Observations of the Treatment of Women in the United States With Myocardial Infarction

A Report From the National Registry of Myocardial Infarction-I

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Background: To determine whether there are sex differences in the demographics, treatment, and outcome of patients with acute myocardial infarction in the United States, data from the National Registry of Myocardial Infarction-I from September 1990 to September 1994 were examined.

Methods: The National Registry of Myocardial Infarction-I is a national observational database consisting of 1234 US hospitals in which each hospital submits data from each patient with acute myocardial infarction to a central data collection center. For these analyses, the following variables were examined in 354,435 patients with acute myocardial infarction: demographics; use of medical therapy including thrombolytic agents; use of procedures including cardiac catheterization, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery; length of hospital stay; adverse events (stroke, major bleeding, or recurrent myocardial infarction); and causes of death.

Results: In comparison with men, women experiencing acute myocardial infarction in the United States are older, with 55.7% older than 70 years. Women have a higher mortality rate than men even when controlled for age and die less often from arrhythmia but more often from cardiac rupture whether or not thrombolytic therapy is used. Treatment with aspirin, heparin, or β-blockers is less frequent in women. When thrombolytic therapy is used, women are treated an average of almost 14 minutes later than men and experience a greater incidence of major bleeding. Cardiac catheterization, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery are used less often in women.

Conclusions: Observations from the National Registry of Myocardial Infarction-I document important sex differences in demographics, treatment, and outcome of patients with acute myocardial infarction in the United States.

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Coronary artery disease is the leading cause of death and is responsible for more than one third of all deaths in women in the United States.1 While the clinical manifestations of coronary artery disease in women are delayed by approximately a decade compared with men, this sex difference nearly disappears in older age.2 Studies of acute myocardial infarction (AMI) from the prethrombolytic era demonstrate that women have a worse prognosis than men.3,5 This observation has been supported by more recent large clinical trials of thrombolytic agents in both placebo and thrombolysis groups6-10 and was emphasized recently by the GUSTO-I investigators.11 This difference in outcome may be explained in part by older age, more advanced disease, higher Killip class, and a greater prevalence of underlying medical illness in women than in men.12 Recent attention has also focused on the role of sex differences in diagnostic and therapeutic strategies in patients with known or suspected coronary artery disease. Many13-19 but not all20 studies have reported that physicians are less likely to pursue an aggressive approach in women than in men.

No recent large study has focused on the demographics and routine clinical use of drug therapy or procedures in women experiencing AMIs in the United States, including both those treated and not treated with thrombolytic therapy. In this article, we describe observations relating to the treatment and outcome of men and women with AMI in the United States based on data from more than 350,000 patients in the National Registry of Myocardial Infarction-I (NRMI-I) from September 1990 to September 1994.
METHODS

The detailed methods for this study have been reported previously.21 In brief, the NRMI is a voluntary observational database sponsored by Genentech Inc, South San Francisco, Calif. The purpose of the NRMI is to collect uniform prospective data on the treatment of patients with AMI that can be used to analyze practice patterns and treatment outcomes. Participating sites receive quarterly information on local care to facilitate quality improvement. Phase I of the registry (NRMI-I), from which this study is drawn, entered 354,435 patients from September 1990 to September 1994. A second registry, NRMI-II, is ongoing.

Demographic, procedural, and outcome data on patients with AMI are recorded by participating hospitals throughout the United States. To facilitate uniform data collection, each registry data coordinator received in-service training on data collection methods and terminology as defined in the 38-page manual for form completion for NRMI. Thus, standardized terminology and criteria for item entry are defined for each hospital. Data from each hospital are tabulated by a central data collection center (ClinTrials Research Inc, Lexington, Ky). Participating hospitals receive quarterly summaries of the cumulative study-wide NRMI-I data together with confidential, individualized, parallel tabulations of the hospital data.

Approval of the NRMI-I data collection process at participating hospitals included review by individual institutional committees on human research as determined by local policies and procedures.

DEFINITIONS

To be included in NRMI-I, patients had to have an AMI documented as the discharge diagnosis according to local hospital criteria, encompassing elevated levels of cardiac enzymes (total or creatine kinase–MB), electrocardiographic (ECG) changes, or findings supported by coronary angiography. Time of chest pain onset was defined as the time when chest pain intensified or became prolonged or intolerable such that the patient decided to seek treatment. Time of initial presentation was defined as the time that the patient arrived at the NRMI-I hospital or the referral hospital if that was earlier. Patient initials and birth dates were recorded to minimize double counting of patients who might have been transferred from one registry hospital to another. For purposes of this analysis, MI location was classified as anterior, nonanterior, or other, including nonspecific ST- or T-wave abnormalities or no ECG evidence of MI. The location of MI, as defined by the attending physician, was determined by chart review. The use of concomitant medications (intravenous [IV] heparin, inotropic agents, IV β-blockers, aspirin, calcium channel blockers, or IV nitroglycerin), invasive procedures, and adverse events were recorded if they were implemented or occurred at any time during the hospitalization. Peri-MI arrhythmias included any arrhythmia occurring within 24 hours of the index infarction. Recurrent MIs required the patient to evolve ECG changes and elevated levels of creatine kinase indicative of a second infarct. Drug-induced hypotension was described as hypotension requiring at least fluid replacement therapy. Cause of death was determined by review of the patient’s chart and/or death certificate (as noted by the attending physician) and categorized as being due to sudden cardiac arrest (collapse in an unmonitored situation); cardiogenic shock (low blood pressure [usually <90 mm Hg] with signs of hypoperfusion, cool, clammy skin, oliguria or altered sensorium, and nonresponsiveness to fluid resuscitation or pressor agents); recurrent MI (as defined earlier); arrhythmia (to include supraventricular tachycardia, ventricular tachycardia or fibrillation, or any arrhythmia resulting in hemodynamic compromise); cardiac rupture and/or electromechanical dissociation (EMD) (based either on autopsy findings, clinical course, or the sudden development of pulseless electrical activity); other cardiac causes (pericarditis or valvular insults); or noncardiac causes of death (eg, pneumonia, pulmonary embolism, or sepsis).

STATISTICAL METHODS

Group differences based on categorical variables were assessed using the χ² test. Differences based on continuous variables (such as age and weight) were assessed using the 2-sample t test, and differences based on time intervals were assessed using the nonparametric Wilcoxon signed rank test. When appropriate, data were expressed as mean (± SD). Multivariate logistic regression analyses were performed to assess sex differences after accounting for the presence of those potential confounding variables that were recorded in NRMI-I. All statistical analyses were performed using SAS 6.06 statistical package programs (SAS Institute Inc, Cary, NC). To adjust for the large number of comparisons, a Bonferroni adjustment was applied.22 This adjustment identified a P value of .003 as corresponding to an α level of .05. Thus, significance was defined as P ≤.003.

RESULTS

DEMOGRAPHICS: GENERAL CHARACTERISTICS

From September 1990 to September 1994, 354,435 patients were enrolled in the NRMI-I from 1234 contributing hospitals. Table 1 lists the main demographic features of the patients enrolled and divides them by sex and use of thrombolytic therapy. The majority of the NRMI-I population was male (63.7%). Only 34.8% of all patients received thrombolytic therapy. Those who received thrombolytic agents were younger than those who did not. The average time to presentation for all patients was more than 5 hours (mean ± SD, 307.9 ± 444 minutes) and was approximately 3 hours longer for those not treated with thrombolytic therapy than for those who received thrombolytic agents (mean ± SD, 397.9 ± 513.3 minutes vs 176.8 ± 267.3 minutes) (P < .001). The average hospital stay was a mean ± SD of 9.2 ± 15.3 days and was longer for those not treated with thrombolytic therapy (mean ± SD, 9.5 ± 16.1 days vs 8.7 ± 15.6 days) (P < .001). Patients who received thrombolytic therapy were more likely to have an MI in which location could be specified compared with those who did not receive thrombolytic therapy. In those who received thrombolytic therapy, the initial ECG was commonly used to make the diag-
Patients Receiving TT

For both men and women, additional procedures (cardiac catheterization, percutaneous transluminal coronary angioplasty, or bypass surgery) were more likely to be used in those who received thrombolytic therapy compared with those who did not (Table 2). For example, 69.1% of those who received thrombolytic agents underwent cardiac catheterization compared with only 48.5% of those who were not treated with thrombolytic therapy (P<.001). Almost twice as many patients who received thrombolytic therapy underwent percutaneous transluminal coronary angioplasty (29.9%) as those who were not treated with thrombolytic agents (16.9%) (P<.001). However, in both treatment groups women were less likely than men to undergo additional procedures. Of those not treated with thrombolytic therapy, women were less likely to undergo cardiac catheterization (40% vs 54.4% of men), percutaneous transluminal coronary angioplasty (13.8% vs 19% of men), and coronary artery bypass grafting (8% vs 12.6% of men) (P<.001 for all). Similarly, in those who received thrombolytic therapy, these procedures were used less often in women than in men (64.3% vs 71% of men for catheterization; 28.3% vs 30.6% of men for percutaneous transluminal coronary angioplasty; and 11% vs 13.5% of men for coronary artery bypass grafting) (P<.001).

ADVERSE EVENTS

All adverse events recorded for stroke, major bleeding, and recurrent MIs were more common in patients receiving thrombolytic therapy. Women had a higher occurrence of stroke, major bleeding, and recurrent MIs than men, whether or not they received thrombolytic therapy.
agents. Allergic and anaphylactic reactions were reported only in patients receiving thrombolytic therapy (Table 2).

MORTALITY AND CAUSE OF DEATH AFTER MYOCARDIAL INFARCTION

The mortality rate was substantially lower in men than in women for similar treatment strategies and age groups. However, the mortality in both treatment groups increased as a function of age (Table 3 and Figure 1). The most common causes of death in all patients with AMI were cardiogenic shock and sudden cardiac arrest. A lower mortality rate was observed for men and women who received thrombolytic therapy compared with those who did not (Figure 1). Cardiogenic shock and rupture and/or EMD were more common causes of death in those who received thrombolytic therapy, while sudden cardiac arrest and death due to noncardiac causes were less common in these patients. In women, death from arrhythmias occurred less frequently than in men, but a higher frequency of rupture and/or EMD was noted (Table 3). Comparing cause of death in men treated with thrombolytic therapy with men who did not receive such therapy, similar relationships were found, with a higher incidence of cardiogenic shock and myocardial rupture, although a lower frequency of sudden cardiac arrest and death due to noncardiac causes was noted in patients treated with thrombolytic agents. For those who did not receive thrombolytic therapy, death from recurrent MIs and rupture and/or EMD was more common and death from arrhythmia less common in women than in men.

CONCOMITANT MEDICATIONS

The NRMI database tracked the use of IV heparin, inotropic agents, IV or oral B-blockers, aspirin, calcium channel blockers, and IV nitroglycerin. In both men and women treated with thrombolytic agents, the use of heparin, B-blockers, aspirin, and IV nitroglycerin was substantially higher than in those not treated with thrombolytic therapy (Table 4). In all patients not treated with thrombolytic therapy, the use of calcium
channel blockers was more common. In both those treated with thrombolytic therapy and those who did not receive thrombolytic agents, survivors were more likely to have received heparin, β-blockers, aspirin, and IV nitroglycerin compared with those who died. However, irrespective of treatment with thrombolytic agents, the use of these concomitant medications was always lower in women with the least frequent use being noted in women who died. Mean time to death in all patients was longer than 5 days (Table 3), suggesting that the reason for not using concomitant therapy was unlikely to be very early death. When the median time to death was examined (3.75 days for all patients) similar observations were noted (median time: 4.1 days for men not treated with thrombolytic therapy, 4.0 days for women not treated with thrombolytic therapy, 2.6 days for men treated with thrombolytic therapy, and 2.3 days for women treated with thrombolytic therapy).

MULTIVARIATE LOGISTIC REGRESSION ANALYSIS

A multivariate logistic regression analysis was performed to address the relative importance of the following variables in predicting mortality: age, sex, anterior MI, and use of IV heparin, oral or IV β-blockers, aspirin and IV nitroglycerin, calcium channel blockers, or thrombolytic therapy (Figure 2). Although mortality was most dependent on age and use of thrombolytic therapy, female sex still emerged as a predictor of poor outcome (Figure 2) \((P<.001; \text{odds ratio, 0.78; 95\% confidence interval [CI] 0.77-0.80})\). Further analyses were performed to test the interaction of age and sex, since most women were older than 70 years. A significant interaction effect was detected between ages 65 to 75 years and sex \((P<.001; \text{odds ratio, 1.35; 95\% CI, 1.26-1.44})\) and also between ages older than 75 years and sex \((P<.001; \text{odds ratio, 1.59; 95\% CI, 1.49-1.69})\).

TEMPORAL TRENDS

As depicted in Figure 3, the number of patients recruited per year into this observational database has increased. Between 1990 and 1993, 39%, 40%, 39%, and 39% of men were treated with thrombolytic agents compared with 26%, 27%, 27%, and 28% of women for comparable years. The mortality rate remained comparable for men and women during this time.

COMMENT

Coronary artery disease is the leading cause of death in women in the United States.\(^1\) This observational study of more than 350,000 patients reflects clinical practice in more than 1200 hospitals nationwide and demonstrates that, compared with men, women with AMI have a higher mortality rate whether or not they receive thrombolytic therapy; die more often from cardiac rupture; and are less likely to be treated with aspirin, heparin, or β-blockers. Several studies have demonstrated that women who sustain an AMI have a worse prognosis than men.\(^2-11\) While several studies examining prac-

![Figure 1. Mortality rates in females (F) and males (M) with no thrombolytic therapy (No TT) and in those treated with thrombolytic agents (TT) in patients aged 50 years and younger, 50 to 60 years, 60 to 70 years, 70 to 80 years, and older than 80 years. Absolute mortality in each category is also displayed. Mortality figures were not adjusted for other confounding variables (hypertension, diabetes, tobacco use, or hyperlipidemia).](image-url)
percentage of women (55%) in the Western Washington trial received thrombolytic therapy compared with eligible men (78%).  

In the International Tissue Plasminogen Activator/Streptokinase Mortality Study, 12 even when women received thrombolytic therapy they were given treatment considerably later (18 minutes) than men, a finding similar to our observations. While there was no sex difference in the use of nitrates, β-blockers, and calcium channel blockers in the Survival and Ventricular Enlargement Trial 14 more men were receiving aspirin before the index infarction.

Advanced age has been previously identified as a predictor of poor outcome following MI 23 and our data were receiving aspirin before the index infarction. While a cause and effect relationship cannot be established in an observational study like this one, women were also treated less often with aspirin, heparin, or β-blockers, especially those who died. The low administration rates of these drugs cannot be ascribed to early death since the mean time to death was 5 days or longer, certainly more than enough time to initiate therapy with heparin or aspirin.

The present study also documents important differences in the cause of death, with women being more likely to die of cardiac rupture. In the group of patients in the NRMI-I not treated with thrombolytic therapy, women (compared with men) were more likely to die of recurrent MI and rupture. While a cause and effect relationship cannot be established in an observational study like this one, women were also treated less often with aspirin, heparin, or β-blockers, especially those who died. The low administration rates of these drugs cannot be ascribed to early death since the mean time to death was 5 days or longer, certainly more than enough time to initiate therapy with heparin or aspirin. The use of heparin (38%), β-blockers (14%), and aspirin (36%) was remark-

### Table 4. Concomitant Medication Use

<table>
<thead>
<tr>
<th>Patients Not Receiving TT</th>
<th>Patients Receiving TT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td><strong>Women</strong></td>
</tr>
<tr>
<td>Alive (A)</td>
<td>Dead (B)</td>
</tr>
<tr>
<td>Alive (C)</td>
<td>Dead (D)</td>
</tr>
<tr>
<td>Alive (E)</td>
<td>Dead (F)</td>
</tr>
<tr>
<td>Alive (G)</td>
<td>Dead (H)</td>
</tr>
<tr>
<td>No. (%) of patients</td>
<td></td>
</tr>
<tr>
<td>(a) Heparin</td>
<td>79,352 (65.2)</td>
</tr>
<tr>
<td>(b) Inotropic agent</td>
<td>16,444 (13.5)</td>
</tr>
<tr>
<td>(c) IV β-blocker</td>
<td>7833 (6.4)</td>
</tr>
<tr>
<td>(d) Oral β-blocker</td>
<td>42,506 (34.9)</td>
</tr>
<tr>
<td>(e) Aspirin</td>
<td>87,645 (72.1)</td>
</tr>
<tr>
<td>(f) Calcium channel blocker</td>
<td>51,144 (42.0)</td>
</tr>
<tr>
<td>(g) IV nitroglycerin</td>
<td>66,786 (54.9)</td>
</tr>
</tbody>
</table>

### Figure 2. Odds ratios and 95% confidence intervals for mortality effects for the variables listed. IV indicates intravenous; MI, myocardial infarction.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td></td>
</tr>
<tr>
<td>Male Sex</td>
<td></td>
</tr>
<tr>
<td>IV Heparin</td>
<td></td>
</tr>
<tr>
<td>IV Nitroglycerin</td>
<td></td>
</tr>
<tr>
<td>Anterior MI</td>
<td></td>
</tr>
<tr>
<td>Age, 65-75 y</td>
<td></td>
</tr>
<tr>
<td>Age, &gt;75 y</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 3. Total patient recruitment in thousands for the years 1990 to 1993 for all patients (first bar); all males (M) (second bar); and all females (F) (third bar). The dark portion of each bar reflects the number of patients receiving thrombolytic therapy (TT). The percentage of patients treated with thrombolytic therapy each year for all patients and for all men and women is noted. The mortality rate in those treated with and those not treated (no TT) with thrombolytic agents is also noted.
ably low in women who died and did not receive thrombolytic therapy. These data also illustrate that the use of such beneficial concomitant therapy was much lower than that recommended for patients not receiving thrombolytic therapy. The low use of aspirin is particularly noteworthy. The multivariate analysis demonstrates the importance of concomitant therapy but also shows that despite controlling for thrombolytic therapy, age, anterior MI, and use of concomitant therapy, female sex is an independent predictor of poor outcome.

These data demonstrate that even when the constraints and guidelines for therapy of rigorous clinical trials are removed, cardiac catheterization and revascularization procedures are used more often in men than in women, with less use of these procedures in those not treated with thrombolytic agents.  

The NRMI-I database, by virtue of its ongoing data collection and tabulation, allows temporal trends to be examined. Despite the increasing awareness of the value of thrombolytic therapy and the publication of various thrombolytic megalatrials, Figure 3 demonstrates that there has been no substantial change in the percentage of patients being treated with thrombolytic therapy from 1990 to 1993, and also no substantial change in the mortality rate either in those receiving thrombolytic agents or not. For all treatment modalities, women have a higher mortality rate, although it appears that the number of women being treated with thrombolytic therapy may be increasing. However, these mortality figures are unadjusted for variables such as diabetes and hypertension, which were not recorded on the NRMI-I data collection form. Other studies have reported a higher incidence of hypertension and diabetes in women, which would favor increasing mortality.

This study has several limitations, similar to those reported by Rogers et al. Although large, the NRMI-I is an observational database rather than a randomized trial, and it is therefore more valuable for documenting practice patterns and temporal trends than for comparing effectiveness of various treatment interventions. Like many of the recent megalatrials in thrombolysis, the data obtained on each NRMI-I patient had no independent validation of data forms, and there exists the potential for underreporting adverse events or for the enrollment of nonconsecutive patients. Also, although encompassing more than 1000 hospitals nationwide, NRMI-I hospitals are not necessarily representative of all US hospitals and likely reflect practice in larger, more procedure-related centers. The modest collection of demographic information in NRMI-I limits data interpretation. Although the percentage of use of aspirin, β-blockers, and other adjunctive therapy is likely to be correct, the presence of contraindications to these agents (that may, in part, explain their low use) was not recorded. These data are also limited in that potentially important confounding variables, such as the prevalence of diabetes, hypertension, tobacco use, and hyperlipidemia, were not recorded and hence could not be studied. Despite these limitations, the NRMI-I data reflect recent practice trends in more than 350,000 patients and make compelling observations regarding the limited use of recommended adjunctive therapy. In the GUSTO trial, the use of β-blockers, heparin, and aspirin was standard protocol and the use of β-blockers in appropriate candidates was as high as 46% IV and 71% orally. Intravenous nitroglycerin was used in 77% of all patients. Recently, the GUSTO investigators reported outcomes in women, confirming their higher mortality rate compared with men. However, the authors did not comment on the percentage of use of such adjunctive therapy, which becomes particularly relevant (given the proven benefits of β-blocker use) if morbidity, in addition to mortality, is considered. In this article using data from the NRMI-I database, only in-hospital mortality is recorded and reported. When studying sex differences the GUSTO investigators reported 30-day mortality rates, limiting our ability to compare the NRMI-I data with those from the GUSTO trial. Furthermore, 30-day mortality rates may be additionally affected by adjunctive medical therapy. Our data suggest that in clinical practice in the United States, there may be an inappropriately conservative approach to the care of patients with AMI, especially in terms of using adjunctive therapy. This becomes particularly relevant in the case of women with MI, in which the actual use of β-blockers has been less than 50% of that reported in clinical trials. As supported by the multivariate analysis, this conservatism is associated with increased mortality and should be the focus of future studies.

CONCLUSIONS

These observations from more than 350,000 patients hospitalized in the United States over a 4-year period suggest that important sex differences exist in demographics, treatment, and outcome of patients with AMI. The less frequent use in women of thrombolytic therapy, cardiac catheterization, coronary artery bypass surgery, aspirin, heparin, and β-blockers may, in part, explain their higher mortality rate compared with men.

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REFERENCES


