Prevalence, Clinical Characteristics, and Mortality Among Patients With Myocardial Infarction Presenting Without Chest Pain

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Context Although chest pain is widely considered a key symptom in the diagnosis of myocardial infarction (MI), not all patients with MI present with chest pain. The extent to which this phenomenon occurs is largely unknown.

Objectives To determine the frequency with which patients with MI present without chest pain and to examine their subsequent management and outcome.

Design Prospective observational study.

Setting and Patients A total of 434 877 patients with confirmed MI enrolled June 1994 to March 1998 in the National Registry of Myocardial Infarction 2, which includes 1674 hospitals in the United States.

Main Outcome Measures Prevalence of presentation without chest pain; clinical characteristics, treatment, and mortality among MI patients without chest pain vs those with chest pain.

Results Of all patients diagnosed as having MI, 142 445 (33%) did not have chest pain on presentation to the hospital. This group of MI patients was, on average, 7 years older than those with chest pain (74.2 vs 66.9 years), with a higher proportion of women (49.0% vs 38.0%) and patients with diabetes mellitus (32.6% vs 25.4%) or prior heart failure (26.4% vs 12.3%). Also, MI patients without chest pain had a longer delay before hospital presentation (mean, 7.9 vs 5.3 hours), were less likely to be diagnosed as having confirmed MI at the time of admission (22.2% vs 50.3%), and were less likely to receive thrombolysis or primary angioplasty (25.3% vs 74.0%), aspirin (60.4% vs 84.5%), β-blockers (28.0% vs 48.0%), or heparin (53.4% vs 83.2%). Myocardial infarction patients without chest pain had a 23.3% in-hospital mortality rate compared with 9.3% among patients with chest pain (adjusted odds ratio for mortality, 2.21 [95% confidence interval, 2.17-2.26]).

Conclusions Our results suggest that patients without chest pain on presentation represent a large segment of the MI population and are at increased risk for delays in seeking medical attention, less aggressive treatments, and in-hospital mortality.

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CHEST PAIN HAS BEEN REported as the cardinal clinical feature among patients who present with acute myocardial infarction (MI).[1] The World Health Organization requires the presence of chest pain as one of the cornerstone features in its diagnosis of MI.[2] The Rapid Early Action for Coronary Treatment study, a randomized controlled clinical trial sponsored by the National Institutes of Health, was designed in part to test the effect of educating the public about the symptoms of MI and the benefits of early MI treatment.[3] This media campaign used as its hallmark feature the presence of chest pain.

Although not all MI patients exhibit the classic symptoms of chest pain,[4] the extent to which this phenomenon occurs is largely unknown. Barron et al[5] reported that the absence of chest pain at hospital presentation was among the most significant factors predicting lower use of thrombolytic therapy among a subset of MI patients eligible for such treatments in the National Registry of Myocardial Infarction 2 (NRMI-2). Whether these patients are also less likely to receive other important treatments in the management of MI remains unclear.

The population of MI patients who present without chest pain has not been well characterized. Although it is widely known that patients with diabetes mellitus may not have chest pain during MI

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(possibly secondary to autonomic dysfunction),[6] other clinical factors associated in patients who do not experience chest pain remain largely undefined. Understanding the factors associated with atypical presentations (ie, no chest pain) may help in the earlier identification and treatment of these patients with MI.

The primary objective of this study was to determine the proportion of MI patients in NRMI-2 who presented to the hospital without chest pain, and to evaluate clinical factors associated with this type of presentation. We tested the hypotheses that MI patients without chest pain compared with those with chest pain would present later for medical attention, would be less likely to be diagnosed as having acute MI on initial evaluation, and would receive fewer appropriate medical treatments within the first 24 hours. We also evaluated the association between the presence of atypical presenting symptoms and hospital mortality related to MI.

METHODS

Patient Population and Data Collection

The NRMI-2 is a national registry designed to collect, analyze, and report hospital data on patients admitted with confirmed MI at 1674 participating hospitals. The list of hospitals and investigators participating in the NRMI-2 can be obtained from Stat Probe Inc (Lexington, Ky). A total of 772 586 patients were enrolled from June 1994 to March 1998.

Patients involved with interhospital transfers were excluded from this analysis due to the potential for incomplete reporting of their presenting characteristics at the hospital at which they were evaluated initially and of their subsequent outcome (41.0%). Patients also were excluded if the variable chest pain was present but was not listed in the case report form (4.4%).

The majority of patients included in this study presented with acute MI, and few cases (<4%) were diagnosed subsequently as having MI during the course of hospitalization. Diagnosis of MI was based on a clinical presentation consistent with MI and at least 1 of the following: (1) a total creatine kinase or creatine kinase-MB level greater than or equal to twice the upper limits of normal, (2) electrocardiographic evidence indicative of acute MI, (3) alternative enzymatic, scintigraphic, or autopsy evidence indicative of acute MI, or (4) *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code of 410.X1.

Data from each patient were entered onto a 2-page case report form by trained chart abstractors and forwarded to ClinTrials Research (Lexington, Ky). Double key data entry and 87 electronic data checks were routinely performed by the data collection center to help ensure the accuracy, consistency, and completeness of the data. Inaccurate and internally inconsistent case report forms were excluded from analysis and returned to the registry hospital for additional review and correction. Hospitals were strongly encouraged to enroll consecutive patients with acute MI. This study is based on NRMI-2 data processed as of March 1998.

Study Variables

Chest pain was defined as any symptom of chest discomfort, sensation or pressure, or arm, neck, or jaw pain occuring at a period of time before hospital arrival or preceding a diagnosis of acute MI. The chest pain variable was defined as the absence of chest pain before or during admission, and may have included (but not limited to) dyspnea (alone), nausea/vomiting, palpitations, syncope, or cardiac arrest. However, the specific symptom (other than chest pain) was not abstracted from the medical record. Other variables included in this study were age, sex, race, diabetes, hypertension, stroke, prior infarction, prior heart failure, prior coronary artery angioplasty, prior coronary artery bypass graft (CABG) surgery, hypercholesterolemia (history or current serum total cholesterol >6.22 mmol/L [240 mg/dL]), family history of coronary artery disease (immediate relative diagnosed as having coronary artery disease before age 60 years), first recorded blood pressure and pulse, mode of transportation (self or ambulance), Killip class at the initial evaluation, characteristics of the initial electrocardiogram (ECG), MI type (Q-wave infarction, non–Q-wave infarction), MI location (anterior, inferior, posterior, lateral, right ventricle, other), admission diagnosis (MI, rule-out MI, other), time interval from symptom onset to hospital arrival, time from hospital arrival to first ECG, and time from hospital arrival to receipt of thrombolytic therapy or primary angioplasty, medications within the first 24 hours (aspirin, heparin, β-blocker, nitrates, calcium channel blocker), invasive cardiac procedures (coronary angiography, coronary artery angioplasty, CABG surgery), hypotension requiring intervention, heart failure requiring drug treatment, cardiogenic shock, recurrent ischemia (symptoms accompanied by ECG changes, new heart failure, or both), recurrent infarction (as confirmed by new diagnostic ST-segment changes or a second elevation of cardiac enzyme levels), left ventricular ejection fraction, overall length of stay, total days in the intensive care unit, and in-hospital mortality. Patients eligible for reperfusion therapy were defined as candidates who presented within 12 hours of symptom onset, with ST-segment elevation or left bundle-branch block on the initial ECG, and without contraindications to thrombolytic therapy.

Statistical Methods

Differences between the 2 study groups were assessed by χ^2 test for categorical variables, by the *t* test for continuous variables, and by the nonparametric median test for median comparisons. Logistic regression analysis was used to determine the risk factor profile associated with atypical presentation (dependent variable). Only those preexisting variables that may have preceded the development of presenting symptoms (such as demographic characteristics, prior cardiac and medical histories, payer status, and region) were included in the first model. In addition, delay in seeking medical atten-

tion, defined as time interval from symptom onset to hospital arrival of 6 or more hours, was included in the model as a binary field.

Logistic regression analysis was used to identify independent predictors of mortality, and the main independent variable, chest pain, was forced into the model. Other variables included in the mortality model were age, race, sex, region, payer status, time of MI symptom onset, initial ECG findings (ST-segment elevation, left bundle-branch block), MI location, Killip class, MI type, and medical history of hypercholesterolemia, smoking status, diabetes, hypertension, angina, prior MI, coronary artery angioplasty, CABG surgery, heart failure, and stroke. A separate model was developed to include the additional influence of adjunctive medications administered within the initial 24 hours: aspirin, heparin, β-blockers, intravenous nitroglycerin, and angiotensin-converting enzyme inhibitors. Adjusted mortality (odds ratios [ORs] and 95% confidence intervals [CIs]) was determined for the overall study population.

RESULTS

Patient Characteristics

One third of MI patients in the study population presented without chest pain (ie, atypical symptoms) on initial evaluation, and two thirds presented with chest pain (TABLE 1). Patients experiencing MI without chest pain tended to be older (mean age, 74.2 vs 66.9 years), and were women (49.0% vs 38.0% men). Patients who were 75 years or older were more likely to present without chest pain, and those younger than 65 years were more likely to present with chest pain. Patients without chest pain had a higher prevalence of diabetes, hypertension, prior heart failure, and stroke, and a lower prevalence of smoking history, hypercholesterolemia, family history of coronary artery disease, or prior revascularization with either coronary artery angioplasty or CABG surgery.

Patients experiencing MI without chest pain were more likely to have delays from the time of symptom onset until presenting to the hospital (mean, 7.9 vs 5.3 hours), although they were more likely to be transported to the hospital via an ambulance (56.8% vs 46.5%). At initial evaluation, MI patients without chest pain tended to be in a higher Killip class than patients who presented with chest pain, had a higher proportion of non–Q-wave infarction, and were slightly less likely to have an anterior infarction. The MI group without chest pain at initial presentation was significantly less likely to be admitted with an initial diagnosis of MI.

Table 1. Characteristics of Patients Presenting Without and With Chest Pain and Diagnosed With Myocardial Infarction During Same Hospitalization

Variable	Without Chest Pain	With Chest Pain
No. (%) of patients	142 445 (33)	292 432 (67)
Age, mean (median), y	74.2 (76.0)	66.9 (68.1)
Age, y		
<65	20.9	42.4
65-74	25.8	25.7
75-84	33.9	22.8
≥85	19.4	9.1
Women	49.0	38.0
Race		
White	87.6	88.0
Black	8.4	7.5
Hispanic	2.4	3.1
Asian	1.2	1.0
Other	0.4	0.4
Diabetes mellitus	32.6	25.4
Hypertension	54.6	51.2
Prior event		
Stroke	14.1	7.7
Myocardial infarction	26.4	26.8
Heart failure	26.4	12.3
Coronary angioplasty	5.2	9.2
Coronary artery bypass graft surgery	10.6	13.3
Current smoker	15.8	28.1
Hypercholesterolemia	16.4	27.1
Family history of coronary artery disease	17.8	30.0
First systolic blood pressure, mean, mm Hg	137.2	145.2
First pulse, mean, beats/min	92.8	84.2
Symptom onset to hospital arrival, mean (median), h	7.9 (2.4)	5.4 (2.2)
Mode of transportation		
Ambulance	56.8	46.5
Self	43.0	53.2
Killip class		
I	56.7	78.2
II	25.7	15.1
III	15.1	5.4
IV	2.4	1.2
ST-segment elevation on initial electrocardiogram	23.3	47.3
Left bundle-branch block	9.7	5.4
Type of myocardial infarction		
Q wave	36.2	51.7
Non-Q wave	63.7	48.3
Anterior myocardial infarction	24.0	27.2
Admission diagnosis of myocardial infarction	22.2	50.3

*Values are expressed as percentages unless otherwise indicated. *P* values are statistically significant (*P*<.001) for all values except for the variable other for race.

Table 2. Adjusted Odds Ratios for Clinical Characteristics of Patients Without Chest Pain Diagnosed With Myocardial Infarction*

Variable	Odds Ratio (95% Confidence Interval)
Prior angina	0.69 (0.68-0.71)
Prior coronary angioplasty	0.73 (0.71-0.76)
Hypercholesterolemia	0.77 (0.75-0.78)
Family history of coronary artery disease	0.74 (0.73-0.76)
Prior coronary artery bypass graft surgery	0.82 (0.80-0.84)
Smoker	0.87 (0.85-0.88)
Prior myocardial infarction	0.93 (0.91-0.95)
Nonwhite	1.05 (1.03-1.07)
Women	1.06 (1.04-1.08)
Diabetes mellitus	1.21 (1.19-1.23)
Age (10-year interval)	1.28 (1.26-1.28)
Prior stroke	1.43 (1.40-1.47)
Prior heart failure	1.77 (1.74-1.81)

*Nine US census regions and payer status were included in the model but values are not shown. $P<.001$ for all values listed.

Table 3. Six Major Risk Factors For Presentation Without and With Chest Pain for Patients With Myocardial Infarction

Risk Factor	Total No. of Patients	Without Chest Pain, %	With Chest Pain, %
Prior heart failure	73 737	51.0	49.0
Prior stroke	42 493	47.0	53.0
Age >75 y	168 937	44.9	55.1
Diabetes mellitus	120 878	38.5	61.5
Nonwhite	50 607	33.7	66.3
Women	181 065	38.6	61.4
Total No. of risk factors*			
0	108 455	17.5	82.5
1	126 567	28.4	71.6
2	113 755	40.1	59.9
3	61 985	47.1	52.9
4	20 364	52.0	48.0
5	3505	56.1	43.9
6	246	63.4	36.6

*Refers to any combination of the above 6 risk factors.

Table 4. Process of Care for Myocardial Infarction Patients Without and With Chest Pain*

Variable	Without Chest Pain	With Chest Pain
Initial reperfusion therapy among ideal candidates†		
Thrombolysis	18.7	56.4
Primary percutaneous coronary angioplasty	6.2	16.6
Immediate coronary artery bypass graft	0.4	1.2
Any reperfusion	25.3	74.0
Time interval (mean [median], min) from hospital arrival to		
First electrocardiogram	31.8 (19.8)	15.6 (10.2)
Thrombolysis	139.8 (73.2)	65.4 (42.0)
Primary percutaneous coronary angioplasty	282.0 (169.9)	171.6 (120.0)
Medication within 24 h		
Aspirin or other antiplatelet agent	60.4	84.5
Heparin	53.4	83.2
β-Blocker	28.0	48.0
Nitrates	31.4	68.8
Calcium channel blocker	19.1	17.1
Invasive cardiac procedures		
Coronary angiography	26.9	59.0
Any catheter-based revascularization	9.4	28.8
Coronary artery bypass graft surgery	6.2	10.9

*Values are expressed as percentages unless otherwise indicated. $P<.001$ for all value comparisons.
†Ideal candidates for reperfusion therapy have ST-segment elevation or left bundle-branch block on the initial electrocardiogram, present within 12 hours of symptom onset, and have no contraindications to thrombolytic therapy.

Multivariate Predictors of Atypical Symptoms

The risk factor profile of MI patients without chest pain is presented in TABLE 2. Six important variables associated with atypical presentation (in descending hierarchy) were prior heart failure, prior stroke, older age, diabetes, female sex, and nonwhite racial/ethnic group. Patients who smoked, had hypercholesterolemia, or had a prior history of ischemic heart disease (angina, infarction, coronary angioplasty, or CABG surgery) had a greater likelihood of chest pain on initial hospital presentation. The presence of a greater number of these 6 risk factors (as determined from Table 2) was associated with an increased likelihood that an MI patient would not have chest pain (TABLE 3). For example, if an MI patient did not have any of these 6 risk factors, only 17.5% of such patients would not have chest pain. Conversely, if a patient had at least 3 risk factors, there was almost a 50% or greater probability that these patients would not have chest pain.

Process of Care

Among a subset of MI patients who were eligible for acute reperfusion therapy, those without chest pain were significantly less likely to be treated with thrombolysis, primary angioplasty, or any reperfusion therapy (TABLE 4). Patients experiencing MI without chest pain also had signficantly longer door-to-treatment time intervals with either thrombolytic therapy (mean, 2.3 vs 1.1 hours) or primary angioplasty (mean, 4.7 vs 2.9 hours). The initial ECG was obtained much later in the MI group without chest pain (mean, 31.8 vs 15.6 minutes). Patients experiencing MI without chest pain were less likely to receive aspirin or other antiplatelet agents, heparin, or β-blockers within the initial 24 hours, and also received significantly fewer coronary angiograms or subsequent coronary revascularization with either angioplasty or CABG surgery.

Outcome

Patients who experienced MI without chest pain were significantly more likely

Table 5. Outcomes of Myocardial Infarction Patients Presenting Without and With Chest Pain*

Variable	Without Chest Pain	With Chest Pain
Hypotension requiring intervention	18.7	14.0
Recurrent ischemia	6.4	12.9
Recurrent infarction	2.1	2.4
Sudden cardiac arrest	8.5	4.3
Stroke (all patients)	2.0	1.2
Stroke (only patients who received thrombolysis)	3.9	2.2
Heart failure requiring drug treatment	29.3	15.0
Cardiogenic shock	8.1	5.0
Mean ejection fraction	42.4	47.2
Overall length of stay, mean, d†	8.8	7.0
Total days in intensive care unit, mean	3.1	3.0
In-hospital death	23.3	9.3
Hospital arrival to time to death, mean (median), d	6.0 (3.3)	5.1 (2.7)

*Values are expressed as percentages unless otherwise indicated. $P<.001$ for all value comparisons.
†Refers to patients discharged alive.

Table 6. Variables Predicting In-Hospital Mortality for Myocardial Infarction Patients

Variable	Odds Ratio (95% Confidence Interval)
Hypercholesterolemia	0.61 (0.59-0.63)
Family history of coronary artery disease	0.77 (0.75-0.79)
Prior percutaneous transluminal coronary angioplasty	0.81 (0.78-0.85)
Smoker	0.84 (0.82-0.87)
Prehospital delay >6 h	0.86 (0.84-0.88)
Prior angina	1.05 (1.02-1.08)
Prior myocardial infarction	1.05 (1.03-1.08)
Women	1.09 (1.06-1.11)
White	1.09 (1.06-1.12)
Prior heart failure	1.12 (1.09-1.14)
Health maintenance organization vs commercial insurance	1.12 (1.06-1.17)
Pacific vs New England	1.13 (1.07-1.19)
West North Central vs New England	1.14 (1.08-1.21)
Diabetes mellitus	1.16 (1.14-1.19)
Mountain vs New England	1.16 (1.09-1.24)
ST-segment elevation	1.19 (1.17-1.22)
Anterior myocardial infarction	1.20 (1.18-1.23)
Prior coronary artery bypass graft	1.22 (1.18-1.26)
East North Central vs New England	1.22 (1.16-1.28)
West South Central vs New England	1.29 (1.22-1.37)
Middle Atlantic vs New England	1.30 (1.23-1.36)
East South Central vs New England	1.32 (1.24-1.40)
South Atlantic vs New England	1.33 (1.26-1.39)
Age (10-year interval)	1.36 (1.34-1.37)
Medicare vs commercial	1.40 (1.34-1.45)
Self-pay vs commercial	1.44 (1.35-1.53)
Medicaid vs commercial	1.54 (1.44-1.65)
Killip class II	1.61 (1.57-1.65)
Presentation without chest pain	2.21 (2.17-2.26)
Q wave	2.36 (2.30-2.41)
Killip class III, IV	2.63 (2.56-2.70)

to die in the hospital compared with MI patients with chest pain (23.3% vs 9.3%). However, MI patients with chest pain, on average, were more likely to die sooner than MI patients without chest pain. Patients who experienced MI without chest pain were more likely to develop stroke, hypotension, or heart failure that required intervention and had a lower mean ejection fraction when measured. Overall length of stay was significantly longer in MI patients without chest pain, but there was little difference in the total days in the intensive care unit (TABLE 5).

In a multivariate logistic regression analysis, presentation with the absence of chest pain was among the most important independent predictors associated with mortality (>2-fold increased risk of in-hospital death) compared with MI patients with chest pain (OR, 2.21; 95% CI, 2.17-2.26)(TABLE 6). In a separate logistic regression model that included the additional influence of adjunctive medications administered within the initial 24 hours (ie, use of aspirin, heparin, β-blockers, intravenous nitroglycerin, and angiotensin-converting enzyme inhibitors), the OR of in-hospital death among MI patients without chest pain was 1.59 (95% CI, 1.57-1.61) compared with MI patients with chest pain. This differential (lower) use of early pharmacological therapies in patients with MI without chest pain accounted for more than 28% of the higher mortality observed in this high-risk patient population.

COMMENT

To our knowledge, this analysis represents the largest observational study comparing the presenting characteristics, treatments, and outcomes of MI patients with and without chest pain in the United States. We found that 1 of 3 patients diagnosed as having MI on the index admission did not have chest pain on presentation, and contrary to prior knowledge, patients with diabetes comprised less than one third of this group. Although diabetes was an important risk factor for atypical presentation, other risk factors associated with the absence of chest pain included older age, female sex, nonwhite racial/ethnic group, and a prior history of congestive heart failure and stroke.

Importantly, presentation to the hospital was delayed by more than 2 hours for MI patients without chest pain in comparison with delay times for patients with chest pain. Furthermore, after arriving at the hospital, patients without chest pain were less likely to be recognized as having an MI, and were less likely to receive therapy known to improve survival, such as thrombolysis or primary angioplasty (among eligible candidates), aspirin, β-blocker therapy, or heparin. Also, MI patients without chest pain were significantly less likely to receive a timely ECG or reperfusion strategies. Patients who experienced MI without chest pain had more than a 2-fold increased risk of in-hospital death than MI patients who presented with chest pain, even after adjusting for differences in clinical presentation characteristics. Twenty-eight percent of the higher mortality observed in MI patients without chest pain

may be attributed to the lower use of early pharmacological therapies.

In this analysis, we examined a national sample of patients who were admitted with MI. Thus, we can estimate the sensitivity of the symptom of chest pain (number of MI patients with chest pain divided by the total number of MI patients), and the false-negative rate (number of MI patients without chest pain divided by the total number of MI patients). However, this observational study did not include a cohort of patients without MI. Thus, we could not determine the specificity or predictive value of this symptom. Although this may be the case, it is important to emphasize that our findings of a relatively low sensitivity of chest pain (or relatively high false-negative rate for the lack of chest pain) among patients with documented MI should make physicians use caution in considering the diagnosis of MI unlikely in the absence of chest pain, especially in view of the worse outcomes for MI patients without chest pain.

Although it was possible to characterize whether MI patients had chest pain on initial presentation, additional details of the presenting complaints were beyond the scope of the NRMI-2. In a 1977 report of atypical presentations of MI, Bean[4] described the following 10 "masquerades of MI" in likely rank order of frequency: (1) congestive heart failure, (2) classic angina pectoris without a particularly severe or prolonged attack, (3) cardiac arrhythmia, (4) atypical location of the pain, (5) central nervous system manifestations, resembling those of stroke, (6) apprehension and nervousness, (7) sudden mania or psychosis, (8) syncope, (9) overwhelming weakness, and (10) acute indigestion. Although atypical presentations have been reported, Bean acknowledged that the true extent that MI patients lack chest pain remains largely unknown. Almost 25 years later, even with the development of better methods to detect MI, the prevalence of atypical presentations of patients with documented MI still remain unknown.

History of chest pain and other symptoms may be more difficult to obtain from patients with atypical presentation of MI. We found that MI patients with chest pain, on average, were more likely to die sooner than MI patients without chest pain. The NRMI-2 data suggest that shortness of breath may have represented a major component of the presenting complaints in MI patients without chest pain. For example, MI patients without chest pain were more likely to present with pulmonary edema (Killip class II and III), require drug treatment for heart failure, and have a prior history of congestive heart failure than patients who experienced MI with chest pain. Furthermore, in this national registry, MI patients without chest pain were more likely to have cardiac arrest and stroke. The inability to capture the patient's true chief complaint in this study (in the absence of chest pain) is an important limitation, but we believe it does not compromise our findings. The extent of this problem may be further underestimated because a substantial number of MI patients may present with atypical chest pain, although their pain may be pleuritic, positional, or reproducible on chest wall palpation. Moreover, some MI patients are completely asymptomatic and not hospitalized, and the diagnosis is only recognized after the interpretation of a subsequent (routine) ECG.

Identifying the signs and symptoms of acute MI is paramount for successful management and early treatment. Patients must realize that their symptoms may be consistent with a cardiac cause, and numerous reports have shown that patients may delay seeking care if they do not know that their symptoms may be consistent with an MI.[3] This problem is further compounded if patients believe that chest pain is a necessary hallmark feature of MI.

Even if an emergency response system, such as 911, is activated early, emergency medical service personnel must decide whether to transport a patient, and subsequently nurses and physicians must decide how to triage and treat these patients on arrival at the emergency department. Health care professionals need information to alert them to recognize atypical presentations in high-risk groups, such as those with a prior history of heart failure, stroke, or diabetes, age older than 75 years, female sex, and nonwhite racial/ethnic group. The latter 3 groups (the elderly, women, and ethnic minorities) represent especially vulnerable populations, who have been found in other studies to be at risk for undertreatment in MI.[5,7-11] Increasing awareness of MI presentations without chest pain may reduce disparities in the treatment of these groups.

To our knowledge, outcome in patients with MI without chest pain has not been previously reported. In this data set, MI patients without chest pain had more than twice the in-hospital mortality of patients with chest pain. The magnitude of these differences in mortality were not expected, and persisted despite adjusting for differences in age, comorbidities, and severity of presentation. We cannot exclude the possibility that residual confounding may have partially accounted for the higher hospital mortality in the group without chest pain. However, the degree of the differences observed in patient delay and the lower use of therapies for MI shown to improve survival significantly contributed to the worse outcome in MI patients without chest pain.

A majority of the randomized clinical trials of treatment for MI have required the presence of chest pain, and few studies have addressed the clinical significance and outcome of MI patients without chest pain. Beller[12] reported that chest pain is often the last marker of ischemia in the ischemic cascade, and often is preceded by perfusion abnormalities, wall-motion abnormalities, and ECG changes. Several studies have shown the discordance between chest pain and arterial patency. Califf et al[13] have shown in the Thrombolysis and Angioplasty in Myocardial Infarction study that 16% of patients with complete relief of chest pain after tissue-type plasminogen activator had an occluded artery at 90 minutes, and 29% with partial relief of chest pain still had an occluded artery at 90 minutes. Ohman et al[14] showed that in this same Thrombolysis and Angioplasty in Myocardial Infarction cohort, 12% of patients

had reocclusion after successful lytic therapy, but 42% did not exhibit symptoms. These analyses illustrate the uncertainty and discordance that may exist between the resolution of a patient's chest pain and patency of an infarct-related coronary artery after reperfusion. More recently, using data from the Thrombolysis in Myocardial Infarction registry, Cox et al[15] have shown that administration of thrombolytic therapy for ST-segment elevation MI in a cohort whose chest pain was resolved was safe, and was not associated with excessive complications. In that study, more than 90% of these patients without chest pain went on to develop enzymatic evidence of MI. The Thrombolysis in Myocardial Infarction investigators suggest that it is reasonable to administer reperfusion therapy among otherwise eligible MI patients, even if their symptoms have abated.[15]

The major limitations of the NRMI-2 data have been described previously.[16,17] Data from the NRMI-2 have been externally validated, and were found to be comparable with the Cooperative Cardiovascular Project with respect to major process and outcome measures in retrospective chart review.[18] The major limitations of our study include the absence of a cohort without MI and the absence of additional details of the presenting complaints in the absence of chest pain. In addition, verification bias, introduced as a result of a higher likelihood that physicians will admit patients with chest pain and send home those MI patients without chest pain, may have been possible. However, patients with missed MIs who are inappropriately discharged home from the emergency department have significantly worse outcomes.[19-21] Thus, although verification bias is possible, the effect of excluding this cohort of patients with missed MI would tend to bias our results toward the null, and the true impact (after including this high-risk cohort of the missed MI, which is more likely in patients with atypical presentations) would be even greater than we observed. Also, as in any observational study, unmeasured confounders may, in part, have explained our observations, though the magnitude of the differences in patient delay and treatments cannot be ignored.

The potential ramification of our findings for clinical practice is to educate patients and clinicians on the extent of MI presentations associated with atypical features and to allow more rapid and accurate identification of these MI patients by raising the index of suspicion in certain patients without chest pain, but not all patients without chest pain. If physicians were to misinterpret our findings and indiscriminantly raise the index of suspicion for all patients, and lower their threshold for subsequent hospitalizations, the frequency of hospital admissions may increase, at the expense of lower accuracy and greater economic consequences.

CONCLUSION

A substantial number of patients with MI present without chest pain on initial evaluation. We found that these patients had considerable delay in seeking care, were less likely to receive important therapies, and had worse outcomes. National health care initiatives that educate the public and medical professionals must emphasize that the presence of chest pain is not necessarily a hallmark feature in MI, and should incorporate other features of MI to facilitate a more expedient recognition and treatment of MI in the absence of chest pain. Earlier recognition of this fact may allow high-risk patient groups to consider presenting earlier to the medical establishment and medical professionals to identify such patients so that they may receive timely diagnostic and therapeutic interventions known to improve survival. Additional studies are needed to prospectively and accurately identify MI patients without chest pain.

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