Reperfusion Therapy for Acute Myocardial Infarction

Observations from the National Registry of Myocardial Infarction 2

HAL V. BARRON, MD
AMY RUNDLE, MS
JERRY GURWITZ, MD
ALAN TIEFENBRUNN for the NRMI-2 Investigators
Department of Medicine, University of California, San Francisco
Department of Medical Affairs, Genentech Inc.; San Francisco, California
Department of Medicine, University of Massachusetts Medical School, Worchester, Massachusetts
Department of Medicine, Washington University School of Medicine, St. Louis, Missouri

The National Registry of Myocardial Infarction 2 (NRMI-2) provides a unique opportunity to evaluate the practice patterns among participating cardiology and emergency medicine departments involved in the care of patients with acute myocardial infarction. The data from NRMI-2 suggest that almost 1/3 of all non–transfer-in and non–transfer-out patients are eligible for reperfusion therapy. Furthermore, of those patients who are clearly eligible for reperfusion therapy, 24% are not given this proven therapy. Specifically, women, the elderly, patients without chest pain on presentation, and those patients at highest risk for in-hospital mortality were least likely to be treated with reperfusion therapy. The reason for underuse of reperfusion therapy may in part reflect a concern for adverse bleeding events associated with the use of thrombolytic therapy. The data from NRMI-2 also suggest that patients with contraindications to thrombolysis may be very appropriate for primary angioplasty. Realizing the full potential benefits of reperfusion therapy in terms of reduced cardiovascular morbidity and mortality will require that clinical practice patterns be aligned more closely with the recommended national guidelines, which are based on extensive clinical trial data that show the benefit of reperfusion therapy in a wide range of patients with acute myocardial infarction. By using observational databases, such as the NRMI-2, which describe how clinical care is administered in nonclinical trial settings, we can continually monitor our progress and initiate changes to ensure that patients are given access to the many therapies that have been shown to improve their quality of life and survival.

Key Words *National Registry of Myocardial Infarction, Myocardial infarction*

The National Registry of Myocardial Infarction 2 (NRMI-2) provides a unique opportunity to evaluate the practice patterns among participating cardiology and emergency medicine departments involved in the care of patients with acute myocardial infarction (AMI). One of the primary goals of NRMI-2 was to help participating centers evaluate and assess the delivery of care to patients with AMI in an effort to improve treatment outcomes. Among the most crucial aspects of this care is the timely delivery of acute interventions, such as reperfusion therapy, to eligible patients. The most recent practice guidelines of the American Heart Association (AHA) and the American College of Cardiology (ACC) (1) define those patients with AMI in whom there is clear evidence for the benefits and efficacy of thrombolytic therapy, primary percutaneous transluminal coronary angioplasty (PTCA), and immediate coronary artery bypass grafting (CABG). The extent to which the guidelines are followed remains a question of great importance. To address this question, Barron et al. (2) recently reviewed data from NRMI-2 regarding the appropriate use of these strategies in eligible patients. The following article summarizes those findings and in addition reviews important work by Tiefenbrunn et al. on specific questions regarding the use of primary angioplasty in AMI as well as work by Gurwitz et al. dealing with risk factors for developing intracranial hemorrhage after thrombolytic therapy.

Address reprint requests to: Hal V. Barron, MD, FACC, 1 DNA Way South San Francisco, CA 94080-4990. E-mail: barron.hal@gene.com.

Date of acceptance: January 20, 1999.

Use of Reperfusion Therapy in AMI

An abundance of clinical trial data provide very clear evidence that thrombolytic therapy reduces the morbidity and mortality associated with AMI. In an overview of 9 trials in a total of 58,600 patients, the Fibrinolytic Therapy Trialists' Collaborative Group found a significant survival advantage in patients who presented with ST-segment elevation or bundle branch block (BBB) and were treated with thrombolytic therapy, irrespective of their age, gender, blood pressure, heart rate, or history of previous AMI or diabetes (3). Their review of these studies also substantiated that earlier treatment was associated with greater benefit.

In support of these findings, the current ACC/AHA guidelines (1, 4) recommend that thrombolytic therapy be administered to all patients, regardless of their age, gender, or race, who have symptoms that are suggestive of an AMI, have diagnostic changes on their 12-lead electrocardiogram (ECG) (ie, ST-segment elevation or BBB), and have no contraindications to thrombolytic

1061-5377/99/703-0156/0
Cardiology in Review, Copyright © 1999 by Lippincott Williams & Wilkins, Inc.

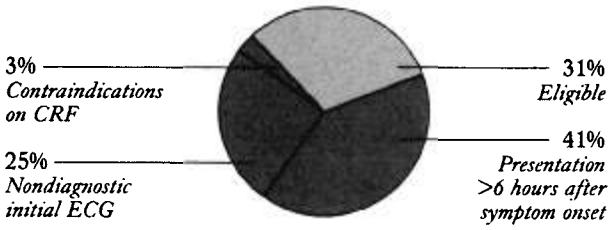
therapy. The guidelines also note that alternative reperfusion strategies (eg, PTCA, CABG) should be considered in patients who are eligible for reperfusion therapy, but who are at greater risk of bleeding (1).

Other data from the United States (5) and Europe (6, 7) indicate that, despite both the AHA/ACC recommendations and the extensive trial data that support the use of reperfusion therapy, such therapy remains underused in routine clinical practice, particularly in women and the elderly. Thus, NRMI-2 data were analyzed to determine what proportion of the patients with an AMI in NRMI-2, who were appropriate candidates for a reperfusion strategy, were not given such treatment (2). The demographic, clinical, and ECG factors that influenced the decision not to use a reperfusion strategy were also investigated.

Study Methods

The clinical centers that are enrolled in NRMI-2 represent a cross section of the acute-care hospitals across the United States that treat patients with AMI, and the data collected from these centers can provide valuable insights into this important aspect of care. Participation in the registry is strictly voluntary. Participating hospitals are expected to enroll all consecutive AMI patients, regardless of treatment or physician affiliation. NRMI-2 hospitals, representing >20% of all United States hospitals, tend to be larger, more procedure-oriented and may use thrombolytic therapy more often than nonparticipating hospitals. Data were collected from the case report forms sent to ClinTrials Research, Inc., by the participating hospitals. Per the NRMI-2 protocol, a diagnosis of AMI was made if there was a history and a presentation suggestive of and ECG evidence indicative of an MI or if the total creatine kinase or myocardial muscle creatine kinase isozyme was 2 times the upper limit of normal or higher. Reperfusion therapy (ie, intravenous or intracoronary thrombolytic therapy, PTCA, or immediate CABG) was defined as the first reperfusion therapy used to restore the blood flow in a suspected or known occluded coronary artery immediately after the diagnosis. Any contraindications to thrombolytic therapy were noted on the case report form by the treating physician. Between-group comparisons were made by using standard statistical tests; a p value of $<.05$ was considered statistically significant.

Between June 1, 1994, and July 31, 1996, there were 330,928 patients with an AMI enrolled in NRMI-2 at 1470 participating hospitals. Of these patients, 58,277 (17.6%) were "transfer-in" or "transfer-out" patients; because they could have been treated at 2 participating centers, data on these patients were excluded from the analysis to prevent "double-counting." For the remaining 272,651 patients, the following categories were reasons for exclusion from the data analysis: *a*) presentation to a hospital >6 hours after the onset of symptoms (41%); *b*) nondiagnostic initial ECG (ie, absence of ST-segment elevation or left BBB) (25%); and *c*) any contraindication to thrombolytic therapy on the case report form (3%) (Fig. 1). A total of 84,663 patients (31%) were considered clearly eligible for reperfusion therapy by these strict criteria, and the data on these were used in the analysis summarized below.



Patients meeting strict criteria for eligibility and included in the analysis

■ *Patients not meeting the criteria and exluded from the analysis*

Fig 1. Distribution of eligible patients and ineligible patients, by reason for exclusion from the data analysis. CRF, case report form.

The demographic and clinical characteristics of the 84,663 eligible patients are shown in Table 1. The majority of eligible patients were white (87.6%) and male (67.0%) with a mean age of 63.8 years. The median time from symptom onset to initial hospital presentation was 1.4 hours. Of the eligible patients, 34.7% had an anterior wall MI and 81.2% had no initial evidence of congestive heart failure on exam. Despite these generally favorable clinical conditions and the lack of complicating factors, approximately 1/4 (24.0%) of the eligible patients were not given any reperfusion therapy (7.5% of all patients).

Several clinical characteristics were significantly different between those eligible patients who were given reperfusion therapy and those who were not (Table 1). The eligible patients who were treated with reperfusion therapy were also more likely to have presented with an anterior MI, to be current smokers, and to have either a family history of coronary artery disease or a history of hypercholesterolemia. These patients also presented to the hospital earlier than those who were not given reperfusion therapy (1.4 vs 1.7 hours) and were more likely to have presented to hospitals that had cardiac catheterization facilities (85% vs 81%).

The patients who were given reperfusion therapy were on average 10 years younger, more often male, and less likely to have had previous cardiovascular disease such as hypertension, MI, angina, congestive heart failure, and stroke. They were also less likely to have diabetes or to have undergone a previous revascularization procedure than were the eligible patients who were not given reperfusion therapy. The percentage of eligible women who were not given reperfusion therapy was significantly greater than that of eligible men (32% vs 20%).Variations in the use of reperfusion therapy by region were also examined. Eligible patients in the Mid-Atlantic region were the least likely to be given reperfusion therapy (70.4%) and those in the Mountain region were the most likely (81.5%).

A multivariate analysis was performed to identify the baseline demographic and clinical characteristics that were independent predictors of reperfusion therapy use. These results validate the findings presented above. The presence of left BBB, no chest pain at presentation,

Table 1. Baseline demographic and clinical characteristics of patients eligible for reperfusion therapy who did and did not receive reperfusion therapy

	All patients (n = 84,663)	Reperfusion therapy (n = 64,344)	No reperfusion therapy (n = 20,319)	p^*
Age, years (mean ± SEM)	63.8 ± 0.05	61.4 ± 0.05	71.3 ± 0.10	<.001
Race/ethnicity				
White (%)	87.6	87.7	87.3	NS
Nonwhite (%)	12.4	12.3	12.7	NS
Urban hospital (%)	85.6	85.6	85.6	NS
Catheterization lab present (%)	83.8	84.6	81.1	<.001
Medical history				
Previous MI (%)	21.5	17.8	33.3	<.001
Angina (%)	14.8	12.5	22.1	<.001
Congestive heart failure (%)	7.9	3.4	22.1	<.001
Stroke (%)	4.3	3.0	8.5	<.001
Diabetes (%)	20.6	17.9	29.1	<.001
Current smoker (%)	34.8	39.0	20.5	<.001
Family history of coronary artery disease (%)	32.7	35.0	25.5	<.001
Hypertension (%)	44.7	42.4	52.2	<.001
Hypercholesterolemia (%)	26.3	27.7	21.8	<.001
Revascularization (%)	14.5	13.0	19.3	<.001
Symptom onset to presentation, hours, median (25th, 75th %)	1.4 (0.9, 2.5)	1.4 (0.9, 2.3)	1.7 (1.0, 3.0)	<.001
≤3 hours (%)	82.7	84.6	76.7	<.001
No chest pain at presentation (%)	9.1	3.9	25.9	<.001
Prehospital ECG obtained	4.2	4.3	4.1	NS
Left BBB (%)	8.8	2.0	30.3	<.001
Anterior MI (%)	34.7	36.2	29.7	<.001
First assessment of congestive heart failure (Killip class)				
1 (%)	81.2	86.6	64.0	<.001
2 (%)	12.3	9.6	20.6	<.001
3 (%)	4.8	2.2	13.0	<.001
4 (%)	1.8	1.6	2.4	<.001

*Reperfusion therapy vs no reperfusion therapy.
Adapted from Ref. 2.

female gender, age >75 years, and various previous cardiovascular diseases (such as MI, angina, or heart failure) were independent predictors of reperfusion therapy not being used.

Overall, the unadjusted mortality rate was much lower in the patients who were given reperfusion therapy than in those who were not (5.7% vs 14.8%). This beneficial association between reperfusion therapy and lower mortality was also apparent in women and patients >65 years. Patient characteristics similar to those that predicted not being treated with reperfusion therapy (eg, age >65 years, female gender, history of congestive heart failure) were also independently associated with a higher risk for in-hospital mortality in the eligible patients.

Thus, by using strict criteria it was found that 31% of all non–transfer-in and non–transfer-out patients enrolled in NRMI-2 were eligible for reperfusion therapy. Furthermore, of those patients who are clearly eligible for reperfusion therapy, 24% are not given this proven therapy. Specifically, women, the elderly, patients without chest pain on presentation, and those patients at highest risk for in-hospital mortality were least likely to be treated with reperfusion therapy. Reperfusion therapy, with the administration of a thrombolytic agent or immediate PTCA or CABG, is clearly beneficial in eligible patients who present with an AMI, yet it remains underused even in hospitals that participate in this national observational study. Realizing the full potential benefits of reperfusion therapy in terms of reduced cardiovascular morbidity and mortality will require that clinical practice patterns be aligned more closely with the recommended national guidelines, which are based on extensive clinical trial data that show the benefit of reperfusion therapy.

The reason for underuse of reperfusion therapy may in part reflect a concern for adverse bleeding events associated with the use of thrombolytic therapy. The Fibrinolytic Therapy Trialists Collaborative Group (3) reported an excess of 10.2 stroke events per 1000 treated patients (95% confidence interval, 5.7 to 14.7) during days 0–1, for those aged 75 years or older. This early excess was largely attributed to cerebral hemorrhage. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator (rt-PA) for Occluded Coronary Arteries (GUSTO-1) trial,[1] at 30 days of follow-up, 0.42% of patients aged 75 years or younger treated with streptokinase and 0.52% of those treated with accelerated rt-PA experienced a hemorrhagic stroke. Among patients >75

years, these percentages were 1.23% and 2.08%, respectively. In a further analysis of data from GUSTO-1, advancing patient age was independently related to the occurrence of primary intracranial hemorrhage, after adjustment for other factors including weight, previous cerebrovascular disease, blood pressure, and type of thrombolytic drug (1). Seventy-seven percent of these hemorrhages occurred within 24 hours of treatment. Sixty percent of the 268 patients who suffered primary intracranial hemorrhage in GUSTO-1 died, and an additional 25% were disabled (8).

Gurwitz et al. (9) reported the findings of a study on the frequency of and risk factors for, intracranial hemorrhage after treatment with recombinant tissue-type plasminogen activator for AMI as observed in NRMI-2. Despite the rare occurrence of an intracranial hemorrhage, it is the most feared complication of thrombolytic therapy. Of 71,703 patients treated with rt-PA, from June 1, 1994 through September 30, 1996, 0.95% (n = 673) were reported to have suffered intracranial hemorrhage during hospitalization for their AMI. Risk for this event increased dramatically with advancing patient age. Patients aged 65 to 74 were 2.7 times (95% confidence interval, 2.2–3.4) as likely to suffer this event as compared with patients <65 years of age; patients 75 years of age or older were 4.3 times as likely to suffer intracranial hemorrhage (95% confidence interval, 3.5–5.5). Other independent risk factors for intracranial hemorrhage with rt-PA treatment in the setting of AMI included: female gender, black race, systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥100 mmHg, rt-PA dose ≥1.50 mg/kg, and history of previous stroke. History of previous stroke was a particularly strong risk factor for the occurrence of intracranial hemorrhage, with a significantly increased risk for this event among all patients regardless of age.

Although the information presented above concentrates on patients with AMI who have clear indications for reperfusion therapy, many patients with AMI may present with atypical symptoms or a nondiagnostic ECG. Patients with a high clinical suspicion for AMI but a nondiagnostic electrocardiogram may be candidates for emergent angiography and, if appropriate, primary angioplasty. In the NRMI-2 database, nontransfer patients undergoing primary angioplasty had approximately twice the percentage of nondiagnostic ECGs at initial presentation compared with those undergoing thrombolytic therapy (23.8 vs 12.4%; $p < .0001$) (10). This appears to reflect a tendency to refer selected patients for angiography when electrocardiographic criteria for initiating thrombolytic therapy are not initially met (3).

Patients felt to have a contraindication to activation of the fibrinolytic system may also be good candidates for referral for early angiography. Of 4939 patients undergoing primary angioplasty in the NRMI-2 data base, 18% were identified as having a contraindication to thrombolytic therapy (1). This group of patients had higher risk baseline characteristics than patients referred for angioplasty who did not have a contraindication to thrombolytic therapy (they were older, more likely to be female, and had a higher rate of previous stroke). These "lytic ineligible" patients had an in-hospital mortality after primary angioplasty that was approximately twice as high as the mortality rate for lytic eligible patients after angioplasty (13.6% vs 6.2% for all patients, 12.5% vs 5.2% excluding those presenting in cardiogenic shock; both $p < .001$). For lytic eligible, nonshock patients, in-hospital mortality was similar for patients receiving rt-PA and those undergoing primary angioplasty (5.4 vs 5.2%, respectively; p = NS).

. . .women, the elderly, patients without chest pain on presentation, and those patients at highest risk for in-hospital mortality were least likely to be treated with reperfusion therapy.

The proportion of patients undergoing primary angioplasty has been increasing. From 1994 through the first half of 1997, the proportion of patients receiving reperfusion therapy who underwent primary angioplasty increased by approximately 1/3, from approximately 15% to 20.5% in the NRMI-2 database (11). The proportion of reperfusion patients with a diagnostic ECG at presentation who received primary angioplasty increased approximately 50%. There has been no significant change in the proportion of patients who are male undergoing primary angioplasty, those with anterior myocardial infarction, or mean or median age of these patients. There has been a modest improvement in median door-to-balloon time for non–transfer-in patients undergoing primary angioplasty, with this value recently at approximately 2 hours. However, this is related primarily to a decrease in the longer time until dilation. There has been no significant change in the 25th percentile for time to dilation, which remains relatively constant at approximately 90 minutes.

Patients who are transferred from one institution to another to undergo primary angioplasty experience significantly longer intervals from initial presentation until first balloon inflation when compared with those undergoing primary angioplasty at the site where they present (12). In an analysis from the NRMI-2 database, lytic eligible patients with a diagnostic ECG who were not in cardiogenic shock and were transferred for primary angioplasty had similar baseline characteristics to nontransfer patients meeting the same criteria. However, the patients who were transferred had a median time from symptom onset until first balloon inflation of 6 hours, compared with 3.7 hours for nontransfer patients ($p < .0001$). Although baseline characteristics were similar between the 2 groups, the in-hospital mortality rate was significantly higher for those primary angioplasty patients undergoing transfer (7.7% vs 5.0%; $p < .0001$).

Summary

By using strict criteria, almost 1/3 of all non–transfer-in and non–transfer-out patients enrolled in

NRMI-2 were eligible for reperfusion therapy. The data from NRMI-2 suggest that of those patients who are clearly eligible for reperfusion therapy, 24% are not given this proven therapy. Specifically, women, the elderly, patients without chest pain on presentation, and those patients at highest risk for in-hospital mortality were least likely to be treated with reperfusion therapy. The reason for underuse of reperfusion therapy may in part reflect a concern for adverse bleeding events associated with the use of thrombolytic therapy. However, patients with contraindications to thrombolysis may be very appropriate for primary angioplasty. Realizing the full potential benefits of reperfusion therapy in terms of reduced cardiovascular morbidity and mortality will require that clinical practice patterns be aligned more closely with the recommended national guidelines, which are based on extensive clinical trial data that show the benefit of reperfusion therapy in a wide range of patients with AMI. By using observational databases, such as the NRMI-2, which describe how clinical care is administered in nonclinical trial settings, we can continually monitor our progress and initiate changes to ensure that patients are given access to the many therapies that have been shown to improve their quality of life and survival.

References

1. **Ryan TJ, Anderson JL, Antman EM, et al:** ACC/AHA guidelines for the management of patients with acute myocardial infarction: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (committee on management of acute myocardial infarction). J Am Coll Cardiol 1996;28:1328–1428.

This is a publication from the ACC/AHA on the guidelines for the management of patients with AMI.

2. **Barron HV, Bowlby LJ, Breen T, et al:** Use of reperfusion therapy for acute myocardial infarction in the United States: Data from the National Registry of Myocardial Infarction 2. Circulation 1998;97: 1150–1156.

This publication is an observational study suggesting that both thrombolytic therapy and primary angioplasty may be underused in the United States.

3. **Fibrinolytic Therapy Trialists' (FTT) Collaborative Group:** Indications for fibrinolytic therapy in suspected acute myocardial infarction: Collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Lancet 1994;343:311–322.

This publication is a meta analysis of numerous studies that have assessed the value of thrombolytic therapy. The review concentrates on the use of thrombolytic therapy in various subgroups.

4. **McLaughlin TJ, Soumerai SB, Willison DJ, et al:** Adherence to national guidelines for drug treatment of suspected acute myocardial infarction: Evidence for undertreatment in women and the elderly. Arch Intern Med 1996;156:799–805.

This publication describes how lifesaving therapies for eligible patients with AMI is higher than previously reported, particularly for aspirin and thrombolytic use in nonelderly patients. However, they concluded that increased adherence to AMI treatment guidelines is required for elderly patients and women.

5. **Phillips BG, Yim JM, Brown EJ Jr, et al:** Pharmacologic profile of survivors of acute myocardial infarction at United States academic hospitals. Am Heart J 1996;131:872–878.

This publication describes data on the actual pharmacologic management of patients surviving AMI at academic hospitals and concludes that improvements could still be made in the number of patients who receive thrombolytic and acute and chronic beta-blocker therapies after AMI, particularly in women.

6. **Ketley D, Woods KL:** Impact of clinical trials on clinical practice: Example of thrombolysis for acute myocardial infarction. Lancet 1993;342:891–894.

This publication describes the increasing use of thrombolytic therapy over time. Rates of use per 1000 patients admitted with MI varied almost sixfold between districts in 1989–1990 and more than twofold in 1991–1992.

7. **European Secondary Prevention Study Group:** Translation of clinical trials into practice: A European population-based study of the use of thrombolysis for acute myocardial infarction. Lancet 1996;347: 1203–1207.

This study confirmed that only approximately 1/3 of patients admitted to European hospitals with AMI receive a thrombolytic drug. It also determined that after allowing for delays to presentation and difficulty of early diagnosis, the maximum rate of thrombolysis is approximately 55%.

8. **Gore JM, Granger CB, Simoons ML, et al:** Stroke after thrombolysis: Mortality and functional outcomes in the GUSTO-I trial—Global Use of Strategies to Open Occluded Coronary Arteries. Circulation 1995;92:2811–2818.

This publication, from the GUSTO investigators, concluded that stroke remains a rare but catastrophic complication of thrombolysis, and particularly the elderly and patients with previous cerebrovascular events are at high risk.

9. **Gurwitz JH, Gore JM, Goldberg RJ, et al:** Risk factors for intracranial hemorrhage associated with TPA treatment in acute myocardial infarction: Findings from the National Registry of Myocardial Infarction-2 (NRMI-2). Ann Intern Med 1998;129:597–604.

This publication from the NRMI investigators concluded that appropriate drug dosing may reduce the risk for intracranial hemorrhage associated with tissue plasminogen activator treatment in AMI and that other therapies, such as primary coronary angioplasty, may be preferable in patients with AMI who have a history of stroke.

10. **Tiefenbrunn AJ, Chandra NC, French WJ, et al:** Clinical experience with primary PTCA compared with Alteplase (recombinant tissue-type plasminogen activator) in patients with acute myocardial infarction: A report from the Second National Registry of Myocardial Infarction (NRMI-2). J Am Coll Cardiol 1998;31:1240–1245.

These investigators from the NRMI conclude that in lytic-eligible patients not in shock, PTCA and rt-PA are comparable alternative methods of reperfusion when analyzed in terms of in-hospital mortality, mortality plus nonfatal stroke, and reinfarction.

11. **Tiefenbrunn AJ, Every NR, Pirzada SR, et al:** Improving outcomes in patients undergoing primary angioplasty for acute myocardial infarction: Trend data from the National Registry of Myocardial Infarction 2. (Abstract) J Am Coll Cardiol 1998;31:211A.

12. **Tiefenbrunn AJ, Chandra NC, Every NR, et al:** High mortality in patients with myocardial infarction transferred for primary angioplasty: A report form the National Registry of Myocardial Infarction 2. (Abstract) Circulation 1997;96:I-531.