocardial infarction, heart failure, or MACE in the first 6 months postdischarge. In a multivariable analysis, older age, higher heart rate, and higher Killip class but not SMuRF status were predictors of MACE at 6 months (Table 6).

Discussion

This large, multicenter study highlights the importance of the often-overlooked subgroup of STEMI patients with atherosclerosis not predicted by SMuRFs. We validate our previous published findings, from a single-center study, that the proportion of SMuRF-less STEMI patients is not insubstantial and has been significantly increasing in recent years. The

Table 3. Medical Management and Cardiac Procedures

Variable	0 SMuRFs (N=91)	>0 SMuRFs (N=2490)	Overall (N=3081)
In-hospital treatment, n (%)			
Statin	535 (91)	2267 (91)	2802 (91)
Aspirin	571 (97)	2437 (98)	3008 (98)
P ₂ Y ₁₂ receptor inhibitor	502 (85)	2077 (83)	2579 (84)
ACE inhibitor	446 (76)	1728 (70)	2174 (71)
ARB	5 (1)	317 (13)	322 (10)
Heparin	461 (78)	1939 (78)	2400 (78)
Low-molecular-weight heparin	203 (34)	793 (32)	996 (32)
Thrombolysis	188 (32)	919 (37)	1107 (36)
Primary PCI in STEMI patients	291 (49)	1099 (44)	1390 (45)
Hospital transfer	219 (37)	1086 (44)	1305 (42)
PCI	415 (70)	1708 (69)	2123 (69)
CABG	25 (4)	150 (6)	175 (6)
Discharge medications, n (%)			
Statin	495 (91)	2152 (92)	2647 (92)
Aspirin	486 (89)	2122 (91)	2608 (90)
P ₂ Y ₁₂ inhibitor	437 (80)	1813 (78)	2250 (78)
β-blocker	453 (83)	1953 (84)	2406 (83)
ACE inhibitor	390 (71)	1588 (68)	1978 (69)
ARB	9 (2)	256 (11)	265 (9)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist blocker; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SMuRFs, standard modifiable cardiovascular risk factors; STEMI, ST-segment–elevation myocardial infarction.

relevance of this underappreciated group of STEMI patients is further highlighted by the observed higher in-hospital mortality in this group.

The substantial proportion with no SMuRFs at the time of their index event is consistent with previously published studies at 18% overall^{12,15-17} and represents a significant burden of CVD at a national and global scale, with an estimated 7.3 million acute myocardial infarctions per year worldwide.⁵ The STEMIs in the SMuRF-less group were not explained by obesity, family history of premature coronary artery disease, or age (with body mass index being less in the SMuRF-less group than the explained STEMI group, similar rates of relevant family history, and similar ages). It is interesting to observe that the proportion of SMuRF-less STEMI patients was a third higher in men than women.

The YOUNG-MI registry similarly found that 17% of ACS patients aged less than 50 years old presenting with a type 1 acute myocardial infarction had no SMuRFs and in addition found that fewer than 50% of patients in their cohort would have met the

criteria for primary prevention statin therapy according to current American guidelines.¹⁷ Although it is essential that we continue at a community and primary healthcare level to identify and address the burden of known risk factors for atherosclerosis, parallel efforts should continue toward unraveling the biological mechanisms underlying disease in SMuRF-less individuals. New technologies and data science advances in omics and multiomics approaches will allow novel discovery approaches to be adopted in accurately phenotyped cohorts with the potential to identify as yet unknown biological networks and processes.¹⁸ Polygenic risk scores have been developed that can stratify an individual's risk largely independent of the individual's SMuRFs and can improve risk prediction over traditional risk factor–derived scores.¹⁹ Future cohort studies such as GRACE and CONCORDANCE registries would benefit from building biobanks into their study design to enable validation of these scores as well as identification of new biomarkers.

The ultimate marker of risk for myocardial infarction is a noninvasive measure of early atherosclerotic disease itself, integrating not just the “attacking” risk factors but also the host “response.”¹⁸ Currently, in clinical practice, cardiac computed tomography—both coronary calcium score and coronary angiography—are all that we have available. Research tools measuring early vascular dysfunction or disease include carotid intimal medial thickness and brachial artery reactivity.^{20,21} But there is an absence of circulating blood markers of atherosclerosis “activity,” with the non-specific inflammatory marker high-sensitive C-reactive protein being the closest clinically available measure that we have. Application of noninvasive imaging of subclinical vascular disease supports the importance of the problem. One recent study demonstrated evidence of atherosclerosis in 50% of adults without SMuRFs.²¹ Another study showed that in asymptomatic adults with no SMuRFs, 32% had evidence of coronary artery calcification, and 12% had moderate or severe coronary artery calcification, defined as a coronary artery calcium score greater than 100 Agatston units.²² Currently, international guidelines do not recommend screening with coronary artery calcium or computed tomographic coronary angiography in patients deemed at low risk based on traditional risk factor scores.²³⁻²⁵ Data highlighting the burden of disease in the SMuRF-less population and the dramatic difference earlier detection and targeted prevention would make suggest the need for more widely accessible markers of subclinical disease particularly relevant for these individuals.

This is the first report, in a large, multicenter study, of an increase in the proportion of SMuRF-less STEMI patients. This increase may be explained by a simple competing risks principle, with improved identification and effective management of SMuRFs in primary care effectively increasing the relative proportion of patients with minimal risk factors that have received little recognition to date. Alternatively, it is

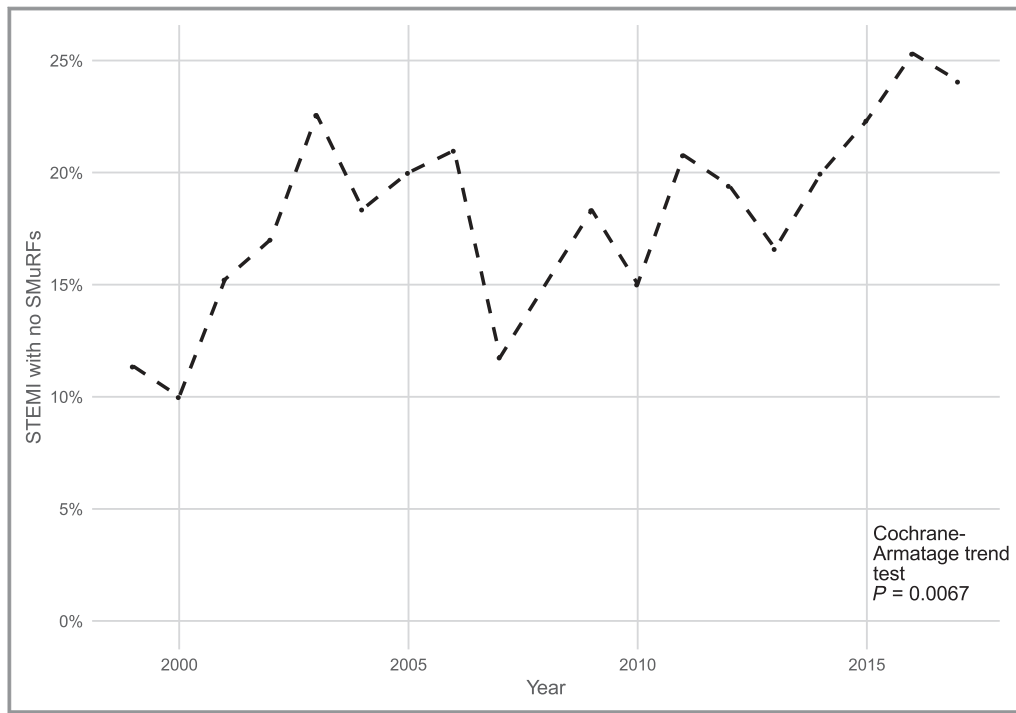


Figure 1. Increasing proportion of ST-segment-elevation myocardial infarction (STEMI) patients with 0 standard modifiable cardiovascular risk factors (SMuRFs) during the study period. Cochrane-Armatage trend test $P=0.0067$.

plausible that environmental factors such as air particulate matter and heavy metal exposure levels or other unknown factors may have changed and may be contributing to atherosclerotic events in individuals without SMuRFs.²⁶⁻²⁸

A major goal of these analyses was to investigate the outcomes of SMuRF-less STEMI patients compared with their counterparts whose myocardial infarctions were more easily explained by traditional risk factors. We confirmed previous

observations that SMuRF-less myocardial infarction patients were more likely to die in hospital than those with 1 or more SMuRFs.^{15,16,29} This does not appear to reflect treatment differences (Table 3). These data need to be more widely communicated to front-line physicians to ensure that timely evidence-based care is provided to this vulnerable group of patients. Despite the higher in-hospital mortality in SMuRF-less individuals, the rates of MACE, including in-hospital

Table 4. Unadjusted In-Hospital Outcomes

Variable	Statistic (Level)	0 SMuRFs (N=91)	>0 SMuRFs (N=2490)	Overall (N=3081)
In-hospital MACE, %		88 (16%)	406 (18%)	494 (18%)
In-hospital death, %		36 (6)	107 (4)	143 (5)
Myocardial infarction, %		11 (2)	54 (2)	65 (2)
Cardiogenic shock, %		38 (6)	117 (5)	155 (5)
In-hospital death or myocardial infarction, %		44 (8)	154 (7)	198 (7)
Recurrent ischemic symptoms, %		68 (12)	386 (16)	454 (15)
Heart failure, %		43 (7)	277 (11)	320 (10)
Major bleeding, %		40 (7)	149 (6)	189 (6)
Stroke, %		2 (0)	16 (1)	18 (1)
Length of stay, d	Mean, SD	6.7 (17.13)	6.4 (9.90)	6.4 (11.62)
	Median, IQR	4 (3-6)	4 (3-7)	4 (3-6)

IQR indicates interquartile range; MACE, major adverse cardiovascular events (death/myocardial infarction/heart failure/shock); SMuRFs, standard modifiable cardiovascular risk factors.

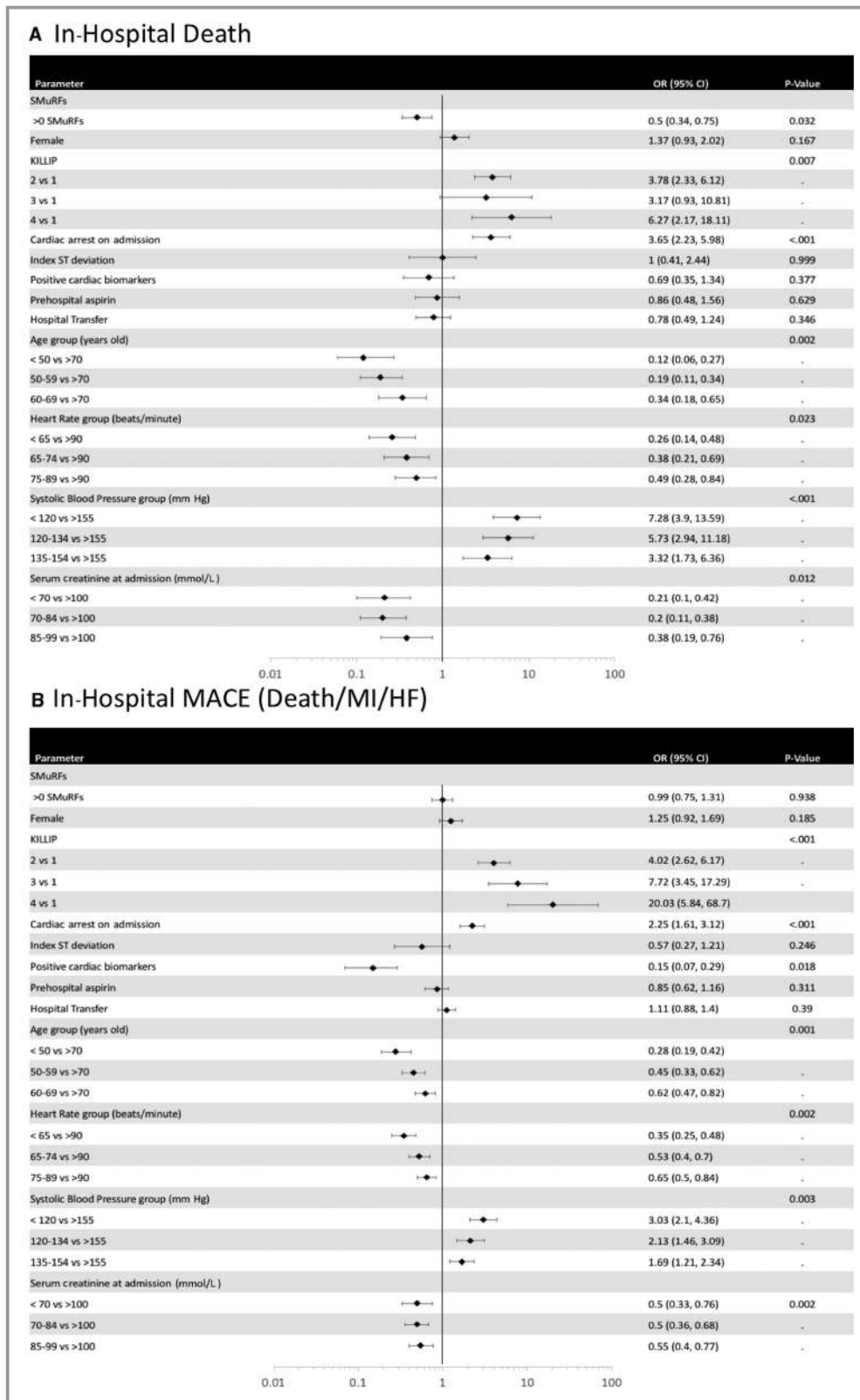


Figure 2. Multivariate odds ratios for in-hospital (A) death and (B) major adverse cardiac events (MACE: death/recurrent myocardial infarction/heart failure/cardiogenic shock). Bars indicate 95% CIs. HF indicates heart failure; MI, myocardial infarction; OR, odds ratio; SMuRFs, standard modifiable cardiovascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, and smoking).

Table 5. Unadjusted Outcomes 6 Months Postdischarge

Variable	0 SMuRFs n (%) N=471	>0 SMuRFs n (%) N 016	Overall n (%) N=2487
MACE, %	20 (6)	101 (7)	121 (7)
Death/MI, %	16 (4)	76 (4)	92 (4)
Death, %	9 (2)	48 (2)	57 (2)
MI, %	7 (2)	34 (2)	41 (2)
Recurrent revascularization, %	14 (3)	62 (3)	76 (3)
CHF, %	6 (2)	29 (2)	35 (2)
Recurrent angina, %	24 (7)	98 (7)	122 (7)
Major bleeding, %	2 (1)	6 (0)	8 (0)
Stroke, %	0 (0)	15 (1)	15 (1)

CHF indicates congestive heart failure; MACE, major adverse cardiovascular events (death/myocardial infarction/heart failure/shock); MI, myocardial infarction; SMuRFs, standard modifiable cardiovascular risk factors.

recurrent myocardial infarctions and cardiogenic shock were similar. The higher in-hospital mortality rate may reflect differing underlying biological processes or a reduced capacity to tolerate myocardial ischemia, and mechanisms of in-hospital mortality in SMuRF-less individuals warrant further investigation.³⁰

There are a number of limitations in our study deserving of mention. SMuRFs were documented as categorical variables, although each SMuRF is actually a continuous variable.³¹ Identification of SMuRF status is based on interrogation of medical records and was not independently validated with biochemical testing; thus, it may be susceptible to underdiagnoses. Furthermore, less commonly used risk factors such as lipoprotein(a), high-sensitivity C-reactive protein, coronary artery calcium score, and genetic risk scores were not available and therefore not assessed in this study.³² However, this real-world study reflects the information that is readily available to clinicians. A total of 19% of subjects were lost to follow-up at 6 months; this may have resulted in a potential bias. However, as shown in Table S1, there were only subtle differences in the demographic and clinical features between the 2 groups, with a slightly higher Grace Risk Score, creatinine, and Killip class in those lost to follow-up compared with those who were able to be contacted for follow-up. It was due to the loss to follow-up that the 6-month data were considered secondary and treated as descriptive. The specific timing of events within the 6-month follow-up period was not captured, and we were unable to assess the proximity of events to the index event or to learn whether there was an association between length of stay and early postdischarge events. Continued efforts are required to examine progression of atherosclerosis and related outcomes in SMuRF-less subjects.

Table 6. Multivariable Logistic Regression Model for 6-Month MACE

Parameter	Effect	Odds Ratio (95% CI)	P Value
SMuRFs	>0 SMuRFs	1.27 (0.72, 2.26)	0.407
	0 SMuRFs	Ref	
Killip class	2	2.8 (1.58, 4.97)	0.013
	3	8.42 (2.71, 26.18)	
	4	2.59 (0.57, 11.8)	
	1	Ref	
Cardiac arrest on admission	Yes	0.35 (0.13, 0.94)	0.019
	No	Ref	
Index ST deviation	Yes	0.79 (0.27, 2.31)	0.696
	No	Ref	
Positive cardiac biomarkers	Yes	0.21 (0.07, 0.61)	0.095
	No	Ref	
Prehospital aspirin	Yes	1.25 (0.77, 2.05)	0.388
	No	Ref	
Hospital transfer	Yes	0.82 (0.53, 1.28)	0.371
	No	Ref	
Age group, y	<50	0.29 (0.17, 0.51)	0.010
	50 to 59	0.22 (0.12, 0.42)	
	60 to 69	0.41 (0.23, 0.74)	
	70+	Ref	
Heart rate group, bpm	<65	0.54 (0.31, 0.94)	0.094
	65 to 74	0.37 (0.17, 0.83)	
	75 to 89	0.68 (0.38, 1.22)	
	90+	Ref	
Systolic blood pressure group, mm Hg	<120	1.18 (0.68, 2.05)	0.798
	120 to 134	1.12 (0.56, 2.23)	
	135 to 154	0.89 (0.5, 1.59)	
	155+	Ref	
Serum creatinine at admission, mmol/L	<70	0.59 (0.35, 1)	0.033
	70 to 84	0.54 (0.37, 0.78)	
	85 to 99	0.42 (0.25, 0.69)	
	100+	Ref	

MACE indicates major adverse cardiovascular events (death/myocardial infarction/heart failure/shock); SMuRFs, standard modifiable cardiovascular risk factors.

Conclusions

In these multicenter registry studies spanning nearly 20 years, 19% of STEMI patients without a prior history of CVD also had no prior history of SMuRFs. The proportion of

STEMI patients with no SMuRFs increased from 14% to 23% during the study period. SMuRF-less STEMI patients had higher in-hospital mortality rates when compared with patients with 1 or more SMuRFs. Our study highlights the need for ongoing investigation and for discovery of novel risk factors, biomarkers, biological processes, and treatment targets in order to better address the changing nature of coronary artery disease in the 21st century.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline, presentation and in-hospital management characteristics of subjects with 6 month follow up data versus those without 6 month follow up data.

Variable	Statistic/Level	6 month follow up data collected N=2487	Lost to follow up N=594	Overall N=3081
Age	Mean (SD)	60.3 (12.6)	62.3 (12.5)	60.6 (12.8)
	Minimum	23.0	23.0	23.0
	Median (IQR)	60 (51-79)	62 (52-71)	60 (52-69)
Sex	Female (%)	606 (24)	165 (28)	771 (25)
	Male (%)	1881 (76)	429 (72)	2310 (75)
SMuRFs*				
Diabetes (%)		442 (18)	112 (19)	554 (18)
Hypertension (%)		1096 (44)	267 (45)	1363 (44)
Dyslipidaemia (%)		933 (38)	193 (32)	1126 (37)
Current smoker (%)		1008 (41)	235 (40)	1243 (40)
Family history of coronary heart disease (%)		805 (37)	165 (29)	970 (35)
BMI†	Mean (SD)	28.3 (5.3)	28.1 (5.3)	28.2 (5.3)
	Median (IQR)	27.4 (24.8-30.9)	27.5 (24.5-30.9)	27.4 (24.7-30.9)
Previous atrial fibrillation (%)		67 (3)	25 (4)	92 (3)

Variable	Statistic/Level	6 month follow up data collected N=2487	Lost to follow up N=594	Overall N=3081
History of bleeding (%)		24 (1)	3 (1)	27 (1)
Pre-hospital medications				
Statin (%)		398 (16)	91 (15)	489 (16)
Aspirin (%)		309 (12)	63 (11)	372 (12)
P2Y12 Inhibitor (%)		40 (2)	12 (2)	52 (2)
Betablocker (%)		175 (7)	44 (7)	219 (7)
ACE inhibitor (%)§		284 (11)	60 (10)	344 (11)
ARB (%)		337 (14)	92 (16)	429 (14)
Systolic blood pressure (mmHg)	Mean (SD)	138.1 (21.2)	135.3 (29.7)	137.6 (27.7)
	Median (IQR)	136 (120-155)	135 (115-155)	136 (119-155)
Diastolic blood pressure (mmHg)	Mean (SD)	82.5 (17.2)	81.0 (18.3)	82.2 (17.4)
	Median (IQR)	80 (70-92)	80 (70-93)	80 (70-93)
Heart rate (per min)	Mean (SD)	78.0 (19.3)	80.9 (22.0)	78.6 (19.9)
	Median (IQR)	76 (64-90)	78 (65-94)	76 (65-90)
Killip class	1	2268 (92)	508 (86)	2776 (91)
	2	159 (6)	46 (8)	205 (7)
	3	34 (1)	20 (3)	54 (2)
	4	12 (0)	15 (3)	27 (1)

Variable	Statistic/Level	6 month follow up data collected N=2487	Lost to follow up N=594	Overall N=3081
Cardiac arrest on admission		154 (6)	74 (13)	228 (7)
Abnormal cardiac biomarker		2052 (98)	494 (98)	2546 (98)
Serum creatinine	Mean (SD)	89.1 (29.0)	97.5 (63.3)	90.7 (38.2)
	Median (IQR)	84 (72-100)	88 (73-104)	85 (72-100)
Grace Risk Score (Fox)	Mean (SD)	107.5 (28.1)	116.5 (34.4)	109.2 (29.6)
	Median (IQR)	106 (88-125)	111 (91-136)	107 (89-127)
Left Ventricular function grade				
Normal (%)		508 (36)	118 (36)	626 (36)
Mild impairment (%)		512 (36)	97 (29)	609 (35)
Moderate impairment (%)		329 (23)	89 (27)	418 (24)
Severe impairment (%)		73 (5)	28 (8)	101 (6)
Culprit Lesion Territory				
Left main (%)		4 (1)	1 (2)	5 (1)
Left Anterior Descending (%)		153 (38)	25 (39)	178 (38)
Circumflex Artery (%)		48 (12)	7 (11)	55 (12)
Right Coronary (%)		148 (37)	25 (39)	173 (37)
Unknown (%)		46 (12)	6 (9)	52 (11)
Multi-vessel disease > 50% stenosis (%)		1013 (41)	228 (42)	1241 (41)

Variable	Statistic/Level	6 month follow up data collected N=2487	Lost to follow up N=594	Overall N=3081
In-hospital treatment				
Statin (%)		2318 (93)	484 (82)	2802 (91)
Aspirin (%)		2452 (99)	556 (94)	3008 (98)
P2Y12 Inhibitor (%)		2071 (83)	508 (86)	2579 (84)
ACE Inhibitor (%)§		1819 (73)	355 (60)	2174 (71)
ARB (%)		251 (10)	71 (12)	322 (10)
Heparin (%)		1938 (78)	462 (78)	2400 (78)
Low molecular weight heparin (%)		830 (33)	166 (28)	996 (32)
Thrombolysis (%)		921 (37)	186 (31)	1107 (36)
Primary PCI in STEMI patients (%)‡§		1113 (45)	277 (47)	1390 (45)
Hospital transfer (%)		1055 (42)	250 (42)	1305 (42)
PCI (%)‡		1724 (69)	399 (67)	2123 (69)
CABG (%)Ī		143 (6)	32 (5)	175 (6)
Discharge medications				
Statin (%)		2192 (93)	455 (84)	2647 (92)
Aspirin (%)		2144 (92)	464 (86)	2608 (90)
P2Y12 Inhibitor (%)		1832 (78)	418 (77)	2250 (78)
Betablocker (%)		2003 (85)	403 (74)	2406 (83)

Variable	Statistic/Level	6 month follow up data collected N=2487	Lost to follow up N=594	Overall N=3081
ACE inhibitor (%)§		1675 (71)	303 (56)	1978 (69)
ARB (%)		205 (9)	60 (11)	265 (9)

*Standard modifiable cardiovascular risk factors (SMuRFs)

†Body mass index (BMI)

‡Coronary heart disease(CHD)

§Angiotensin converting enzyme (ACE)

|| Angiotensin II Receptor Antagonist Blocker (ARB)

‡Percutaneous coronary intervention (PCI)

§ST elevation myocardial infarction (STEMI)

‡ Coronary artery bypass graft surgery (CABG)