Number of Coronary Heart Disease Risk Factors and Mortality in Patients With First Myocardial Infarction

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Context Few studies have examined the association between the number of coronary heart disease risk factors and outcomes of acute myocardial infarction in community practice.

Objective To determine the association between the number of coronary heart disease risk factors in patients with first myocardial infarction and hospital mortality.

Design Observational study from the National Registry of Myocardial Infarction, 1994-2006.

Patients We examined the presence and absence of 5 major traditional coronary heart disease risk factors (hypertension, smoking, dyslipidemia, diabetes, and family history of coronary heart disease) and hospital mortality among 542 008 patients with first myocardial infarction and without prior cardiovascular disease.

Main Outcome Measure All-cause in-hospital mortality.

Results A majority (85.6%) of patients who presented with initial myocardial infarction had at least 1 of the 5 coronary heart disease risk factors, and 14.4% had none of the 5 risk factors. Age varied inversely with the number of coronary heart disease risk factors, from a mean age of 71.5 years with 0 risk factors to 56.7 years with 5 risk factors (P for trend $<.001$). The total number of in-hospital deaths for all causes was 50 788. Unadjusted in-hospital mortality rates were 14.9%, 10.9%, 7.9%, 5.3%, 4.2%, and 3.6% for patients with 0, 1, 2, 3, 4, and 5 risk factors, respectively. After adjusting for age and other clinical factors, there was an inverse association between the number of coronary heart disease risk factors and hospital mortality adjusted odds ratio (1.54; 95% CI, 1.23-1.94) among individuals with 0 vs 5 risk factors. This association was consistent among several age strata and important patient subgroups.

Conclusion Among patients with incident acute myocardial infarction without prior cardiovascular disease, in-hospital mortality was inversely related to the number of coronary heart disease risk factors.

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Previous studies have examined the prevalence of coronary heart disease (CHD) risk factors in patients with myocardial infarction (MI).[1-5] These studies have included a meta-analysis from 14 international randomized clinical trials,[1] a case-control study,[2] results from 3 epidemiologic cohort studies,[3] a single-center academic institution,[4] and a community-based registry of patients with non–ST-segment elevation MI only.[5] In all of these reports, a majority of patients with MI presented with at least 1 of the 4 major modifiable cardiac risk factors (hypertension, smoking, dyslipidemia, and diabetes). However, these studies were limited to specific populations (those selected for clinical trials, cohorts restricted to a certain geographical area [Chicago or Framingham, Massachusetts], or patients with non–ST-segment elevation MI). Most of these studies did not focus on inpatient mortality during hospitalization for first MI. However, a recent study from a quality improvement initiative reported a modest but surprising inverse association between number of CHD risk factors and mortality in patients with non–ST-segment elevation MI only.[5]

The National Registry of Myocardial Infarction (NRMI) represents a large and generalizable community-based cohort study of patients hospitalized with acute MI. The main objectives of our study were to ascertain the CHD risk factor distribution of pa-

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tients hospitalized with first MI, study the relationship between age at first MI and CHD risk factors, and determine the association of the number of risk factors and hospital mortality both overall and after adjusting for age and other clinical factors.

METHODS

Patient Population and Data Collection

The NRMI is an industry-sponsored national registry, the largest of its kind in the world, that has collected and analyzed hospital data from 2 160 671 patients admitted from 1994 to 2006 with confirmed MI at 1977 participating hospitals. NRMI analysis targeted 4 distinct periods during which data collection was modified to reflect changing MI care: NRMI 2 (1994-1998; n = 772 586), NRMI 3 (1998-2000; n = 537 444), NRMI 4 (2000-2004; n = 664 374), and NRMI 5 (2004-2006; n = 186 267). Institutional review board approval of data collection was obtained if required by the local hospital. Shown in FIGURE 1 is the flow diagram of the total registry population, the patients excluded, reasons for exclusion, and the final study population.

The diagnosis of MI was based on a clinical presentation consistent with acute MI and was determined by each local hospital. This process primarily involved an *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code of 410.X1 or elevated cardiac biomarker level, electrocardiographic evidence of acute MI, or alternative enzymatic, nuclear cardiac imaging, or autopsy evidence indicative of acute MI. Case ascertainment and clinical data were previously validated by comparison with the Medicare Cooperative Cardiovascular Project.[6]

Study Variables

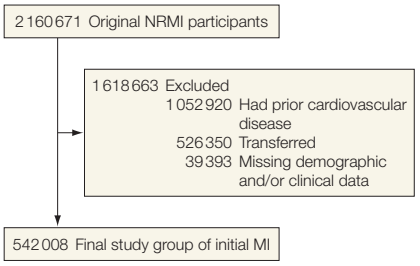
Five major CHD risk factors were recorded at hospitalization and included any smoking history, diabetes, hypertension, dyslipidemia, or family history of CHD, defined as an immediate relative receiving a diagnosis of having CHD before age 60 years. These risk factors were identified before and during hospitalization, as documented in the medical record, and were based on patient/family self-report or previous medical records.

Other variables included in this study are listed in TABLE 1. Weight (in kilograms) was available throughout the entire study period, and body mass index (BMI) was available only in NRMI 4-5 (2000-2006). The categories of BMI were defined as follows: underweight, BMI less than 18.5; normal, BMI 18.5 to less than 25; overweight, BMI 25 to less than 30; obese, BMI 30 to less than 40; and morbidly obese, BMI of 40 or higher. Killip classification is used for the stratification of risk for early death (30-day mortality) after MI.[7] The Thrombolysis in Myocardial Infarction (TIMI) risk index is another tool for the stratification of risk for early death (hospital or 30-day mortality) in patients with ST-segment elevation and non–ST-segment elevation MI[8] and is reported in 3 categories in which a higher risk index is associated with greater mortality.

Statistical Methods

The descriptive results were displayed by the number of cardiovascular risk factors and first MI. Test for trend was performed to ascertain statistical significance of trends observed. The Mantel-Haenszel χ^2 test was used for trend in binomial proportions. For parametric continuous data, linear regression was used to test for zero slope of the regression line. Multivariable logistic regression was performed to assess the association of the number of CHD risk factors (up to 5) and hospital mortality. Other variables entered in a mortality model are listed in Table 1, with the year the patient was enrolled. Given a potential concern of bias among patients with no recorded risk factors at presentation, crude mortality rates were reassessed, stratifying by (1) 5 distinct age groups; (2) excluding patients who died within either the initial 24 hours or 48 hours; (3) Killip classification I to IV; (4) TIMI risk index tertiles; and (5) BMI. Two-tailed tests were used and $P \leq .001$ was considered significant. All statistical analyses were conducted with SAS version 9.13.

Figure 1. Total NRMI Population, Exclusions, and the Final Study Population



NRMI indicates National Registry of Myocardial Infarction. Prior cardiovascular disease included previous MI, coronary heart disease, angina, heart failure, percutaneous coronary intervention, coronary artery bypass surgery, stroke, cerebrovascular disease, and peripheral vascular disease.

RESULTS

Study Population and CHD Risk Factors

A total of 542 008 MI patients fulfilled study criteria (NRMI 1994-2006). Only 14.4% had no risk factors identified at hospitalization, 81% had a clustering of 1 to 3 CHD risk factors, and 4.5% had 4 or 5 risk factors at presentation. The demographic features, presenting characteristics, and treatment of patients with or without CHD risk factors are shown in the Tables.

With increasing number of CHD risk factors, there was an inverse relationship whereby median age declined (P for trend $<.001$). There was no significant relationship between number of CHD risk factors and sex. Black patients had a greater number of CHD risk factors at first MI presentation; otherwise, there were no significant differences across the other races (Table 1).

The most common risk factor among patients with initial MI was hypertension (52.3%), followed by smoking (31.3%), dyslipidemia (28.0%), family history of CHD (28.0%), and the least common traditional risk factor, diabetes (22.4%) (Table 1). It was relatively uncommon for first MI patients to have only dyslipidemia, diabetes, or family his-

tory alone as a sole risk factor at hospitalization (each of these 3 groups represents about 3%-5% of the overall first MI population). Also, it was rare for first MI patients to have been obese or morbidly obese (alone) without any of the 5 traditional risk factors (5% of the overall population but 23% of those without any of the 5 risk factors). However, there was a direct association between obesity and increasing number of risk factors (P for trend $<.001$).

Presenting Characteristics, Process of Care Indicators, and Cardiovascular Morbidity

Among patients with 0 to 5 risk factors, there were only slight differences in symptom onset delay. However, there

Table 1. Demographics and Coronary Heart Disease and Hospital Characteristics of Patients With First Myocardial Infarction by Number of Cardiovascular Risk Factors: National Registry of Myocardial Infarction, 1994-2006[a]

	No. of Risk Factors at Presentation[b]						
	0	1	2	3	4	5	All
No. (%)	78 103 (14.4)	184 596 (34.1)	171 314 (31.6)	83 591 (15.4)	22 054 (4.1)	2350 (0.4)	542 008 (100.0)
Demographics							
Age, mean (SD), y	71.5 (13.7)	68.6 (14.0)	64.8 (13.2)	61.7 (12.1)	58.8 (10.7)	56.7 (9.5)	66.3 (13.8)
Median (IQR), y	74.0 (61.0-83.0)	70.0 (57.0-80.0)	65.0 (53.0-76.0)	61.0 (51.0-71.0)	57.0 (50.0-66.0)	56.0 (49.0-63.0)	67.0 (54.0-78.0)
Female, %	41.4	42.4	41.0	40.2	40.0	42.3	41.4
Race/ethnicity, %							
White	85.5	84.1	82.3	81.8	81.4	80.1	83.3
Black	4.8	6.7	8.5	9.0	10.0	11.3	7.5
Hispanic	3.6	3.6	3.8	3.8	3.7	4.1	3.7
Asian	2.2	2.1	2.1	2.0	1.6	1.9	2.1
CHD risk factors, %							
Smoker		23.1	37.8	52.3	73.3	100.0	31.3
Diabetes mellitus		10.1	29.2	43.8	62.8	100.0	22.4
Dyslipidemia		9.6	33.6	65.5	87.7	100.0	28.0
Hypertension		44.1	64.8	80.8	94.6	100.0	52.3
Family history of heart disease		13.0	34.6	57.5	81.7	100.0	28.0
Body mass index, mean (SD)[c]	26.6 (5.8)	27.3 (6.0)	28.5 (6.2)	29.8 (6.5)	31.1 (6.8)	32.6 (6.9)	28.2 (6.3)
Body mass index by category, %							
Underweight (<18.5) (n = 5115)	5.3	4.0	2.4	1.6	1.1	0.3	3.1
Normal (18.5-<25) (n = 46 409)	36.3	32.8	26.5	19.9	14.6	10.4	28.0
Overweight (25-<30) (n = 60 031)	35.6	36.7	37.0	35.9	32.8	27.3	36.3
Obese (30-<40) (n = 46 311)	20.2	23.4	29.3	35.7	42.1	50.1	28.0
Morbidly obese (≥40) (n = 7586)	2.6	3.2	4.8	6.9	9.3	11.8	4.6
Hospital Characteristics							
Bed size, %							
<151	16.7	15.2	13.4	12.5	11.7	11.5	14.3
151-250	23.7	22.8	22.4	21.9	22.3	20.5	22.6
>250	59.6	62.0	64.2	65.7	66.0	68.0	63.1
Census region, %							
West	29.5	27.2	25.7	24.9	23.5	21.5	26.6
South	27.7	29.8	31.6	32.1	33.4	33.8	30.6
Midwest	27.9	29.1	30.0	31.3	32.2	34.6	29.7
Northeast	14.8	13.8	12.6	11.7	10.9	10.1	13.1
Facility type, %							
Noninvasive	11.7	10.1	8.1	6.7	5.6	4.8	9.0
Catheterization	17.0	15.6	13.7	11.7	10.8	9.3	14.4
Catheterization/PCI/OHS	65.5	68.5	72.5	75.7	77.4	79.2	70.9
Catheterization/PCI	5.8	5.8	5.7	5.9	6.1	6.7	5.8
Teaching	11.3	11.9	12.8	13.6	14.2	14.9	12.4
Urban	91.0	91.3	91.6	92.0	92.4	91.9	91.5
MI volume, mean (SD), per year	340.6 (239.2)	350.4 (243.4)	360.9 (246.1)	370.4 (247.7)	375.3 (247.3)	377.7 (249.5)	356.5 (244.7)

Abbreviations: CHD, coronary heart disease; IQR, interquartile range; MI, myocardial infarction; OHS, open heart surgery; PCI, percutaneous coronary intervention.
[a] $P<.001$ for all comparisons.
[b] Five major risk factors: smoking, diabetes, dyslipidemia, hypertension, family history of coronary heart disease.
[c] Available in the National Registry of Myocardial Infarction 4-5. Calculated as weight in kilograms divided by height in meters squared.

were clear differences in severity of illness, as based on either Killip classification or TIMI risk index. Generally, we observed an inverse relationship between number of CHD risk factors at presentation and the proportion of patients with cardiogenic shock at presentation (highest in patients with 0 risk factors at presentation [6.1%] and lowest in patients with 4 risk factors [3.3%]) or who had a TIMI risk index score of 30 or more (TABLE 2).

Patients with few or no CHD risk factors were less likely to receive evidence-based medications within the initial 24 hours or invasive cardiac procedures such as coronary angiograms and coronary revascularization with either percutaneous coronary intervention or coronary artery bypass graft surgery (*P* for trend <.001) (TABLE 3).

Patients with few or no CHD risk factors had significantly lower ejection fraction and more cardiac rupture, stroke, heart failure, shock, and ventricular tachycardia or fibrillation but little difference in bleeding and recurrent MI.

Crude and Adjusted Mortality

TABLE 4 shows mortality stratified by the number of CHD risk factors and by severity at presentation. The total number of in-hospital all-cause deaths was 50 788. Overall, there was an inverse relationship between overall crude mortality and the number of CHD risk factors ascertained at presentation: 0 risk factors = 14.9%, 1 risk factor = 10.9%, 2 risk factors = 7.9%, 3 risk factors = 5.3%, 4 risk factors = 4.2%, and 5 risk factors = 3.6% (*P* for trend <.001). Given a concern of possible bias because of patients with more severe presentation and potentially providing less complete history, we reassessed mortality, stratified as follows: 5 age groups, after excluding patients who died within the initial 24 hours and 48 hours, Killip class, TIMI risk index, and BMI. In each category of stratification, the inverse relationship of higher mortality and decreasing number of CHD risk factors that was observed in the overall

Table 2. Presenting Characteristics of Patients With First Myocardial Infarction by Number of Cardiovascular Risk Factors: National Registry of Myocardial Infarction, 1994-2006[a]

	No. of Risk Factors at Presentation[b]						
	0	1	2	3	4	5	All
No. (%)	78 103 (14.4)	184 596 (34.1)	171 314 (31.6)	83 591 (15.4)	22 054 (4.1)	2350 (0.4)	542 008 (100.0)
Symptom onset to arrival, mean (SD), h	5.5 (9.4)	5.6 (9.3)	5.7 (9.3)	5.8 (9.4)	5.9 (9.1)	6.1 (9.50	5.7 (9.3)
Median (IQR), h	2.0 (1.0-5.3)	2.1 (1.0-5.5)	2.1 (1.0-5.8)	2.2 (1.1-6.0)	2.3 (1.1-6.3)	2.4 (1.2-6.4)	2.1 (1.0-5.7)
Killip classification, %							
I	79.9	81.3	82.9	84.8	85.9	83.7	82.3
II	13.3	12.3	10.9	9.7	9.1	10.3	11.5
III	5.0	5.0	5.0	4.7	4.2	5.1	4.9
IV	1.8	1.3	1.1	0.9	0.8	0.9	1.2
TIMI risk index, %[c]							
<30	46.3	56.5	67.6	76.0	83.2	87.6	62.9
30-60	42.5	36.3	28.5	21.9	15.9	11.8	31.5
>60	11.3	7.2	3.9	2.0	0.9	0.6	5.6
Median (IQR)	31.8 (20.5-46.2)	27.1 (17.6-40.3)	22.9 (15.5-34.0)	20.3 (14.3-29.4)	18.3 (13.5-25.8)	17.5 (13.3-23.9)	24.4 (16.1-36.9)
Initial systolic blood pressure, mean (SD), mm Hg	137.7 (31.3)	142.7 (32.4)	146.1 (32.4)	149.0 (32.1)	150.7 (31.9)	149.6 (32.2)	144.4 (32.4)
Initial pulse, mean (SD), beats/min	88.2 (26.0)	86.5 (24.6)	85.6 (23.5)	85.7 (22.5)	86.6 (21.8)	87.8 (22.3)	86.3 (24.0)
Initial electrocardiogram findings, %							
ST-segment elevation	40.1	41.3	42.0	41.6	42.1	41.4	41.4
ST-segment depression	26.1	28.0	29.2	29.9	29.8	28.3	28.5
Nonspecific	29.7	30.1	30.3	31.4	31.9	32.8	30.4
Q wave	10.1	10.6	10.8	11.0	11.9	12.1	10.7
Left bundle-branch block	4.3	4.1	3.6	3.0	2.7	2.6	3.8
MI location, %							
Anterior/septal	27.6	26.4	25.1	23.7	22.8	22.3	25.6
Inferior	30.1	32.8	35.1	36.6	37.8	37.7	33.9
Posterior	4.6	4.8	5.3	5.4	5.0	4.6	5.0
Lateral	12.9	13.0	13.1	13.1	13.3	12.3	13.1
Right ventricle	0.8	0.8	0.9	0.8	0.9	0.9	0.8
Unspecified	39.6	37.9	36.5	36.1	35.9	37.0	37.4

Abbreviations: IQR, interquartile range; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.
[a] *P* <.001 for all comparisons.
[b] Five major risk factors: smoking, diabetes, dyslipidemia, hypertension, family history of coronary heart disease.
[c] The TIMI risk index is a simple tool for the stratification of risk for early death (30-day mortality) in MI patients in the hospital. Essentially, a higher risk index score is associated with higher mortality. Median (IQR) is 24 (16-37), with 1st and 99th percentiles 8 and 87, respectively.

study population was also consistently observed within each subgroup of risk. After adjusting for age and other important outcome-associated factors at presentation, there was a significant inverse relationship between adjusted mortality and number of CHD risk factors present at hospitalization (*P* for trend <.001) (FIGURE 2).

COMMENT

To our knowledge, this analysis represents the largest study to date examining the relationship of the number of traditional CHD risk factors and mortality after initial MI in community practice. We confirmed the high prevalence of risk factor exposure in patients with MI, consistent with results in the previous literature. We observed a striking inverse relationship between age and the number of CHD risk factors and also observed a significant inverse relationship between hospital mortality and number of CHD risk factors ascertained at hospitalization.

Our analysis confirms that a majority (more than 85%) of patients have at least 1 of the 5 major traditional CHD risk factors. Our results are consistent with those of previous studies that reported between 80% and 90% of patients with CHD have at least 1 of 4 modifiable risk factors (diabetes, hypertension, hypercholesterolemia, and smoking).[1-5] However, many of these studies were limited to specific populations and therefore may not be generalizable to the overall population. In our analysis, perhaps not surprisingly, given the high correlation known to exist between BMI and individual risk factors such as hypertension, dyslipidemia, and diabetes, we observed a positive association between the number of CHD risk factors and higher levels of BMI. Taken together, these studies and our report should dispel the myth that a large number of MI patients may not have traditional CHD risk factors.

Little is known about the group of MI patients who present without traditional CHD risk factors. In the NRMI study, for the group with no major CHD risk factors, it is conceivable that risk factors were below the threshold of detection or recognition by either the patient or even the clinician, which would have underestimated their true prevalence be-

Table 3. Initial Medications, Cardiac Procedures, and Outcomes of Patients With First Myocardial Infarction by Number of Cardiovascular Risk Factors: National Registry of Myocardial Infarction, 1994-2006[a]

	Number of Risk Factors at Presentation, %[b]						
	0	1	2	3	4	5	All
No. (%)	78 103 (14.4)	184 596 (34.1)	171 314 (31.6)	83 591 (15.4)	22 054 (4.1)	2350 (0.4)	542 008 (100.0)
Initial 24 h, %							
Aspirin/antiplatelet	79.6	83.7	87.1	90.1	91.7	90.9	85.5
Heparin	59.8	64.1	68.0	70.4	71.5	70.4	66.0
ACE inhibitor	17.6	22.3	25.9	29.1	32.6	37.2	24.3
β-Blocker	50.4	56.4	61.4	66.2	69.3	69.0	59.2
Calcium channel blocker	9.2	11.4	12.1	12.5	12.6	13.0	11.5
Acute reperfusion therapies, eligible, %[c]							
Primary PCI	29.3	30.5	31.5	32.0	33.1	32.3	31.0
Fibrinolytic	37.7	40.5	41.7	42.6	42.5	39.9	41.0
No reperfusion	31.5	27.6	25.4	23.8	22.8	25.0	26.6
Invasive cardiac procedures, %							
Coronary angiogram	50.1	57.5	67.2	74.6	79.7	82.4	63.1
Any PCI	29.0	33.9	39.4	43.4	47.2	45.9	37.0
Any CABG surgery	7.1	8.7	11.5	14.1	16.2	18.8	10.5
Outcomes							
Ejection fraction, %							
<40	16.1	15.3	14.7	13.8	13.7	14.6	14.9
≥40	49.9	54.7	58.9	62.9	64.8	65.7	57.0
Missing data	34.0	30.1	26.3	23.3	21.5	19.7	28.0
Recurrent angina	6.4	7.6	8.7	9.8	10.8	10.5	8.3
Bleeding	6.5	6.5	6.7	7.1	7.1	7.4	6.7
Cardiac rupture	6.9	6.0	5.0	4.0	3.6	2.9	5.4
Stroke	1.4	1.4	1.2	1.1	1.0	0.9	1.3
Heart failure	15.5	15.1	14.2	13.1	12.4	13.3	14.5
Recurrent MI	1.5	1.5	1.6	1.7	1.7	1.7	1.5
Cardiogenic shock	6.1	5.0	4.4	3.7	3.5	3.3	4.7
Ventricular tachycardia or ventricular fibrillation	6.4	6.2	5.9	5.4	5.2	4.9	6.0

Abbreviations: ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; MI, myocardial infarction; PCI, percutaneous coronary intervention.
[a] *P* < .001 for all comparisons.
[b] Five major risk factors: smoking, diabetes, dyslipidemia, hypertension, family history of coronary heart disease.
[c] Eligible patients are defined as arrival to hospital within 12 h, initial electrocardiograph demonstrating ST-segment elevation or left bundle-branch block, and no contraindications to fibrinolytic therapy.

cause first MI patients may be unaware of the risk factors or not have received a diagnosis of one at evaluation. In addition, MI patients in the 0 risk factor group may have had other factors that may have influenced progression of disease, such as prediabetes, insulin resistance, abdominal obesity, psychosocial factors, poor nutrition, or physical inactivity.

Patients with a greater number of measurable CHD risk factors may have atherosclerotic progression of disease at a much faster rate (younger age) compared with those with few or no risk factors, such as diabetes, hypertension, dyslipidemia, or smoking, a finding that is biologically plausible. Eventually, age may increase the absolute baseline risk of CHD independent of risk factors; therefore, patients who present without risk factors tend to present at a later age once their baseline risk increases significantly enough to cause disease.[1]

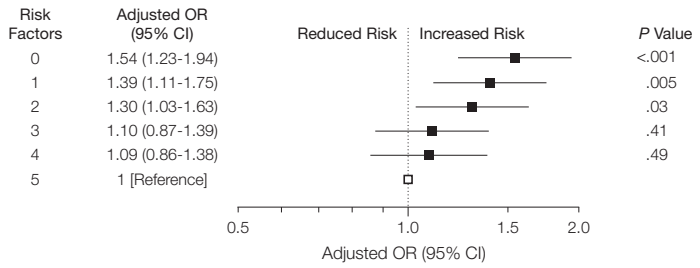
We observed a strong association of an inverse relationship between number of risk factors and hospital mortal-

Table 4. Crude Hospital Mortality of Patients With First Myocardial Infarction, by Number of Cardiovascular Risk Factors and by Selected Characteristics: National Registry of Myocardial Infarction, 1994-2006 (N = 542 008)[a]

	Number of Risk Factors at Presentation, No. (%)[b]					
	0	1	2	3	4	5
Absolute	11 611/ 78 103 (14.9)	20 174/ 184 596 (10.9)	13 560/ 171 314 (7.9)	4427/ 83 591 (5.3)	931/ 22 054 (4.2)	85/ 2350 (3.6)
Unadjusted OR (95% CI)	4.65 (3.73-5.78)	3.27 (2.63-4.06)	2.29 (1.84-2.84)	1.49 (1.20-1.85)	1.17 (0.94-1.47)	1 [Reference]
Subgroups						
Age groups, y[c]						
≤45 (n = 49 583)	287/ 4874 (5.9)	427/ 14 375 (3.0)	332/ 17 003 (2.0)	115/ 9904 (1.2)	37/ 3030 (1.2)	4/ 397 (1.0)
46-55 (n = 86 681)	425/ 7186 (5.9)	836/ 24 677 (3.4)	750/ 29 986 (2.5)	339/ 18 125 (1.9)	100/ 6005 (1.7)	13/ 702 (1.9)
56-64 (n = 111 062)	909/ 11 500 (7.9)	1874/ 32 855 (5.7)	1730/ 37 863 (4.6)	761/ 21 608 (3.5)	234/ 6478 (3.6)	29/ 758 (3.8)
65-74 (n = 119 317)	2125/ 16 745 (12.7)	4099/ 39 533 (10.4)	3562/ 39 282 (9.1)	1355/ 18 979 (7.1)	325/ 4404 (7.4)	31/ 374 (8.3)
≥75 (n = 175 365)	7865/ 37 798 (20.8)	12 938/ 73 156 (17.7)	7186/ 47 180 (15.2)	1857/ 14 975 (12.4)	235/ 2137 (11.0)	8/ 119 (6.7)
Excluding patients who died within initial 24 h[d] (n = 530 035)	8531/ 75 023 (11.4)	15 316/ 179 738 (8.5)	10 598/ 168 352 (6.3)	3530/ 82 694 (4.3)	770/ 21 893 (3.5)	70/ 2335 (3.0)
Excluding patients who died within initial 48 h[d] (n = 522 889)	6843/ 73 335 (9.3)	12 455/ 176 877 (7.0)	8712/ 166 466 (5.2)	2964/ 82 128 (3.6)	635/ 21 758 (2.9)	60/ 2325 (2.6)
Killip class[e]						
I (n = 446 317)	7193/ 62 390 (11.5)	12 356/ 150 160 (8.2)	8102/ 142 002 (5.7)	2646/ 70 863 (3.7)	567/ 18 934 (3.0)	47/ 1968 (2.4)
II (n = 62 222)	2410/ 10 394 (23.2)	4331/ 22 733 (19.1)	2912/ 18 743 (15.5)	947/ 8094 (11.7)	185/ 2017 (9.2)	23/ 241 (9.5)
III (n = 26 740)	1087/ 3924 (27.7)	2081/ 9256 (22.5)	1561/ 8603 (18.1)	551/ 3904 (14.1)	125/ 933 (13.4)	7/ 120 (5.8)
IV (n = 6726)	921/ 1395 (66.0)	1406/ 2447 (57.5)	985/ 1964 (50.2)	283/ 729 (38.8)	54/ 170 (31.8)	8/21 (38.1)
TIMI risk index[f]						
<30 (n = 322 377)	1652/ 33 657 (4.9)	3785/ 98 300 (3.9)	3462/ 109 952 (3.1)	1454/ 60 841 (2.4)	392/ 17 664 (2.2)	34/ 1963 (1.7)
30-60 (n = 161 485)	5398/ 30 882 (17.5)	9785/ 63 094 (15.5)	6485/ 46 317 (14.0)	2024/ 17 554 (11.5)	399/ 3373 (11.8)	34/ 265 (12.8)
>60 (n = 28 891)	2882/ 8198 (35.2)	4036/ 12 523 (32.2)	1871/ 6333 (29.5)	436/ 1634 (26.7)	50/ 190 (26.3)	4/ 13 (30.8)
BMI[g]						
<18.5 (n = 5115)	229/ 1154 (19.8)	331/ 2148 (15.4)	154/ 1282 (12.0)	44/ 439 (10.0)	5/ 89 (5.6)	0/3
18.5-<25 (n = 46 409)	928/ 7872 (11.8)	1621/ 17 665 (9.2)	985/ 14 049 (7.0)	262/ 5563 (4.7)	47/ 1167 (4.0)	4/ 93 (4.3)
25-<30 (n = 60 031)	514/ 7706 (6.7)	1028/ 19 771 (5.2)	821/ 19 630 (4.2)	293/ 10 049 (2.9)	79/ 2632 (3.0)	9/ 243 (3.7)
30-<40 (n = 46 311)	259/ 4368 (5.9)	552/ 12 626 (4.4)	543/ 15 513 (3.5)	253/ 9982 (2.5)	77/ 3376 (2.3)	10/ 446 (2.2)
≥40 (n = 7586)	35/ 560 (6.3)	84/ 1702 (4.9)	85/ 2549 (3.3)	47/ 1921 (2.4)	7/ 749 (0.9)	1/ 105 (1.0)

Abbreviations: BMI, body mass index; OR, odds ratio; TIMI, Thrombolysis in Myocardial Infarction.
[a] The denominator of each row represents all patients in the overall group or subgroup. *P* for trend in each row < .001.
[b] Five major risk factors: smoking, diabetes, dyslipidemia, hypertension, family history of coronary heart disease.
[c] Crude hospital mortality data stratified by age groups and number of risk factors.
[d] Crude hospital mortality data stratified after excluding patients who died within 24 to 48 hours and number of risk factors.
[e] Crude hospital mortality data stratified by Killip class and number of risk factors.
[f] Crude hospital mortality data stratified by TIMI risk index and number of risk factors.
[g] Crude hospital mortality data stratified by BMI and number of risk factors, National Registry of Myocardial Infarction 4 to 5 only.

Figure 2. Mortality Risk of Patients With and Without Cardiovascular Risk Factors and First Myocardial Infarction



In the multivariable model, candidate variables for inclusion included age (continuous), number of coronary heart disease risk factors (0 to 5), weight (<50, 50-59, 60-69, 70-79, 80-89, 90-99, 100-109, 110-119, ≥120 kg), sex, race/ethnicity (white, black, Hispanic, Asian, other), payer status (commercial, preferred provider organization, Medicare, Medicare + other, Medicaid, uninsured), systolic blood pressure, pulse, prehospital delay (0-<2, 2-<4, ≥4 hours), Killip class (I-IV), hospital characteristics with myocardial infarction volume (quartile), interventional capabilities (noninvasive, interventional, interventional without open heart surgery), region (West, South, Midwest, Northeast), hospital type (urban teaching, urban nonteaching, rural), ST-segment elevation/non–ST-segment elevation, left bundle-branch block, myocardial infarction location (anterior, other), and calendar year. $P<.001$ for all comparisons. OR indicates odds ratio.

ity. This finding persisted despite the fact that patients with few or no risk factors were older and had more cardiogenic shock, higher TIMI risk score, and higher Killip class on initial presentation. In one smaller study of non–ST-segment elevation MI patients in the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines study (CRUSADE), investigators reported an inverse association between number of risk factors and mortality, but this association was less consistent and was attenuated markedly after multivariable adjustment.[5]

The absence of CHD risk factor exposure should not necessarily be viewed as a guarantee of a favorable prognostic sign. There may be multiple explanations for our finding of an inverse association between number of risk factors and mortality. These explanations can be grouped into methodological issues of ascertainment and other biases that limit useful inferences regarding causality vs real differences in pathophysiology, medical management, or both across groups with different numbers of risk factors.

First, and most concerning, would be that artifact from risk factor misclassification and bias with case ascertainment might explain our findings. The group with no identifiable risk factors on initial presentation was also at higher risk for mortality (higher Killip class and TIMI scores). Thus, patients without risk factors may have been too "sick" to provide an adequate history or report CHD risk factors. Similarly, ascertainment of the history could be age related, with history being less complete or reliable in the elderly. To address this concern of risk factor misclassification and bias with case ascertainment, we performed extensive sensitivity analyses. In each case, whether we restratified mortality into 5 distinct age groups or clinical severity of illness, or whether we excluded patients who died early, among patients with no or fewer risk factors, mortality was still consistently higher. Even if the 0 risk factor group was excluded from the analysis, a significant inverse relationship was observed among patients with 1 to 5 risk factors. In clinical practice, it is rare not to obtain any history either from previous records or interview of the spouse or family members. In our study, the percentage of uninsured patients was lowest in the MI group without any risk factors (5%), and such patients presumably would have had some access to medical care. Although bias with case ascertainment will always be a concern, our sensitivity analyses suggest that bias alone is not a likely explanation of an inverse relationship between number of risk factors and mortality.

Another possible explanation for the findings is that patients with conventional risk factors may die at a much younger age. If so, residual confounding by age is another potential methodological explanation of the association between number of risk factors and mortality. Similarly, selection bias could have limited enrollment of the elderly population to those who were healthier. However, given that our results persisted after stratification by age, these potential biases do not necessarily affect the relationship we observed between number of risk factors and mortality.

There may be potential explanations based on differences in pathophysiology or medical management across groups with different numbers of risk factors. First, MI patients with few or no risk factors received fewer evidence-based medications and invasive cardiac procedures, and this undertreatment may in part have contributed to worse outcome. Second, the presence of risk factors before first MI may modify medical management. Patients with more risk factors may be more likely to receive medications that treat their CHD risk factors before initial index MI, such as aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and β-blockers. Although such patients may have eventually experienced MI, the severity of the infarct in patients with multiple CHD risk factors may have been attenuated through more aggressive treatment of risk factors before hospitalization and thus improved prognosis of their acute event.

A favorable management of risk factors has been one of the major explanations of declining mortality from MI during the past 25 years, for which half of the reduction in mortality is attributable to better treatment of risk factors.[9] Similarly, patients with a higher number of CHD risk factors may be more likely to have regularly consulted a physician as outpatients, and routine medical care is generally associated with a better prognosis.

There may be differences in the biology of atherosclerosis and in patients with few or no risk factors. Virmani et al[10] showed that risk factors influence the process of atherosclerosis in pathologic studies of atherothrombosis. Also, angiogenesis may be impaired with increasing age,[11] and the lack of collateral coronary blood flow before vessel occlusion may increase infarct size and worsen hospital survival. In addition, an apparent obesity paradox, or index event bias, by which overweight or obese patients with established CHD disease have lower long-term mortality than nonobese patients, has been observed.[12-14] Because obesity is strongly and positively associated with 3 of the 5 risk factors we studied (hypertension, dyslipidemia, and diabetes), we may be observing an acute event analog of this phenomenon, by which these risk factors appear to confer a "protective" effect at first MI.

Our study has several limitations. Although the presence of traditional CHD risk factors may lower our threshold for detecting clinically relevant CHD, the high prevalence of the same risk factors among patients without CHD decreases the discriminatory power of these risk factors to accurately predict which patients will develop MI or even clinically significant atherosclerosis (NRMI did not include a cohort without CHD). An important feature of these risk factors in general is that each has a continuous, dose-dependent effect on CHD risk, factors that we did not have available in our study (level of blood pressure, lipid and blood glucose control). The NRMI is an observational study and our results may be limited by bias, unmeasured confounders, and residual confounding. Thus, we cannot make causal inferences from our study. In addition, we examined only all-cause mortality, not CHD mortality specifically. We also had only limited data on comorbid illnesses. Last, ascertainment of risk factors was through medical record review at hospitalization. Still, we believe that our main finding of a strong inverse association between number of CHD risk factors and hospital mortality on first MI is robust.

CONCLUSION

We confirm the high likelihood of risk factor prevalence in patients with first MI, which is consistent with results of previous literature. We found that hospital mortality increased consistently as the number of risk factors declined, which may be due to residual confounding from older age and other unmeasured factors, although this finding persisted even after extensive adjustment for clinical factors and in subgroups stratified by age and severity. Future studies should seek to gain insight into the possible explanations of such an association.

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