Use of Reperfusion Therapy for Acute Myocardial Infarction in the United States
Data From the National Registry of Myocardial Infarction 2

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Background—There is clear evidence that reperfusion therapy improves survival in selected patients with an acute myocardial infarction. However, several studies have suggested that many patients with an acute myocardial infarction do not receive this therapy. Whether this underutilization occurs in patients appropriate for such therapy remains unclear.

Methods and Results—We examined the use of reperfusion therapy in patients with an acute myocardial infarction hospitalized at 1470 hospitals participating in the National Registry of Myocardial Infarction 2. We identified 84 663 patients who were eligible for reperfusion therapy as defined by diagnostic changes on the initial 12-lead ECG, presentation to the hospital within 6 hours from symptom onset, and no contraindications to thrombolytic therapy. Twenty-four percent of these eligible patients did not receive any form of reperfusion therapy (7.5% of all patients). When multivariate analyses were used, left bundle-branch block (odds ratio [OR]=0.22; 95% CI=0.20 to 0.24), lack of chest pain at presentation (OR=0.22; 95% CI=0.21 to 0.24), age >75 years (OR=0.40, 95% CI=0.36 to 0.43), female sex (OR=0.88, 95% CI=0.83 to 0.92), and various preexisting cardiovascular conditions were independent predictors that the patient would not receive reperfusion therapy.

Conclusions—Reperfusion therapy may be underutilized in the United States. Increased use of reperfusion therapy could potentially reduce the unnecessarily high mortality rates observed in women, the elderly, and other patient groups with the highest risk of death from an acute myocardial infarction. (Circulation. 1998;97:1150-1156.)

Key Words: myocardial infarction ▪ reperfusion ▪ thrombolysis ▪ angioplasty ▪ prognosis

Overwhelming evidence exists to support the use of reperfusion with thrombolytic therapy to reduce the morbidity and mortality associated with an acute myocardial infarction.1 Furthermore, data from several randomized trials confirm the merits of primary angioplasty as an effective alternative to thrombolytic therapy.2–4 In fact, the observed reduction in the morbidity and mortality associated with coronary heart disease over the past 10 years has been attributed in part to the use of these reperfusion therapies.5 Current American College of Cardiology/American Heart Association guidelines recommend that thrombolytic therapy be administered to all patients regardless of age, sex, or race who have symptoms suggestive of a myocardial infarction and who present to the hospital within 12 hours of symptom onset, have diagnostic changes on their 12-lead ECG (ST-segment elevation or bundle-branch block), and have no contraindications to thrombolytic therapy. In addition, for those patients who are candidates for reperfusion therapy but who have an increased risk of bleeding, it is recommend that primary percutaneous transluminal coronary angioplasty or coronary artery bypass grafting be considered.5

Despite the clear benefits associated with reperfusion therapy and the strong recommendations advocating its use, many observational studies have demonstrated that only a minority of patients admitted with a myocardial infarction actually receive any form of reperfusion therapy.1–10 Several explanations have been put forth to explain this observation, including the possibility that some patients may lack clear indications for reperfusion therapy or that patients may have perceived contraindications to reperfusion therapy. However, it is unknown whether a component of this underutilization is related to physicians’ lack of appreciation of the impact that such therapy has on reducing morbidity and mortality and their willingness to incorporate this therapy into their practice.

The purpose of the present study, therefore, was to determine what proportion of patients with a myocardial infarction who are eligible for reperfusion therapy do not receive this proven therapy. An additional aim was to identify those demographic, clinical, and electrocardiographic factors that are associated with the decision not to use this therapy.

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Methods

Source of Data
The National Registry of Myocardial Infarction 2 (NRMI 2) is a prospective, observational, phase IV study sponsored by Genentech, Inc (South San Francisco, Calif) that examines practice patterns and resource utilization in the treatment of myocardial infarction and monitors the in-hospital safety experience of the use of recombinant tissue plasminogen activator. NRMI 2, which was initiated in June 1994, contains data abstracted from the charts of patients admitted to participating hospitals with a confirmed myocardial infarction. The completed case report form is forwarded from the registry hospital to an independent central data collection center, ClinTrials Research, Inc (Lexington, Ky), for processing and analysis.

Definitions
Myocardial infarction is defined by the study protocol as a patient history and presentation suggestive of a myocardial infarction and ECG evidence indicative of a myocardial infarction or total creatine kinase or creatine kinase–MB ≥2× the upper limit of normal. Reperfusion therapy is defined as the first reperfusion therapy used to restore blood flow through a suspected or known occluded coronary artery immediately on diagnosis and includes intravenous thrombolysis, primary angioplasty, or immediate coronary artery bypass grafting surgery. Patients are defined as having a contraindication to thrombolytic therapy if the treating physician indicates that a contraindication is present, as reflected by the case report form. Killip class is assigned to each patient on the basis of the severity of signs of heart failure at first assessment. Killip 1 is defined as the absence of rales in the lung fields and the absence of an S3 heart sound; Killip 2 is defined as rales in ≤50% of the lung fields, the presence of an S3, or jugular venous distention; Killip 3 is defined as rales in >50% of the lung fields; and Killip 4 is defined as the presence of pulmonary edema with hypotension. Participating hospitals are classified according to whether they had the capability of performing cardiac catheterization, primary angioplasty, or coronary artery bypass grafting. Hospitals are classified as urban if they are located in a county that has at least one city with a population of at least 50,000 people or twin cities with a combined population of at least 50,000. Patients are assigned to a geographic region based on the treating hospital location according to the US census regions (see “Appendix”).

Quality Control
The study coordinator from each participating hospital attended a half-day training course and was provided a reference study manual that included case report form field definitions and examples of correct responses. Double-key entry was used by the data collection center to add each case report form to the database. Eighty-seven electronic data checks were performed to detect internal inconsistencies, omissions, errors, and out-of-range variables. Data management issues were addressed in a quarterly study newsletter and at periodic local and national meetings of study coordinators and physician investigators.

Statistical Methods
Comparisons between different groups were made by use of the Student’s t test and one-way ANOVA for continuous variables and the χ² test for categorical variables. Nonparametric statistical analyses were used for time-dependent variables. A multiple logistic model was developed to identify predictors of receipt of reperfusion therapy and in-hospital mortality. The model included all of the variables listed in Table 1. A value of P<.05 was considered statistically significant. The SAS (version 6.06) statistical package was used for all statistical analyses.

Results
From June 1, 1994, to July 31, 1996, 330,928 patients with an acute myocardial infarction were enrolled in the registry from 1470 participating hospitals. Of the 330,928 patients, 58,277 (17.6%) were transferred into a registry hospital from another hospital 12 hours or more after symptom onset or were transferred out of the registry hospital within 12 hours of symptom onset. These transfer patients were excluded from this analysis because such patients could have received care at two participating registry hospitals and therefore been entered into the database twice. In addition, some of the patients who transferred out of a registry hospital without receiving reperfusion therapy could have received reperfusion at the transfer hospital. Because these data were unavailable, these patients were excluded. Of the remaining 272,651 patients, we identified those eligible for reperfusion therapy by excluding, in a hierarchical fashion, patients who presented to a hospital >6 hours after symptom onset (n=111,041), patients without ST elevation or left bundle-branch block on the initial ECG (n=68,395), and patients indicated by the investigator to have any contraindications to thrombolytic therapy (n=8552) (Fig 1). The remaining 84,663 patients were defined as eligible for reperfusion therapy and make up the main study cohort.

Patient Characteristics
The 84,663 patients eligible for reperfusion therapy were predominantly male (67.0%) and white (87.6%), with a mean age of 63.8 years (Table 1). Their median time from symptom onset to initial hospital presentation was 89 minutes. Thirty-five percent of the patients had an anterior-wall myocardial infarction and 81% initially had no evidence of congestive heart failure on examination. Approximately one quarter (24%) received reperfusion therapy. Of those who did receive reperfusion therapy, 87.3% received intravenous thrombolytic therapy. There was no significant change during the study period in the percent of patients defined as eligible for reperfusion therapy.

Numerous differences were observed between those patients eligible for reperfusion therapy who were and were not treated with reperfusion therapy (Table 1). Patients who received reperfusion therapy were on average 10 years younger, more often male, and less likely to have had previous cardiovascular disease such as hypertension, myocardial infarction, angina, congestive heart failure, stroke, diabetes, or a previous revascularization procedure than were eligible patients who did not receive reperfusion therapy. Eligible treated patients were more likely to present with an anterior myocardial infarction, to be a current smoker, and have either a family history of coronary artery disease or a history of hyperlipidemia. Eligible treated patients presented to the hospital earlier than those who did not receive reperfusion therapy (1.4 versus 1.7 hours) and were more likely to present to hospitals that had cardiac catheterization facilities (85% versus 81%). There was no difference between the two groups with respect to the percent of patients who presented to a hospital in an urban area. There were 27,902 women included in the present analysis with a mean age of 69.2 years. The percentage of eligible women not receiving reperfusion therapy was significantly greater than that of eligible males (32% versus 20%). Eligible women were, however, more likely to present with a history of angina,
congestive heart failure, stroke, diabetes, and evidence of heart failure on initial examination but were less likely to have had a prior myocardial infarction or revascularization procedure.

Variation in the use of reperfusion therapy by region was also examined (Table 2). Eligible patients in the mid-Atlantic states were the least likely to receive reperfusion therapy (70.4%), whereas those patients in the Mountain region were most likely to receive reperfusion therapy (81.5%).

### Independent Predictor of Receiving Reperfusion Therapy

After adjusting for differences in baseline demographic and clinical characteristics, we observed that patients older than 75 years of age were significantly less likely to receive reperfusion therapy than were those patients younger than 65 (odds ratio [OR]=0.40; 95% CI=0.36 to 0.43) (Fig 2). In addition, women remained less likely to receive reperfusion therapy than men (OR=0.88; 95% CI=0.83 to 0.92). Patients who presented with a left bundle-branch block on their initial ECG (OR 0.22; 95% CI=0.20 to 0.24) and patients who did not have chest pain at presentation (OR 0.22; 95% CI=0.21 to 0.24) were also much less likely to receive reperfusion therapy. Patients with previously diagnosed cardiovascular disease, including prior myocardial infarction, angina, or heart failure, were much less likely to receive reperfusion therapy than were patients without such a history (Fig 2). However, patients who presented within 3 hours after symptom onset were more likely to receive reperfusion therapy than patients who presented between 3 and 6 hours after symptom onset.
symptom onset. There were eight variables identified with an OR <0.7 or >1.4 (Fig 2). We examined the relative frequency of these eight predictors in those patients who did not receive reperfusion therapy \( (n = 20,319) \). We found that approximately one third of these patients had no predictors, one third had one predictor, and one third had two, three, or four predictors of not receiving reperfusion therapy.

In addition, there remained a significant regional variation in the use of reperfusion therapy. Eligible patients in the mid-Atlantic \( (OR = 0.73; 95\% \, CI = 0.66 \, \text{to} \, 0.81) \), south-Atlantic \( (OR = 0.88; \, CI = 0.80 \, \text{to} \, 0.97) \), East North Central \( (OR = 0.85; \, 95\% \, CI = 0.77 \, \text{to} \, 0.94) \), and East South Central \( (OR = 0.79; \, 95\% \, CI = 0.67 \, \text{to} \, 0.92) \) regions were all significantly less likely to receive reperfusion therapy than were eligible patients treated in New England.

**Predictors of In-Hospital Mortality**

The overall in-hospital mortality rate in those patients eligible for reperfusion therapy was 7.9%. Patients who received reperfusion therapy had a much lower unadjusted mortality rate than eligible patients who did not (5.7% versus 14.8%). The association between receipt of reperfusion therapy and lower mortality was also observed in women (9.3% versus 17.9%) and in those patients older than 65 years of age (10.5% versus 18.9%). A multivariate analysis was performed to determine which patient characteristics were independently associated with an increased risk of in-hospital mortality (Fig 3). Eligible patients >65 years of age; women; patients with a history of congestive heart failure, stroke, or diabetes; nonsmokers; patients with an anterior-wall myocardial infarction; and those who presented with Killip class >1 were at increased risk for in-hospital death. All of these patient groups were less likely to actually receive reperfusion therapy than their lower-risk counterparts.

**TABLE 2. Regional Variation in the Use of Reperfusion Therapy in Patients Eligible for Reperfusion Therapy**

<table>
<thead>
<tr>
<th>Region</th>
<th>% of Total</th>
<th>% Receiving Reperfusion Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>New England</td>
<td>5.2%</td>
<td>76.9%</td>
</tr>
<tr>
<td>Mid-Atlantic</td>
<td>13.4%</td>
<td>70.4%</td>
</tr>
<tr>
<td>South-Atlantic</td>
<td>18.8%</td>
<td>76.3%</td>
</tr>
<tr>
<td>East North Central</td>
<td>20.1%</td>
<td>75.0%</td>
</tr>
<tr>
<td>East South Central</td>
<td>6.4%</td>
<td>78.7%</td>
</tr>
<tr>
<td>West North Central</td>
<td>7.6%</td>
<td>77.2%</td>
</tr>
<tr>
<td>West South Central</td>
<td>6.7%</td>
<td>79.7%</td>
</tr>
<tr>
<td>Mountain</td>
<td>7.4%</td>
<td>81.5%</td>
</tr>
<tr>
<td>Pacific</td>
<td>14.3%</td>
<td>75.6%</td>
</tr>
</tbody>
</table>

See “Appendix” for definition of regions.

**Discussion**

In previous reports, the proportion of patients eligible for thrombolytic therapy has varied greatly and was dependent on the eligibility criteria chosen and the type of hospital examined. When elderly patients were considered ineligible, eligibility rates of 16% to 33% were reported. More recent estimates, which do not use age as an exclusion criteria, suggest that ~50% of unsolicited, consecutive patients pres-
Reperfusion Therapy in AMI

...nting to community hospitals are eligible for thrombolytic therapy. In certain subgroups of patients, such as those studied in the fourth International Study of Infarct Survival, the rate has been reported to be as high as 79%.

In the present study, we used a very conservative definition of "eligible" for reperfusion therapy. We excluded all patients with any noted contraindication to thrombolytic therapy, despite the fact that many of these patients could have been appropriate for primary angioplasty. In fact, 20.6% of the 8552 patients with contraindications to thrombolytic therapy received primary angioplasty or immediate coronary artery bypass grafting. We only included patients whose time from symptom onset to hospital arrival was <6 hours, despite the fact that there is mounting evidence to suggest that reperfusion therapy can be administered as late as 12 hours after symptom onset. Of the 141,041 patients excluded because they presented beyond 6 hours, 18,374 (16.5%) actually received reperfusion therapy. We also excluded patients whose initial ECGs were nondiagnostic, despite the fact that some of these patients could have developed a diagnostic ECG soon after or had the diagnosis of myocardial infarction made by an alternative method in time to receive reperfusion therapy. Of the 68,395 patients excluded because the initial ECG was nondiagnostic, 11,760 (17.2%) received reperfusion therapy. Using these strict criteria, we observed that 31% of all patients admitted to NRM 2 hospitals were apparently eligible to receive reperfusion therapy as part of their initial treatment. Importantly, however, we found that ~1 in 4 of these patients failed to receive what could be considered appropriate treatment. Although this is the first large study to examine the use of any type of reperfusion therapy, previous studies have evaluated the use of thrombolytic therapy in patients with a myocardial infarction. In fact, using a decision analysis model, Fendrick et al demonstrated that >10,000 deaths are attributable to the underutilization of thrombolytic therapy in the United States annually.

The findings in the present study raise the question of whether clinicians truly appreciate the significance of the many randomized, controlled trials that have demonstrated a benefit of reperfusion therapy in patients with a myocardial infarction. Interestingly, Ayanian et al found that compared with cardiologists, internists and family practice physicians were significantly less likely to believe that thrombolytic agents administered within 6 hours of a myocardial infarction definitely improved survival (OR = 0.44 and 0.26, respectively). This belief translated into the fact that internists and family practice physicians were significantly less likely to prescribe this therapy to patients than were cardiologists (OR = 0.32 and 0.19, respectively).

Compounding the problem of generalized underutilization of reperfusion therapy in the United States, we observed that elderly, female, and nonwhite patients were preferentially undertreated. As in prior studies, the present study demonstrated that women with a myocardial infarction were older, had more comorbidities, and had more severe cardiac disease. However, even after controlling for these baseline differences, women received reperfusion therapy significantly less often than did men. Despite the fact that coronary artery disease is the leading cause of death in women, there is increasing evidence that cardiovascular disease is treated less aggressively in women than men. For example, Ayanian and Epstein found that women hospitalized for coronary heart disease underwent fewer major diagnostic and therapeutic procedures than men. In addition, in the SAVE trial, women were less likely to be referred for cardiac catheterization (15.4% versus 27.3%) and coronary artery bypass grafting (5.9% versus 12.7%) than men, despite reporting greater disability from their symptoms. Previous reports have documented the underutilization of thrombolytic therapy in women. It has been suggested that this was in part related to a longer time from symptom onset to hospital arrival. In the present study, women remained less likely to receive reperfusion therapy after controlling for time from symptom onset to hospital arrival. Although women did present to the hospital later than men, the mean time to presentation in those women who did not receive reperfusion therapy was 126 minutes, well within the time frame when a substantial mortality benefit is expected. We and others have observed that women have a higher mortality rate after a myocardial infarction than do men. The present study suggests that this increased mortality rate may have resulted in part from underutilization of reperfusion therapy.

We also found that patients in certain regions in the country received reperfusion therapy less frequently than others. A similar observation was made by Pilote et al with respect to other nonthrombolytic therapies used in the treatment of patients with a myocardial infarction in the United States. In the present study, this regional variation was not explained by differences in patient or hospital characteristics.

Another important finding in the present study was that patients with the highest risk of death from their myocardial infarction were the least likely to receive reperfusion therapy. For example, eligible patients with a history of congestive heart failure experienced an in-hospital mortality rate of ~20%. These patients were, however, significantly less likely to receive reperfusion therapy than were patients who did not have a history of congestive heart failure. Similarly, other eligible patient subgroups, such as patients with congestive heart failure on examination at presentation and patients with a history of a prior myocardial infarction, angina, or diabetes, had in-hospital mortality rates that were increased relative to the overall mortality rate of 7.9%. All these patients were also significantly less likely to receive reperfusion therapy. One of the strongest predictors that patients would not receive reperfusion therapy was the presence of a left bundle-branch block on the initial ECG, another subgroup with an increased risk of in-hospital death. Such patients were 78% (OR = 0.22) less likely to receive reperfusion therapy than patients who presented with ST-segment elevation. On the basis of the meta-analyses performed by the Fibrinolytic Therapy Trialists collaborative group, thrombolytic therapy is beneficial in a wide range of patients, especially those at high risk of cardiac death. According to that analysis, patients who present with a bundle-branch block experience a 25% relative reduction in 30-day mortality when treated with thrombolytic therapy. Because these patients have an absolute mortality rate in excess of 20%, this relative reduction in mortality translates into a savings of 49 lives per 1000 patients treated.
Thus, data from randomized, controlled trials suggest that withholding reperfusion therapy from high-risk patients who present with a suspected acute myocardial infarction is inappropriate.

Finally, we observed that patients with ST-segment elevation or left bundle-branch block who did not have chest pain at presentation were significantly less likely to receive reperfusion therapy than were patients with chest pain. This observation may reflect either physician uncertainty regarding the diagnosis of acute myocardial infarction or concerns that reperfusion therapy is less beneficial in such patients. However, in several randomized trials in which the benefit of thrombolytic therapy has been demonstrated, ongoing chest pain at the time of drug administration was not required. In the Thrombolysis In Myocardial Infarction trial, 88% of pain-free patients developed enzymatic or ECG evidence of myocardial infarction. Similarly, in the North American Global Utilization of Streptokinase and t-PA for Occluded coronary arteries trial, >90% of patients without chest pain developed evidence of an acute myocardial infarction. On the basis of these analyses, both groups of investigators concluded that among patients who present with ECG evidence of myocardial infarction, it is reasonable to administer thrombolytic therapy even if symptoms have subsided.

Study Limitations
There are several limitations of this analysis. First, although we included data from >1400 hospitals throughout the United States, these hospitals may not be completely reflective of all US hospitals. Participating registry centers tend to be larger and more procedure oriented and thus may be more prone to use reperfusion therapy than nonparticipating hospitals. This bias, however, should tend to increase the observed rate of reperfusion therapy use relative to the country and thus underestimate the magnitude of the problem identified. Second, there is no independent on-site validation of data forms, and thus there exists the potential for nonconsecutive patient enrollment.

Summary
Reperfusion therapy, with either the administration of a thrombolytic agent or immediate angioplasty, is clearly a beneficial therapy for patients presenting with a myocardial infarction, yet it remains underutilized. Our data suggest that of those patients eligible for reperfusion therapy, 24% do not receive this proven therapy. Specifically, women, the elderly, patients without chest pain, and those patients at highest risk for in-hospital mortality were least likely to receive reperfusion therapy. In order for reperfusion therapy to realize its full potential in reducing cardiovascular mortality, the translation of the findings of randomized controlled trials into clinical practice must occur.

Appendix
The US census regions described in this article are as follows: New England—Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, and Connecticut; Mid-Atlantic—New York, New Jersey, and Pennsylvania; South Atlantic—Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, and Florida; East North Central—Ohio, Indiana, Illinois, Michigan, and Wisconsin; East South Central—Kentucky, Tennessee, Alabama, and Mississippi; West North Central—Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, and Kansas; West South Central—Arkansas, Louisiana, Oklahoma, and Texas; Mountain—Montana, Idaho, Wyoming, Colorado, New Mexico, Arizona, Utah, and Nevada; and Pacific—Washington, Oregon, California, Alaska, and Hawaii.

References


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