Treatment of Myocardial Infarction in the United States (1990 to 1993)

Observations From the National Registry of Myocardial Infarction

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Background Multiple clinical trials have provided guidelines for the treatment of myocardial infarction, but there is little documentation as to how consistently their recommendations are being implemented in clinical practice.

Methods and Results Demographic, procedural, and outcome data from patients with acute myocardial infarction were collected at 1073 US hospitals collaborating in the National Registry of Myocardial Infarction during 1990 through 1993. Registry hospitals composed 14.4% of all US hospitals and were more likely to have a coronary care unit and invasive cardiac facilities than nonregistry US hospitals. Among 240,989 patients with myocardial infarction enrolled, 84,477 (35.1%) received thrombolytic therapy. Thrombolytic recipients were younger, more likely to be male, presented sooner after onset of symptoms, and were more likely to have localizing ECG changes. Among the 60,430 patients treated with recombinant tissue-type plasminogen activator (rTPA), 23.2% received it in the coronary care unit rather than in the emergency department. Elapsed time from hospital presentation to starting rTPA averaged 99 minutes (median, 57 minutes). Among patients receiving thrombolytic therapy, concomitant pharmacotherapy included intravenous heparin (96.9%), aspirin (84.0%), intravenous nitroglycerin (76.0%), oral β-blockers (36.3%), calcium channel blockers (29.5%), and intravenous β-blockers (17.4%). Invasive procedures in thrombolytic recipients included coronary arteriography (70.7%), angioplasty (50.3%), and bypass surgery (13.3%).

Conclusions This large registry experience suggests that management of myocardial infarction in the United States does not yet conform to many of the recent clinical trial recommendations. Thrombolytic therapy is underused, particularly in the elderly and late presenters. Although emerging trends toward more appropriate treatment are evident, hospital delay time in initiating thrombolytic therapy remains long, aspirin and β-blockers appear to be underused, and calcium channel blockers and invasive procedures appear to be overused. (Circulation. 1994;90:2103-2114.)

Key Words • thrombolysis • clinical trials • angiography • pharmacology

A acute myocardial infarction, the most common cause of death in most Western industrialized countries, has received considerable clinical research emphasis over the past decade. To examine the impact of new pharmacological and invasive therapy, hundreds of thousands of patients have been enrolled in well-designed, randomized clinical trials,1 and many useful guidelines for management of patients with acute myocardial infarction have been formulated.1,2

However, there is only limited documentation on how patients with acute myocardial infarction are actually being managed in the United States3,4 and how consistently the results of recent clinical trials are being implemented in clinical practice. Some have reported that practice patterns change gradually, over a period of years, following new recommendations from clinical trials.5,6 The National Registry of Myocardial Infarction is an ongoing national database that, since September 1990, has tracked practice patterns and outcome of more than 240,000 patients with acute myocardial infarction enrolled at selected hospitals throughout the United States. The purpose of this article is to report the initial findings of this ongoing registry, to contrast patients receiving thrombolytic therapy with those not receiving it, and to compare US acute myocardial infarction management, as documented in this registry, with recommendations from recent clinical trials.

Methods

Purpose of the Registry

The National Registry of Myocardial Infarction is a phase IV (postmarketing), observational, collaborative endeavor sponsored by Genentech, Inc, in which contributing hospitals...
among patients likely to receive thrombolytic therapy. The thrombolytic agent was rtPA in 72% (60430) of the thrombolytic recipients, higher than the 56% national average for rtPA during the same time frame (IMS America, Plymouth Meeting, Pa). Patients receiving thrombolytic therapy (any agent) were significantly younger than those not receiving thrombolytic therapy (Table 2). The proportion of patients treated with thrombolytic therapy diminished progressively after age 50 years (Fig 4). Among patients <60 years old, 50% received thrombolytic therapy, whereas among patients ≥60 years old, thrombolytic therapy was used in only 28% (P<.001).

Patients receiving thrombolytic therapy weighed more, were more likely to be men, and were more likely to have been transferred to the registry hospital from another hospital (Table 2). Patients receiving thrombolytic therapy were more likely to have ECG evidence localizing the infarction to the anterior, inferior, lateral, or posterior wall and less likely to have a nondiagnostic ECG or evidence of non-Q-wave infarction than those not treated with thrombolytic therapy.

The median time interval from chest pain onset to arrival at the initial hospital was 95 minutes for patients treated with thrombolytic therapy, 180 minutes for those not treated with thrombolytics (P<.001), and 130

Among maladies, administered bolus, administered locally to assess individual hospital practice patterns and outcome to facilitate the continuous quality improvement process, and (3) can be used by the sponsor to monitor the frequency of specific adverse events with the use of their product, recombinant tissue-type plasminogen activator (rtPA) (Activase).

Data Collection Process

A registry coordinator at each participating hospital records data from each patient onto a simple one-page data form (see Fig 1), which is then sent to a central data collection center (ClinTrials Research, Inc, Lexington, Ky) for processing and analysis. Participating hospitals receive quarterly summaries of the cumulative study-wide registry data together with confidential, individualized, parallel tabulations of their local data. (A complete listing of contributing registry hospitals is available from ClinTrials Research, Inc.)

Participation in the registry is entirely voluntary, and hospitals are encouraged to enter consecutive infarcts irrespective of treatment strategy and outcome. During the enrollment period of the recently concluded Global Utilization of Streptokinase and rtPA for Occluded Coronary Arteries (GUSTO) trial7 (December 1990 to February 1993), hospitals participating in both the registry and the GUSTO trial were asked not to enter GUSTO participants in the registry so that the registry would better reflect actual clinical practice rather than treatment mandated by a clinical trial protocol. Approval of the registry data collection process at participating hospitals may include review by institutional committees on human research as dictated by local policies. Demographic data characterizing registry hospitals in comparison to all other US hospitals are obtained from SMG Marketing Group, Inc (Chicago, Ill).

Quality Control

Before initiation of the registry, the clinical coordinator at each site received a training manual that explained how to complete the case report form, defined each variable, and provided examples of correct responses. Double-key entry is used by the data collection center to add each case report form to the database. Audits are performed electronically to detect out-of-range variables, inconsistencies, errors, and omissions. Queries are then telephoned to local registry coordinators for resolution. Periodic regional meetings of registry coordinators and investigators are held to discuss data entry and registry findings.

Definitions

To be included in the registry, patients must have acute myocardial infarction documented according to local hospital criteria, usually by cardiac enzymes (total or MB creatine kinase), ECG, or cardiac angiography. Time of “chest pain onset” is 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” is defined as the time of patient arrival at the registry hospital or at a referral hospital if that was earlier. “Transferred patients” are those who are transferred to a registry hospital from a referral hospital. Patient initials and birth dates are recorded to prevent “double counting” of patients who might have been transferred from one registry hospital to another. A “nondiagnostic ECG MI” includes nonspecific ST or T-wave abnormalities or no ECG evidence of myocardial infarction. The “standard dose” of rtPA (Activase, alteplase) is 60 mg administered in the first hour, of which 6 to 10 mg is given as a bolus, 20 mg over the second hour, and 20 mg over the third hour. Among the reasons for not using rtPA, “physician preference” is coded if none of the other reasons applied. Concomitant medications, invasive procedures, and adverse events are recorded if they are implemented or occur at any time during the hospitalization. “Peri-MI arrhythmias” include any arrhythmia occurring within 24 hours of the index infarction. “Drug-induced hypotension” is hypotension requiring fluid replacement therapy.

Statistical Methods

Group differences were assessed by the χ2 test for categorical variables, by the two-sample t test for age and weight, and by the Wilcoxon test for time intervals. All reported P values were two-sided and were not adjusted for multiple testing. All statistical analyses were performed with SAS 6.06 statistical package programs (SAS Institute). This report is based on data processed by the central data collection center as of December 31, 1993.

Results

Acquisition of Patients and Hospitals

From September 1990 to December 1993, 240 989 patients with myocardial infarction were enrolled from 1073 contributing registry hospitals throughout the United States (Figs 2 and 3). Enrollment continues and is currently proceeding at a rate of approximately 10 000 patients per month.

Registry Hospital Characteristics

The current 1073 registry hospitals compose 14.4% of all 7458 US hospitals (Table 1). Registry hospitals are significantly larger, more likely to be certified by the Joint Commission on Accreditation of Health Care Organizations, more likely to be affiliated with a medical school and to have a residency teaching program, and more likely to have an active emergency department, coronary care unit, cardiac catheterization laboratory, and cardiac surgery program than nonregistry hospitals.

Patient Characteristics

Of the 240 989 patients enrolled, 84 477 (35.1%) received thrombolytic therapy. The thrombolytic agent was rtPA in 72% (60430) of the thrombolytic recipients, higher than the 56% national average for rtPA during the same time frame (IMS America, Plymouth Meeting, Pa). Patients receiving thrombolytic therapy (any agent) were significantly younger than those not receiving thrombolytic therapy (Table 2). The proportion of patients treated with thrombolytic therapy diminished progressively after age 50 years (Fig 4). Among patients <60 years old, 50% received thrombolytic therapy, whereas among patients ≥60 years old, thrombolytic therapy was used in only 28% (P<.001).

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The median time interval from chest pain onset to arrival at the initial hospital was 95 minutes for patients treated with thrombolytic therapy, 180 minutes for those not treated with thrombolytics (P<.001), and 130
For A, B, C or D, please complete AER form for all thrombolytic agents.

<table>
<thead>
<tr>
<th>Discharge Status</th>
<th></th>
<th></th>
<th>Date of Discharge or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deceased</td>
<td>Alive</td>
<td>M</td>
</tr>
</tbody>
</table>

Fig 1. Case report form for National Registry of Myocardial Infarction (primary data collection form). If adverse events A, B, C, or D are coded, a second form (Adverse Event Record, AER) is used to record date of onset, severity, action taken, and outcome.

minutes for all registry patients. The proportion of patients receiving thrombolytic therapy became progressively smaller as the time from onset of chest pain to presentation lengthened (Fig 5).

rTPA-Treated Patients

Detailed information was collected on dosing patterns, time and site of administration, and reasons for not administering rTPA, the most commonly used thrombolytic agent in the registry (Table 3). Of the 60 430 rTPA recipients, 48.7% were given the standard regimen of 100 mg over 3 hours, and 40.2% were treated with an accelerated dosing regimen (generally 100 mg over 90 minutes). The proportion receiving the accelerated rTPA dosing regimen increased each month in an almost linear fashion, from 8% in October 1990 to 65% in December 1993 (Fig 6). Weight-adjusted rTPA dosing was used less frequently (Table 3).
The median time from onset of chest pain to hospital presentation for rtPA recipients was 95 minutes (1.6 hours). An additional 57 minutes (0.95 hours) (median) elapsed from hospital presentation to rtPA administration (“door-to-drug time”). Trend analyses from 1990 to 1993 showed lower median door-to-drug times in 1993 than in preceding years (Fig 7). The site of rtPA initiation was most commonly (69.4%) the emergency department, but 23.2% of rtPA initiation took place in the coronary care unit. Among transferred patients receiving rtPA, the drug was usually (83.8%) begun before transport by the referring hospital. Major reasons cited for not administering rtPA were age >75 years, >6 hours since chest pain onset, use of other thrombolytic agent, a perceived contraindication to thrombolysis, and “physician preference.” Primary angioplasty was rarely used (3.1%).

Concomitant Medications

Other frequently used pharmacological therapies recorded in the registry were oral aspirin, intravenous heparin, intravenous nitroglycerin, oral β-blockers, and oral calcium channel blockers (Table 4). Of these, aspirin, intravenous heparin, and intravenous nitroglycerin were more commonly used in the thrombolytic group, and the other pharmacological agents were more commonly used in the nonthrombolytic group. Intravenous heparin was used in >90% of all patients receiving thrombolytic therapy, whether it was rtPA or another thrombolytic agent. Trend analysis showed small but progressive increases in the use of aspirin and β-blockers and a fall in the use of calcium channel blockers during 1990 through 1993 (Fig 8).

Invasive Procedures

Coronary arteriography was performed in 70.7% of thrombolytic recipients and in 48.3% of the nonthrombolytic group (Table 4). Coronary angioplasty and bypass surgery were also used liberally, especially in the thrombolytic group.

Adverse Events In-Hospital

Although the thrombolytic recipients had more frequent allergic reactions, drug-induced hypotension, peri-infarction arrhythmias, reinfarction, bleeding, and stroke, their mortality (unadjusted for baseline covariates) was less than half that of those not receiving thrombolytic therapy (5.9% versus 13.1%, P<.001) (Table 5). Among the thrombolytic recipients, hospital mortality was significantly higher for those presenting to the hospital later after chest pain onset than those presenting earlier (Fig 9). The primary causes of death were cardiac in the thrombolytic and nonthrombolytic groups, and median durations of hospitalization were similar (Table 5).

Discussion

The National Registry of Myocardial Infarction is the largest voluntary database yet assembled of myocardial infarction patients in the thrombolytic era, and it reveals important insight into the current management of this common and potentially fatal illness. The registry documents the relatively low frequency of use of thrombolytic therapy in the United States, the long delay to presentation and treatment, a growing trend in the use of an accelerated rtPA dosing regimen, a lower than expected use of other proven pharmacological therapy, and a very high use of invasive procedures.

Frequency of Use of Thrombolytic Therapy

Thrombolytic therapy was used in 35% of registry patients, greater than the previously reported 20% use for myocardial infarction in the United States but substantially lower than the estimated 51% to 62% of patients with myocardial infarction potentially eligible for thrombolysis and the ≥70% of patients actually treated with thrombolytics as part of “usual care” in the recent third Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI-3) and fourth International Study of Infarct Survival (ISIS-4) trials. The fact that registry hospitals were larger and more likely to have coronary care units and invasive capabilities may explain the more aggressive use of thrombolytic therapy in registry hospitals compared with prior estimates for US hospitals.

Nevertheless, even among registry hospitals, there was a tendency to target thrombolytic therapy toward relatively young patients presenting within the first few hours after infarction (Figs 4 and 5). Meta-analyses of recent randomized trials have shown that the absolute mortality reduction with thrombolytic therapy is greater in elderly
than in younger patients, and it is therefore now recommended that thrombolytic therapy not be withheld on the basis of age alone. When deciding whether to administer thrombolytic therapy to patients presenting relatively late after symptom onset, some practitioners may reason that the benefit of thrombolytic therapy diminishes rapidly over time, but its risk remains constant, thus favoring selective treatment of the earlier presenting patients. Although significant mortality reduction with the institution of thrombolytic therapy (rtPA) up to 12 hours after infarction has only recently been documented,16,17 it has long been appreciated that the benefit of lytic therapy extends to at least 6 hours after onset of symptoms.1,18,19 However, only about one third of patients presenting within 4 to 6 hours of symptoms are treated (Fig 5). Thus, with regard to age and elapsed time from onset of symptoms, it would seem that practitioners are not yet conforming to recommendations of recent trials when selecting patients for thrombolytic therapy.

Registry patients with non–Q-wave infarction or non-diagnostic ECGs rarely received thrombolytic therapy, whereas those with well-defined infarct location usually received thrombolytic therapy (Table 2). Such practice is consistent with a recent meta-analysis demonstrating no survival advantage at 35 days among patients without ST elevation or bundle branch block treated with thrombolytic therapy.17 Withholding thrombolytic therapy for patients with non–Q-wave infarction or lack of ST elevation is also consistent with recommendations of the Thrombolysis in Myocardial Infarction (TIMI) phase IIIB trial, which showed no reduction in 6-week mortality for patients with prolonged chest pain and no ST elevation randomized to rtPA plus intravenous heparin versus intravenous heparin alone.20

**Time Interval to Presentation and Treatment**

The median time interval from symptom onset until presentation at the registry hospitals was 2.2 hours (130 minutes), consistent with medians ranging from 2 hours to 6.4 hours in previous observational studies.21,22 Public education campaigns to reduce patient delay in the United States have had minimal or no success.23,24 The elapsed time from hospital presentation to initiation of rTPA in the registry (mean, 99 minutes; median, 57 minutes) was shown to be reduced slightly in 1993 (Fig 7) but still exceeded the hospital delay times for initiating thrombolytic therapy in the TIMI phase II trial (mean, 81 minutes),25 the Pre-hospital Study Group (mean, 84 minutes),26 and that reported for hospitals with "streamlined" thrombolytic delivery protocols (mean, 30 minutes).27 Of possible relevance is the fact that the coronary care unit rather than the emergency department was the site of administration of the lytic agent in 23% of registry rTPA recipients, a factor previously shown to increase delay in delivery of thrombolytic therapy.28

Because the benefits of reperfusion therapy diminish rapidly with elapsed time before initiation of therapy27,28 (Fig 9), the National Heart, Lung, and Blood Institute has recently identified community interventions to reduce patient delay as a primary research target. Methods to reduce hospital delay ("door-to-drug time") by utilizing prehospital 12-lead ECG recording and streamlined emergency department protocols are also currently under intensive investigation.29,30 Optimally, thrombolytic therapy should be started within 30 minutes of hospital presentation in patients with typical features of acute myocardial infarction, according to recently published guidelines from the American Heart Association31 and the 1992 National Conference on Cardiopulmonary Resuscitation and Emergency Cardiac Care.32

**Use of Accelerated rTPA Dosing**

The registry documents the extraordinary growth in the use of accelerated or "front-loaded" rTPA dosing
TABLE 2. Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thrombolytic Therapy*</th>
<th>No Thrombolytic Therapy</th>
<th>N</th>
<th>Value</th>
<th>N</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>84 477</td>
<td>156 512</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean, y (median, 25th, 75th percentiles)</td>
<td>83 474 (60.6, 61.1, 57.7, 69.6)</td>
<td>154 836 (66.3, 69.8, 59.7, 78.2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, mean, kg (median, 25, 75th percentiles)</td>
<td>79 452 (81.7, 80.3, 70.3, 90.7)</td>
<td>143 968 (77.3, 76.2, 64.9, 87.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, % men</td>
<td>83 688 (71.9)</td>
<td>155 053 (59.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Male patients

- Age, mean, y: 59 513 (58.9)
- Weight, mean, kg: 56 689 (85.7)

Female patients

- Age, mean, y: 23 227 (64.9)
- Weight, mean, kg: 22 093 (71.4)

Transferred to registry hospital, %

By ambulance: 65.0
By helicopter: 23.9
By other means: 11.1

Time interval, min from chest pain onset to arrival at initial hospital median (25th, 75th percentiles)

- All patients: 73 094 (59, 180) 106 252 (80, 510)
- Transferred patients: 18 448 (50, 175) 17 992 (70, 435)
- Nontransferred patients: 54 646 (60, 180) 88 260 (81, 526)

Infarct location

- Anterior (V1-V4): 37.8 27.5
- Inferior (II, III, aVF): 54.8 30.8
- Lateral (I, aVL): 15.9 13.1
- Posterior (R-V1, Q-V6): 5.8 4.2
- Non-Q wave (subendocardial): 2.4 26.6
- Nondiagnostic ECG: 0.8 12.6
- Other: 5.3 8.3

*All comparisons between thrombolytic therapy and no thrombolytic therapy groups were significantly different at P<.001.

Thrombolytic therapy includes any thrombolytic agent.

†Multiple responses possible. Infarct location was coded as neither subendocardial, nondiagnostic ECG, nor other in 77 523 of the thrombolytic therapy group and 80 367 of the no thrombolytic therapy group.

over the past 3 years (Fig 6). Accelerated dosing, introduced by Neuhaus et al in 1989, was subsequently shown to compare favorably with the “standard” 3-hour infusion of rTPA and bolus anistreplase infusion, but the safety and efficacy of accelerated rTPA was not fully validated until the completion of the recent GUSTO trial. Nevertheless, the implementation of accelerated rTPA dosing among registry hospitals showed striking growth even before release of the GUSTO trial results, probably because of the ease of use of the accelerated regimen and its documented ability to achieve infarct-related artery patency in more than 80% of patients within 90 minutes of initiation.

Pharmacological Therapy Other Than Thrombolytics

Registry data provide valuable insight into the use of pharmacological therapy other than thrombolytics for acute myocardial infarction. Aspirin, given to 84% of registry patients receiving thrombolytic therapy and to 63% of the remainder, has been demonstrated to reduce rates of reinfarction and death after myocardial infarction whether or not thrombolytic therapy is used. Although aspirin was used commonly in registry patients, it is surprising that its use was not even higher, given its proven effectiveness, low spectrum of side effects, and low cost.

Intravenous heparin, used in 97% of registry patients receiving thrombolytics and in more than half the remainder, has never been unequivocally demonstrated to improve longevity in myocardial infarction but has been shown to preserve infarct vessel patency after rTPA therapy. The use of protocol-directed intravenous heparin in combination with rTPA in the recent GUSTO trial may explain, in part, the finding of a lower 30-day mortality with rTPA than with streptokinase-heparin regimens in that trial, whereas prior
thrombolysis megatrials that did not use protocol-directed intravenous heparin showed similar mortality between rTPA and streptokinase therapy. Intravenous heparin may not be required to maintain infarct-related vessel patency in patients treated with streptokinase or anistreplase, agents that, unlike rTPA, cause substantial fibrinogen depletion and a measure of “autoanticoagulation.” The registry data illustrate that US practitioners, even before the results of the above trials were known, were routinely administering intravenous heparin with rTPA and other thrombolytic agents.

Intravenous nitroglycerin, used in 76% of thrombolytic recipients and 50% of the remainder, was reported in late 1993 not to improve survival of acute myocardial infarction. However, the widespread use of intravenous nitrates in the registry is consistent with an earlier meta-analysis suggesting that intravenous nitroglycerin might reduce mortality as much as 35%. Calcium channel blockers have not been proven “cardioprotective” after myocardial infarction and in some studies appeared to be harmful, yet they were used in 30% of thrombolytic recipients in the registry and in 42% of all others.

Although clinical trials involving more than 26,000 patients have confirmed the efficacy of β-blockers in limiting mortality and preventing recurrent ischemia after myocardial infarction, intravenous and oral β-blockers were used in only 17% and 36%, respectively, of registry thrombolytic recipients and in 30% and 42%, respectively, of all others. The GUSTO investigators, on the other hand, used intravenous β-blockers in 46% and oral β-blockers in 71% of patients with acute myocardial infarction. The registry, therefore, reveals patterns of use of pharmacological therapy that, in the case of aspirin, β-blockers, and calcium channel blockers, seem inconsistent with the recommendations of recent clinical trials. However, analysis of trends from 1990 through 1993 suggests that usage of these agents may slowly be coming closer into line with trial recommendations (Fig 8), as previously reported.

### Invasive Procedures

The role of postinfarction coronary arteriography remains controversial. The availability of facilities for cardiac catheterization has been shown to correlate closely with the likelihood of their use after myocardial infarction. Because the primary incentive for coronary arteriography is to identify lesions suitable for revascularization by angioplasty or bypass surgery, several recent trials have randomized patients after infarction between an “invasive strategy” of routine coronary arteriography followed by revascularization, if appropriate, and a “conservative strategy” of “watchful waiting,” with arteriography and revascularization used only for patients with spontaneous or provocable ischemia. None of the trials showed an advantage of the invasive approach in improving ventricular function, reducing the incidence of reinfarction, or reducing mortality up to 3 years after infarction.

If the “conservative” approach to postinfarction arteriography is followed, what frequencies of coronary arteriography, angioplasty, and bypass surgery are to be expected during the initial hospitalization? In the largest of the randomized studies, the Should We Intervene Following Thrombolysis? (SWIFT) trial and the TIMI phase II trial, coronary arteriography was used in the conservative groups in 13% and 33%, angioplasty in 3% and 13%, and bypass surgery in 2% and 7%, respectively. In the National Registry of Myocardial Infarction, coronary arteriography was used in 71% of thrombolytic recipients, angioplasty in 30%, and bypass surgery in 13%. These frequencies are markedly higher than would have been expected had the conservative policy of “watchful waiting” been followed.

### Adverse Events

Patients treated with thrombolytic therapy in randomized trials are known to have higher rates of allergic reactions, bleeding, arrhythmias, and reinfarction, and these trends were confirmed in the registry (Table
### TABLE 3. Patients Treated With rTPA (Alteplase)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients treated with rTPA</td>
<td>60 430</td>
<td></td>
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<tr>
<td>Dosing regimen, %</td>
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<tr>
<td>Standard</td>
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<td>48.7</td>
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<tr>
<td>&lt;65 kg</td>
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<td>2.0</td>
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<tr>
<td>≥65 kg</td>
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<td>6.9</td>
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<tr>
<td>Total dose, mg</td>
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<tr>
<td>Standard</td>
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<td>99.0</td>
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<tr>
<td>Weight-adjusted</td>
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</tr>
<tr>
<td>&lt;65 kg</td>
<td></td>
<td>79.6 (1.4 mg/kg)</td>
</tr>
<tr>
<td>≥65 kg</td>
<td></td>
<td>106.4 (1.2 mg/kg)</td>
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<tr>
<td>Bolus dose, mg</td>
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<tr>
<td>Standard</td>
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<td>Front-loaded</td>
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<tr>
<td>Weight-adjusted</td>
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<td>&lt;65 kg</td>
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<td>10.9</td>
</tr>
<tr>
<td>≥65 kg</td>
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<td>First hour dose, including bolus mg</td>
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<td>Standard</td>
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<td>Front-loaded</td>
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<td>75.4</td>
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<tr>
<td>Time interval, minutes, mean, median (25th, 75th percentiles)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset of chest pain to hospital presentation</td>
<td>52 323</td>
<td>171, 95 (58, 180)</td>
</tr>
<tr>
<td>Onset of chest pain to initiation of rTPA</td>
<td>51 092</td>
<td>251, 165 (108, 268)</td>
</tr>
<tr>
<td>Hospital presentation to initiation of rTPA</td>
<td>52 186</td>
<td>99, 57 (35, 96)</td>
</tr>
<tr>
<td>Site of rTPA initiation, %</td>
<td></td>
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</tr>
<tr>
<td>Emergency department</td>
<td></td>
<td>69.4</td>
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<tr>
<td>Coronary care unit</td>
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<td>23.2</td>
</tr>
<tr>
<td>Other/unknown</td>
<td></td>
<td>7.4</td>
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<tr>
<td>Initiation of rTPA in transferred patients, %</td>
<td>15 455</td>
<td>83.8</td>
</tr>
<tr>
<td>By referring hospital</td>
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<td></td>
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<tr>
<td>During transport</td>
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<td>0.8</td>
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<td>By receiving hospital</td>
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</tr>
<tr>
<td>Reasons cited for not administering rTPA, %*</td>
<td>180 559</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 years</td>
<td></td>
<td>19.7</td>
</tr>
<tr>
<td>&gt;6 hours since chest pain onset</td>
<td></td>
<td>29.7</td>
</tr>
<tr>
<td>Other thrombolytic used</td>
<td></td>
<td>13.3</td>
</tr>
<tr>
<td>Primary angioplasty undertaken</td>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td>Patient refusal</td>
<td></td>
<td>1.1</td>
</tr>
<tr>
<td>Contraindication to thrombolysis</td>
<td></td>
<td>24.2</td>
</tr>
<tr>
<td>Physician preference</td>
<td></td>
<td>32.5</td>
</tr>
</tbody>
</table>

rTPA indicates recombinant tissue-type plasminogen activator.

*Multiple responses possible. "Physician preference" was entered if no other reasons applied.
5). Hospital mortality was substantially lower (5.9%) among patients treated with thrombolytics than those not treated (13.1%). Although thrombolytic therapy was probably life-saving in many instances, it is likely that selection of lower-risk patients for thrombolysis was the primary factor explaining the lower mortality rate.

**Limitations of the Registry**

Multiple limitations of the National Registry of Myocardial Infarction should be acknowledged. Although the registry is composed of hospitals throughout the United States, registry hospitals are not necessarily representative of all US hospitals, as shown in Table 1, but probably reflect practice in larger, more procedure-oriented centers. Registry hospitals may have been more prone to use thrombolytic therapy, and specifically rTPA, than nonregistry hospitals. The registry, although very large, is a simple observational database rather than a randomized trial, and thus it is more valuable for documenting practice patterns and temporal trends than comparing outcomes of patient subsets. Like many of the recent megatrials in thrombolysis, data obtained on each registry patient were rather limited, there was no independent validation of data forms, and there was the potential for nonconsecutive patient enrollment and “underreporting” of adverse events.

The limited baseline data collection in this simple registry renders interpretation of some of the findings less certain than others. Whereas observations on excessive delay to initiate thrombolytic therapy and overuse of calcium channel blockers seem indisputable, the relatively low usage of aspirin and β-blockers might be secondary to contraindications to these agents not

![Graph showing interval use of accelerated recombinant tissue-type plasminogen activator (rTPA) dosing.](image1)

![Graph showing temporal trends for time to presentation and initiation of recombinant tissue-type plasminogen activator (rTPA).](image2)

![Graph showing temporal trends for usage of pharmacotherapy other than thrombolytics.](image3)
**TABLE 5. Adverse Events In-Hospital**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Thrombolytic Therapy*</th>
<th>No Thrombolytic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Value</td>
</tr>
<tr>
<td>N</td>
<td>84 477</td>
<td></td>
</tr>
<tr>
<td>Allergic or anaphylactic reaction, %</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Drug-induced hypotension, %</td>
<td>6.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Peri-infarction arrhythmias, %</td>
<td>26.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Reinfarction (ECG and CK positive), %</td>
<td>3.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Minor surface bleeding, %</td>
<td>9.1</td>
<td>0.9</td>
</tr>
<tr>
<td>Major bleeding (intracranial, life-threatening, or required transfusion), %</td>
<td>2.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Death, %</td>
<td>5.9</td>
<td>13.1</td>
</tr>
<tr>
<td>Total stroke, %†</td>
<td>0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>0.6</td>
<td>0.04</td>
</tr>
<tr>
<td>Cause(s) of death, %‡</td>
<td>Cardiogenic shock 2.3</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias 0.9</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Sudden cardiac arrest 1.5</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Reinfarction 0.4</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Rupture/EMD 0.7</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Other cardiac 0.5</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Noncardiac 0.8</td>
<td>2.1</td>
</tr>
<tr>
<td>Duration of hospitalization, days, median (25th, 75th percentiles)</td>
<td>82 290</td>
<td>7.5 (5.2, 10.4)</td>
</tr>
</tbody>
</table>

CK indicates creatine kinase; EMD, electromechanical dissociation.

*All comparisons between thrombolytic therapy and no thrombolytic therapy groups were significantly different at the P<.001 level. "Thrombolytic therapy" includes any thrombolytic agent.

†Registry hospitals were asked to complete the Adverse Event Record only for patients receiving thrombolytic agents; therefore, total stroke and intracranial bleeding frequencies for the no thrombolytic therapy group may be underepresentative. Intracranial bleeds included any of the following, diagnosed according to the registry hospital's local criteria: cerebral hemorrhage, intracranial hemorrhage, subarachnoid hemorrhage, and subdural hematoma.

‡Multiple responses possible.

% Mortality (Thrombolytic Recipients)

![Bar graph showing hospital mortality as a function of duration of chest pain before hospital presentation among thrombolytic recipients](http://circ.ahajournals.org/)

In all graphs, the cumulative mortality distributions rise only slightly, however, because most patients are clustered in the 0- to 4-hour time frame. The graphs format and numbers of patients in each time stratum are the same as in Fig 5.

recorded on the simple data form, as might be the relatively low use of thrombolyis in the elderly and late presenters. Despite these limitations, the registry data compare favorably with practice trends and outcomes previously reported in smaller surveys and clinical trials.3,4

**Clinical Implications and Future Directions**

The National Registry of Myocardial Infarction suggests that, among the participating institutions, composing about 14% of all US hospitals, the results of recent clinical trials are being implemented in clinical practice in an inconsistent fashion. Although thrombolytic therapy is used in a substantial proportion of infarct patients, it is often withheld from elderly patients, in whom it may save the most lives, and from patients who do not reach the hospital immediately after symptom onset. For patients treated with thrombolytic therapy, the “door-to-drug time” is extraordinarily prolonged. Although adjunctive treatment with intravenous heparin and intravenous nitroglycerin is usually used, aspirin and β-blockers appear to be underused and calcium channel blockers appear to be overused. Furthermore, it is evident that routine coronary arteriography after
infarction followed by revascularization, if feasible, is the policy at many institutions, despite the findings of recent clinical trials showing that such invasive management offers no better short- or long-term outcome than a more conservative approach.

These observations should provide incentive for alterations in current practice patterns: expansion of the use of thrombolytic therapy, more rapid triage and treatment, more appropriate conjunctive pharmacotherapy, and a more rational utilization of invasive resources. As these or other changes begin to occur, the National Registry of Myocardial Infarction will be a valuable tool to detect and track such modifications and their outcome.

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Circulation. 1994;90:2103-2114
doi: 10.1161/01.CIR.90.4.2103

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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