Early Clinical Outcomes and Routine Management of Patients With Non–ST-Segment Elevation Myocardial Infarction

A Nationwide Perspective

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Background: Myocardial infarction (MI) in the absence of electrocardiographic ST-segment elevation or new bundle branch block is the cause of hospitalization for a large and steadily increasing proportion of patients with acute ischemic chest pain. Despite its prevalence, the common demographic features, current hospital-based management, and short-term clinical outcome among patients with non–ST-segment elevation MI remain poorly defined.

Methods: A total of 183,113 patients with non–ST-segment elevation MI were identified in the National Registry of Myocardial Infarction database. Using a validated model, 43,928 patients (24.0%) were retrospectively placed in major, 34,917 (19.1%) in intermediate, and 104,268 (56.9%) in minor severity clinical event categories that included hospital death, recurrent myocardial ischemia, and nonfatal recurrent MI.

Results: The administration of widely available and universally recommended pharmacologic therapies, including aspirin and β-adrenergic blocking agents, was suboptimal, particularly among patients with major severity clinical events. In contrast, coronary angiography and mechanical revascularization procedures were commonplace (>60% of all patients) and most frequently performed in patients within the minor (compared with the major) severity clinical event category (58.2% and 42.7%, respectively).

Conclusions: Patients with non–ST-segment elevation MI are a heterogeneous population, with readily identifiable demographic characteristics and clinical features associated with important early outcomes, including death. Nationwide efforts directed toward maximizing pharmacologic therapy utilization and the performance of invasive procedures according to established guidelines must continue.

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METHODOLOGY

The NRMI was initiated in 1989 as a pilot project of patients with acute MI. The first large-scale registry (NRMI-1), at its conclusion in September 1994, included more than 350,000 patients and was designed to determine national practice patterns and facilitate continuous quality improvement at individual participating hospitals.12

The NRMI-2 represents an expanded data collection instrument that has been used to determine cardiovascular risk factors, resource utilization, and the safety of commonly used therapies and processes of care. Demographic, procedural, and outcome data on patients with suspected acute MI were collected by an appointed coordinator at each site. Participation in the registry was voluntary, and hospitals were encouraged to enter consecutive patients irrespective of treatment strategy and outcome. To be enrolled, patients were required to have experienced an acute MI according to on-site criteria that included elevated cardiac enzyme levels (creatinine kinase or its MB fraction), an abnormal ECG, and/or an abnormal coronary angiogram. A nondiagnostic ECG was defined by the presence of nonspecific ST or T wave abnormalities (no injury pattern or Q waves).

All collected data were sent to a central data collection center (ClinTrials Research Inc, Lexington, Ky) for processing and subsequent analysis. Double key entry was used to add each case report form to the NRMI database.

The original data derived from the NRMI-2 database, inclusive from June 1994 through January 1997, included a total of 446,970 observations. Patients were eliminated from the study for the following reasons: transfer out of an NRMI-2 site, ECG ST-segment elevation or left bundle branch block on presentation, missing discharge data, age older than 110 years (or missing age), and missing region assignment. The final analysis was based on a total of 183,113 observations.

CLINICAL EVENT SEVERITY CATEGORIZATION

Patients were retrospectively divided into major, intermediate, and minor severity clinical event categories. The diagnostic criteria for each predefined category was based on a consensus among the investigators.

Major severity clinical events included the following: hospital death due to cardiac rupture, recurrent MI, cardiogenic shock, ventricular tachycardia or ventricular fibrillation, or intracranial hemorrhage; nonfatal but disabling stroke; nonfatal recurrent MI; and sustained ventricular tachycardia.

Intermediate severity clinical events included recurrent ischemia, congestive heart failure, sustained atrioventricular block, and serious (but non–life-threatening) hemorrhage.

Low-severity clinical events were those not included in either the intermediate or major severity categories.

STATISTICAL ANALYSIS

Patient characteristics across clinical event outcomes were compared with the χ² statistic for categorical variables and 1-way analysis of variance for continuous variables such as age and weight. Patients who experienced in-hospital death (after the first 24 hours) were identified by multivariable logistic regression. First, stepwise logistic regression was used to identify predictors of mortality in a 50% random sample of the patient population. Using the regression coefficients and model constant, we tested the model developed in stage 1 on the remaining half of the population. When the model was applied to the test set, the goodness-of-fit as assessed by the area under the receiver operating characteristic curve was 79.2%.

A model predicting the probability of cardiac catheterization and/or percutaneous coronary interventions (PCIs) (propensity score) was calculated for each data set observation. The score represents the relation between multiple characteristics and the dependent variable as a single characteristic. Based on the median value, the score is then divided into low or high and placed in the original model. The resulting model references the high-propensity category with the low-propensity category. The area under the receiver operating characteristic curve was 76.3%.13

RESULTS

A total of 183,113 patients diagnosed as having acute non–ST-segment elevation MI were identified. The baseline demographic characteristics and clinical features for the overall population are outlined in Table 1.

Patient characteristics for the clinical event severity category groups are summarized in Table 2. From the total cohort of patients, 43,928 (24.0%) were placed in the major severity clinical event category, 34,917 (19.1%) in the intermediate severity clinical event category, and 104,268 (56.9%) in the minor severity clinical event category. Compared with patients in the minor severity clinical event group, patients experiencing major severity events were older, more often female, more likely to have a history of prior MI and diabetes and less likely to abuse tobacco.

The ECG findings and clinical features according to clinical event severity groups are presented in Table 3. Patients with major severity clinical events were more

<table>
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<tr>
<th>Table 1. Baseline Demographic and Clinical Characteristics for the Overall Study Population*</th>
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<tr>
<td>Age, mean, y</td>
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<tr>
<td>Female, %</td>
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<tr>
<td>Weight, mean, kg</td>
</tr>
<tr>
<td>Prior myocardial infarction, %</td>
</tr>
<tr>
<td>Diabetes, %</td>
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<tr>
<td>Hypertension, %</td>
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<td>Smoking, %</td>
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* N = 183,113.
likely to have ST-segment depression and less likely to have either nonspecific ST-T wave changes or a normal ECG at the time of hospital admission than patients in lower-severity categories. In addition, they more often had ECG evidence of anterior site of infarction, a creatine kinase–MB fraction more than 2 times the upper limit of normal, and an ejection fraction less than 0.40.

Overall, 11.7% of study patients enrolled in NRMI-2 did not survive their event. The mortality among patients with major severity clinical events was 48.8%. Recurrent ischemia and reinfarction occurred in 12.4% and 2.6% of patients, respectively (Figure).

The early (within 24 hours of hospital admission) and predischarge administration of adjunctive pharmacologic therapy is summarized in Table 4. Although the use of intravenous heparin sodium, aspirin, and β-adrenergic blocking agents was relatively low in all patients, those within the major severity clinical event group were least likely to be treated. In these individuals, intravenous heparin, aspirin, and β-adrenergic blocking agents were administered 57.4%, 56.0%, and 21.4% of the time, respectively. A similarly low administration rate for aspirin, β-adrenergic blocking agents, and angiotensin-converting enzyme inhibitors was observed at the time of hospital discharge.

Patients with non–ST-segment elevation MI underwent coronary angiography, PCIs, and bypass grafting at rates of 53.7%, 20.5%, and 13.4%, respectively. Invasive diagnostic testing and percutaneous revascularization were more common in patients with minor rather than major severity clinical events, although the latter group did undergo surgical revascularization at a slightly higher rate (12.3% vs 14.8%). By definition, patients in the minor severity clinical event group did not experience recurrent myocardial ischemia during their hospitalization; however, a relatively small proportion of these patients underwent either standard exercise stress testing or an alternative functional study before hospital discharge to better delineate their risk for future cardiac events (Table 5).

A comparison between clinical event severity groups and within groups according to the presence of absence of interventional procedures is shown in Table 6. Pa-
The approach to patients with acute coronary syndromes in general and non–ST-segment elevation MI in particular is based on a clear understanding of pathobiologic principles, results of randomized clinical trials, and decades of clinical experience. Our findings, derived from a large, nationwide registry that reflects routine care, underscore the great diversity of patients who experience non–ST-segment elevation MI and the related spectrum of clinical outcomes, ranging from early death to an uncomplicated hospital course. Yet, despite the observed differences among patients with a common diagnosis, processes of care and initial management strategies were similar, irrespective of in-hospital clinical event severity and overall inherent risk. Of added concern, the administration of time-tested and widely recommended pharmacologic therapies, including β-adrenergic blocking agents and aspirin, was relatively low in all clinical event severity groups, particularly patients at greatest risk for in-hospital mortality.

CLINICAL EVENT OUTCOMES IN NON–ST-SEGMENT ELEVATION MI

The management of patients with ST-segment elevation or bundle branch block MI has been a national health priority for nearly 2 decades. Early recognition of symptoms, prompt transport to a medical facility, and rapid diagnosis and treatment are the goals set forth by the National Heart Attack Alert Program,14-20 the American Heart Association, and the American College of Cardiology.21 Information derived from randomized clinical trials, national registries, and multicenter databases has been formulated to develop clinical scales that reliably identify patients at high22,23 and low24-26 risk for adverse outcomes. Risk scales and clinical event severity scores serve as the basis for management pathways, with the ultimate goal of providing optimal patient care.

The NRMI-2 data and validated model show convincingly that patients with non–ST-segment elevation MI represent a heterogeneous population and, as in patients with ST-segment elevation MI,27 increasing age, female sex, anterior site of infarction, and hemodynamic instability are associated with a poor outcome. Although several respected groups have reported that the risk of recurrent MI and death among patients with non–ST-segment elevation MI is greatest between 30 days and 1 year after the initial event,7,8,11 the NRMI-2 experience suggests that many patients are, in fact, at equal or even greater risk for early events than patients who present to the hospital with ST-segment elevation. It is clear that the recognition and aggressive management of patients with high-risk features, regardless of ECG findings, is of paramount clinical importance.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
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<tr>
<td>High propensity</td>
<td>0.27 (0.25-0.29)</td>
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<tr>
<td>Aspirin (&lt;24 h)</td>
<td>0.46 (0.43-0.48)</td>
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<tr>
<td>Oral β-adrenergic blocking agent (&lt;24 h)</td>
<td>0.59 (0.55-0.63)</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitor</td>
<td>0.66 (0.62-0.71)</td>
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<tr>
<td>Normal electrocardiogram</td>
<td>0.78 (0.70-0.85)</td>
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<tr>
<td>ST depression</td>
<td>1.13 (1.06-1.20)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>1.39 (1.29-1.49)</td>
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<tr>
<td>Killip class III or IV</td>
<td>8.72 (8.56-8.80)</td>
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*Interventional procedures include percutaneous coronary interventions or coronary bypass grafting.
PHARMACOLOGIC THERAPY

The findings derived from large-scale clinical trials do not support the use of fibrinolytic therapy among patients with non–ST-segment elevation MI.\textsuperscript{26-30} In fact, an overview of randomized placebo-controlled trials\textsuperscript{31} leads one to conclude that fibrinolytic therapy is not beneficial and, in fact, may be harmful in this particular clinical setting. Our analysis of routine clinical practice in the United States revealed that nearly 10% of patients with non–ST-segment elevation MI received fibrinolytic therapy within 24 hours of hospitalization. Although it is tempting to speculate that treatment was driven by concomitant high-risk features, more than 50% of patients were in the minor severity clinical event category.

Because the pathobiology of non–ST-segment elevation MI shares common features with other acute coronary syndromes,\textsuperscript{1,2} the initial pharmacologic approach (with the exception of reperfusion modalities) is nearly identical across the spectrum of potential clinical presentations. The American Hospital Association/American College of Cardiology guidelines\textsuperscript{21} recommend that all patients receive aspirin (unfractionated or low molecular weight), aspirin, and β-adrenergic blocking agents. Nitrates are suggested in the care of recurrent angina, and calcium channel blockers are reserved for those who either have a contraindication to β-adrenergic blocking agent use or experience persistent symptoms despite β-blockade. The Unstable Coronary Artery Disease Council\textsuperscript{22} has proposed a similar pharmacologic strategy.

The NRMI-2 data raise concerns regarding compliance with recommended therapies for patients with non–ST-segment elevation MI. Just two thirds of patients received aspirin and heparin during the initial 24 hours, and only one third were treated with β-adrenergic blocking agents. The suboptimal use of standard anti-ischemic and antithrombotic therapies was particularly evident in patients at risk for hospital death and those within the major severity clinical event category. Regrettably, these observations are similar to those reported previously for patients with ST-segment elevation and bundle branch block MI.\textsuperscript{33} Although a somewhat better performance was reported in the TIMI III (Thrombolysis in Myocardial Infarction Phase III) registry,\textsuperscript{34} it remains clear that patients with acute coronary syndromes all too often do not receive a full complement of pharmacologic therapy. Although it could be argued that there are sound, clinically based reasons for withholding certain therapies, the dramatically different treatment rates that emerge when patients with similar diagnoses and demographic characteristics who are enrolled in multicenter registries are compared with those entered into clinical trials suggest that the mere reminder served by an existing protocol has a significant impact on patient management. This observation supports the development of on-site clinical pathways as a mechanism to improve guideline compliance and overall performance.

Most patients enrolled in NRMI-2 were treated at a time before the approval of platelet glycoprotein IIb/IIIa receptor antagonists. Although the management of acute coronary syndromes will progressively evolve, the addition of a new therapy should not detract from the very clear message provided by the current analyses. Because the trials of platelet glycoprotein IIb/IIIa receptor antagonists were designed and conducted on a background of standard anti-ischemic and antithrombotic treatment regimens, their introduction to the armamentarium of management strategies serves to supplement not replace existing treatment.

CORONARY ANGIOGRAPHY AND INTERVENTIONAL THERAPY

There is considerable variation in the use of diagnostic coronary angiography and interventional procedures among patients with non–ST-segment elevation MI.

The ever-increasing rates of PCI procedures and surgical procedures are undoubtedly multifactorial in origin; however, there is little question that the guidelines for coronary angiography published in 1987 strongly influenced management.\textsuperscript{35} At that time it was recommended that all patients (with non–Q wave MI) be considered for coronary angiography. More recently, the guidelines have been modified and recommend that high-risk patients, defined as those with recurring episodes of spontaneous or exercise-induced myocardial ischemia, shock, pulmonary congestion, malignant ventricular arrhythmias, or left ventricular dysfunction, undergo invasive testing.\textsuperscript{20-39}

Coronary angiography was performed in nearly 40% of study patients enrolled in the NRMI-2 and resulted in revascularization procedures, irrespective of clinical event severity category, in approximately one third of individuals. These rates are comparable with those found within the conservative arm of VANQUISH (Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital)\textsuperscript{37} but lower than those reported in TIMI IIIB\textsuperscript{30} and GUSTO IIB (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries IIB),\textsuperscript{30} 3 separate studies that address the potential benefit of an early aggressive management strategy (with or without adjunctive pharmacologic therapy). Although it is difficult to compare studies and draw conclusions, the findings from NRMI-2 suggest that patients with non–ST-segment elevation MI frequently undergo invasive procedures with modest attention to anticipated risk for subsequent clinical events.

The emergence of data that support an aggressive medical regimen for patients with postinfarction myocardial ischemia\textsuperscript{38} coupled with our observations suggest that clinicians should consider pharmacologic therapy with much greater resolve than is currently practiced. Two large-scale clinical trials that are currently in the development phase, SOCRATES (Study Of Coronary Revascularization And Therapeutic Evaluation)\textsuperscript{S} and COURAGE (Clinical Outcomes Utilization Revascularization and Aggressive drug Evaluation), will provide important information for patient management.

STUDY LIMITATIONS

The NRMI-2 is a nationwide registry, not a randomized clinical trial. As a result, patient outcome measures de-
Patients with non–ST-segment elevation MI are a heterogeneous population who exhibit readily identifiable characteristics and clinical features that define their potential risk for adverse outcomes, including early death. Based on the NRMI-2 cohort of nearly 200,000 individuals, it is apparent that a considerable proportion of patients currently do not receive even the most fundamental (and recommended) anti-ischemic and antithrombotic medical therapies and that the use of invasive diagnostic testing, followed often by percutaneous and surgical revascularization procedures, is not routinely tailored according to proposed guidelines and evidence-based risk assessment criteria. These practices likely have an impact on clinical outcome, resource utilization, and nationwide health care costs.

CONCLUSIONS

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REFERENCES

Call for Papers

Call for Papers: Genetic Theme Issue

The November 2001 issue of the Archives of Internal Medicine will join JAMA and the family of Archives journals in publishing a theme issue on human genomics and genetics. This is a critical topic that includes diagnosis of genetic diseases, gene therapy, genetic screening and counseling, ethical issues, confidentiality, and the care of patients and families with inherited diseases.

We welcome manuscripts for consideration in this issue.

James E. Dalen, MD, MPH
Editor