Predictors of Early Morbidity and Mortality After Thrombolytic Therapy of Acute Myocardial Infarction

Analyses of Patient Subgroups in the Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase II

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Background. Thrombolysis has altered treatment of acute myocardial infarction (AMI). Therefore, reevaluation of predictors of outcome and treatment strategies is appropriate.

Methods and Results. Clinical variables collected prospectively for the 3,339 patients of the Thrombolysis in Myocardial Infarction II study were analyzed retrospectively to identify predictors of clinical events at 42 days and earlier and to identify subgroups in which an invasive or conservative strategy might be superior. Pulmonary edema/ cardiogenic shock presented as the strongest independent correlate with death (relative risk, 6.0). In two subgroups, mortality differed between the invasive and conservative strategies: 1) Patients with versus without prior AMI had a higher mortality in the conservative strategy (11.5% versus 3.5%, p<0.001); in the invasive strategy, the mortality rates were similar (6.0% and 5.1%). 2) Patients with diabetes mellitus and no prior AMI had a higher mortality in the invasive than in the conservative strategy (14.8% versus 4.2%, p<0.001). Reinfarction was not independently correlated with baseline characteristics except with history of angina (relative risk, 1.9). Mortality was lower in current smokers and ex-smokers versus never-smokers (3.6% and 4.8% versus 8.0%, p<0.001). Current smokers had a lower risk profile (p<0.001), including age, pulmonary edema/ cardiogenic shock, history of hypertension, and diabetes. The rate of reinfarction was lower in current smokers versus ex-smokers and never-smokers (4.6% versus 8.3% and 8.8%, p<0.001). “Not current smoker” was an independent correlate with reinfarction (relative risk, 1.9). The coronary anatomy did not differ among the current smokers, ex-smokers, and never-smokers.

Conclusions. The strong independent correlation of pulmonary edema/ cardiogenic shock with death suggests that thrombolysis is not sufficient to improve survival in these patients. The higher mortality in patients with versus without prior AMI in the conservative strategy suggests that early catheterization and revascularization of these patients might be beneficial. Conversely, the higher mortality in diabetics without prior AMI in the invasive than in the conservative strategy suggests that early aggressive management might not be suitable in this subgroup except for clinical indications. Reinfarction was not predictable by clinical variables except by history of angina. The finding that “not current smoker” was an independent correlate with reinfarction was unexpected. (Circulation 1992;85:1254–1264)

Key Words • clinical trials • subgroup analyses • early mortality and morbidity predictors

Coronary thrombolysis has altered profoundly the treatment of acute myocardial infarction (AMI) and reduced mortality.1–5 The patient population with AMI, however, is complex, and recanalization strategies may differ in various groups. The results of three independent studies have indicated that immediate percutaneous transluminal coronary angioplasty (PTCA) after thrombolysis was not beneficial compared with thrombolysis alone because of an increased rate of complications without apparent improvement of left ventricular function.6–8 On the other hand, some investigators have emphasized that an immediate invasive approach after thrombolysis will be preferable9–11 because of frequent reocclusion of the infarct artery and because of lack of reperfusion in 15–20% of patients. The pretreatment and posttreatment clinical variables that predict outcome after thrombolytic therapy remain unclear.12 Recently, Hillis et al13 identified advanced age, female sex, previous myocardial infarction, and diabetes mellitus as risk
factors for early death in patients with AMI treated with thrombolytic therapy.

The Thrombolysis in Myocardial Infarction (TIMI) phase II trial was carried out in 3,339 patients with AMI who were treated with recombinant tissue-type plasminogen activator (rt-PA), heparin, and aspirin. The trial compared outcome in an invasive and a conservative strategy. In the present retrospective analysis, we examined clinical variables present at the time of admission and during thrombolytic therapy in an effort to identify predictors of early mortality and morbidity and to identify subgroups of patients in which one or the other of two strategies might be superior.

**Methods**

**Protocol**

The detailed methodology of the TIMI II trial has previously been published. Briefly, patients younger than 76 years of age with more than 30 minutes of chest pain characteristic of myocardial ischemia, with diagnostic electrocardiographic ST segment elevations, presentation within 4 hours of pain, and no contraindications for thrombolytic therapy received intravenous infusion of rt-PA (Activase) and were randomly assigned to either the invasive or conservative strategy. Those assigned to the invasive strategy underwent routine catheterization including left ventricular and coronary angiography within 18–48 hours of randomization and percutaneous transluminal coronary angioplasty (PTCA) of the infarct artery when the anatomy was appropriate. Coronary artery bypass graft (CABG) was recommended for patients assigned to the invasive strategy when coronary anatomy was considered too complex or hazardous for PTCA. Patients assigned to the conservative strategy underwent these procedures only in response to either spontaneous or provoked myocardial ischemia. Patients eligible for enrollment in the trial of β-blocker therapy (TIMI II-B) were randomly assigned to either immediate or delayed administration of metoprolol.

The initial dose of 150 mg rt-PA in the first 520 patients was reduced to 100 mg in the remaining 2,819 patients because of an unacceptably high rate of intracranial hemorrhage. Heparin (bolus of 5,000 units followed by continuous infusion of 1,000 units/hr) was adjusted to maintain an activated partial thromboplastin time of 1.5 to two times the control value. Aspirin 80 mg/day orally was administered on day 1 in 488 patients and on day 2 or later in the remainder when not contraindicated; it was increased to 325 mg/day in all patients on day 6.

Patients were monitored for clinical events such as recurrent myocardial ischemia and recurrent myocardial infarction. The mortality and morbidity classification committee reviewed all reported events without knowledge of treatment assignments and classified the event as definite myocardial infarction, recurrent ischemia, or no event.

**Definitions Prespecified by Protocol**

*Not low-risk patient category.* This was defined by one or more of the following: history of AMI, ST segment elevation in anterior electrocardiographic leads, rales extending upward more than one third of the lung field, systolic blood pressure <100 mm Hg and sinus tachycardia with rate >100 beats per minute, atrial fibrillation/flutter, age ≥70 years, pulmonary edema, cardiogenic shock.

**Recurrent myocardial infarction.** Events occurring <18 hours after study entry were defined by ischemic chest pain for >20 minutes, either new or markedly worse than preexisting pain, and new plasma creatine kinase (CK) elevation and appearance of CK-MB isoenzymes, and not mandatory, new ST segment elevation or depression in at least two contiguous ECG leads. Events occurring ≥18 hours after study entry were defined by ischemic chest pain for >20 minutes and by one or more of the following: major new Q waves in at least two or more ECG leads, new left bundle branch block, new plasma CK elevation and appearance of CK-MB isoenzymes.

**History of AMI.** This was defined by one or more of the following: patient history, physician history, ECG, cardiac enzymes.

**Smoking status.** This was determined at hospital admission. Patients were categorized based on smoking history: current smoker (within 3 weeks before qualifying MI), ex-smoker, and never smoker.

**End Points**

The prespecified primary end point for comparing the invasive and conservative strategies was survival free of recurrent AMI at 42 days. Secondary end points included ejection fraction at rest and during exercise, both at hospital discharge and at 6 weeks after randomization.

**Statistical Considerations**

The results presented in this report are based on all data processed in the TIMI Coordinating Center as of September 1990. For discrete data variables, comparisons using the proportion of patients in different groups with a given attribute were tested with the χ² test. For continuous data variables, comparisons between groups were tested by using a two-tailed Student’s t test of mean values. Subgroups among which the treatment effects differed were identified by a stepwise partition procedure. Baseline variables were used to divide patients into dichotomous subgroups (e.g., male versus female patients, prior AMI versus no prior AMI). For each pair of subgroups defined by a baseline variable, the Breslow-Day test for homogeneity of the odds ratios was calculated to evaluate whether treatment effects were different between the subgroups. The baseline variable giving the highest value of this test statistic for interaction with treatment was used to partition the data set into two subgroups, and the evidence for treatment interactions with the remaining variables was then tested within each of the subgroups so defined. Partitioning of the data set on the basis of tests for interaction continued until no Breslow-Day test statistic was found corresponding to a nominal probability value of less than 0.01.

Baseline variables tested for evidence of interaction included age ≥65 years, sex, anterior AMI, pulmonary edema or shock, not low-risk characteristics, rt-PA infusion ≤2 hours after infarct onset, relief of chest pain during rt-PA, heart rate ≥80 beats per minute, systolic blood pressure ≤120 mm Hg, diastolic blood pressure ≤75 mm Hg, atrial fibrillation, hypotension (systolic
blood pressure <100 mm Hg) with sinus tachycardia (>=100 beats per minute), ST segment elevation >0.1 mV in four or more leads, abnormal Q waves in four or more leads, history of AMI, history of angina, history of diabetes, history of hypertension, history of congestive heart failure, and smoking status.

Cumulative event rates were estimated using the product-limit (Kaplan-Meier) method. Multivariate analyses were performed using a stepwise logistic model. The 20 variables listed above were all candidates for entry into the logistic regression model. A forward stepping algorithm was used with p<0.01 to identify the variables remaining as independent correlates of outcome.

A search for patient characteristics involved with treatment identified three subgroups of patients among which the comparison of invasive and conservative strategy for the outcome death at 42 days or earlier differed: patients with prior AMI, patients with no prior AMI and with diabetes, and patients with no prior AMI and no diabetes. These interactions with treatment were included in a logistic model with appropriate indicator variables and the variables identified by the stepwise logistic analysis. The reference category for relative risk estimation was patients assigned to the conservative strategy with no prior AMI and no diabetes. Bonferroni tests were used for multiple comparisons of the three smoking statuses. All analyses were performed using either STATISTICAL ANALYSIS SYSTEM (SAS) or BIOMEDICAL DATA PACKAGE (BMDP) programs.

Results

The baseline variables of the entire study population were characteristic of patients with AMI eligible for thrombolytic therapy (Table 1). The variables did not differ between patients assigned to the invasive and conservative strategies.

Death at 42 Days or Earlier

Admission clinical characteristics of patients who died within 42 days of study entry are presented for all patients in Table 2. They are the variables previously known to predict high risk of death after AMI in the absence of thrombolytic therapy. Pulmonary edema/cardiogenic shock were dominant risk factors, in particular in patients with early death. Among 63 patients who died within the initial 18 hours of the study (during which, according to protocol, patients in both assigned groups were treated similarly), 27% (17 of 63) had been in pulmonary edema or cardiogenic shock at admission, compared with only 8.8% (nine of 102, p=0.002) of patients who died between 18 hours and 42 days. Never-smokers had a higher risk of death within 42 days than ex-smokers and current smokers. Independent correlates with death by logistic regression analysis (Table 3) did not differ significantly between the invasive and conservative strategies.

In two subgroups defined by patients with history of AMI and patients with diabetes mellitus without prior AMI, the rate of death at 42 days or earlier differed between the two treatment strategies.

Table 1. Baseline Characteristics and Early Treatment Variables in Thrombolysis in Myocardial Infarction II Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients (n=3,339)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean years)</td>
<td>56.8</td>
</tr>
<tr>
<td>Race (white)</td>
<td>88.3</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>82.1</td>
</tr>
<tr>
<td>Not low risk</td>
<td>66.7</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>11.6</td>
</tr>
<tr>
<td>History of AMI</td>
<td>14.0</td>
</tr>
<tr>
<td>Anterior AMI</td>
<td>51.8</td>
</tr>
<tr>
<td>Ages ≥1/3 lung fields</td>
<td>4.0</td>
</tr>
<tr>
<td>Hypotension and sinus tachycardia</td>
<td>5.6</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>2.2</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1.0</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>1.5</td>
</tr>
<tr>
<td>Other risk factors</td>
<td></td>
</tr>
<tr>
<td>History of angina</td>
<td>50.0</td>
</tr>
<tr>
<td>History of CHF</td>
<td>2.8</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>38.3</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>13.1</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>49.1</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>27.7</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>23.2</td>
</tr>
<tr>
<td>Time from onset of pain to study entry (mean hours)</td>
<td>2.6</td>
</tr>
<tr>
<td>Events during rt-PA infusion</td>
<td></td>
</tr>
<tr>
<td>Dramatic relief of chest pain</td>
<td>32.2</td>
</tr>
<tr>
<td>Rapid normalization of ST segments</td>
<td>31.3</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; CHF, congestive heart failure; rt-PA, recombinant tissue-type plasminogen activator.
strategy revealed multivessel disease in 60.0 versus 28.4% \((p<0.001)\) and mean ejection fractions of 42 versus 48% \((p<0.001)\) of patients with and without prior AMI.

**Subgroup 2: Patients with diabetes mellitus without prior AMI.** The 42-day mortality of the entire population of diabetic patients \((n=439)\) compared with nondiabetic patients \((n=2,900)\) was 10.2% versus 4.1% \((p<0.001)\). Among the subgroup of diabetic patients without prior AMI, the 42-day mortality was different in patients randomized to the two strategies (Figure 1B). Mortality was higher in the invasive (25 of 169, 14.8%) than in the conservative strategy (seven of 168, 4.2%, \(p<0.001\)), whereas mortalities were essentially the same in the two treatment arms in patients without diabetes and no prior AMI (43 of 1,256, 3.4% and 49 of 1,280, 3.8%, respectively). Furthermore, in the invasive strategy, diabetics with no prior AMI had a significantly higher mortality (25 of 169, 14.8%) than nondiabetics with no prior AMI (49 of 1,280, 3.8%, \(p<0.001\)).

### Table 3. Multiple Logistic Regression Analyses

<table>
<thead>
<tr>
<th>Event</th>
<th>Variables</th>
<th>Relative risk</th>
<th>99% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 42 days or earlier</td>
<td>Pulmonary edema/shock</td>
<td>6.0</td>
<td>2.9–12.6</td>
</tr>
<tr>
<td>((n=3,339))</td>
<td>Age (\geq 65) years</td>
<td>2.7</td>
<td>1.7–4.3</td>
</tr>
<tr>
<td></td>
<td>Not low risk</td>
<td>2.5</td>
<td>1.3–4.9</td>
</tr>
<tr>
<td></td>
<td>History of diabetes</td>
<td>2.1</td>
<td>1.3–3.5</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>2.0</td>
<td>1.0–4.0*</td>
</tr>
<tr>
<td></td>
<td>Heart rate &gt;80 beats per minute</td>
<td>1.8</td>
<td>1.2–2.8</td>
</tr>
<tr>
<td></td>
<td>No relief of chest pain</td>
<td>1.7</td>
<td>1.0–2.8*</td>
</tr>
<tr>
<td></td>
<td>Female sex</td>
<td>1.6</td>
<td>1.0–2.6*</td>
</tr>
</tbody>
</table>

| Fatal/nonfatal recurrent AMI at 42 days or earlier | History of angina | 1.9 | 1.3–2.8 |
| \((n=3,339)\) | Not current smoker | 1.9 | 1.3–2.8 |

AMI, acute myocardial infarction.

*\(1.02–4.0; 1.004–2.8; 1.001–2.6\).
Among patients without prior AMI, diabetics compared with nondiabetics (univariate analysis) were older (59.1 versus 56.0 years, \( p < 0.001 \)), more frequently were women (27.3% versus 16.8%, \( p < 0.001 \)), more often had an anterior AMI (59.6% versus 50.8%, \( p = 0.002 \)), a history of hypertension (55.4% versus 34.0%, \( p < 0.001 \)), a history of congestive heart failure (5.3% versus 1.1%, \( p < 0.001 \)), and less frequently were current smokers (38.3% versus 52.0%, \( p < 0.001 \)). Coronary arteriography of patients assigned to the invasive strategy showed multivessel disease in 40.8% in the diabetic versus 26.8% (\( p < 0.001 \)) in the nondiabetic patients without prior AMI.

By logistic regression analysis, using the patients without diabetes and no prior AMI in the conservative strategy as reference category (Table 4), the relative risk for death of patients with prior AMI in the conservative strategy was 3.0 and of patients with diabetes and no prior AMI in the invasive strategy was 4.3.

**Fatal and Nonfatal Reinfarction at 42 Days or Earlier**

During the initial 18 hours after rt-PA infusion, when according to protocol patients in both assigned groups were treated similarly, reinfarction was observed in 20 of 3,339 patients (0.6%). Protocol catheterization and PTCA/CABG in the invasive strategy was associated with a sharp increase in the number of reinfarctions in this group (Figure 2). At 42 days, reinfarction rates were similar in the two treatment strategies.

Patients who experienced a reinfarction compared with those who did not (Table 5) were older, more frequently had a history of AMI and of angina, and more often were not current smokers. Independent correlates with reinfarction were history of angina and not current smoker (Table 3).

**Cigarette Smoking**

The baseline variables characterizing the nonsmokers and smokers of the TIMI II patients demonstrate that, aside from smoking itself, the never-smokers had the highest and the current smokers the lowest-risk profile, with the ex-smokers intermediate (Table 6). Comparing

### TABLE 4. Multiple Logistic Regression Analyses Interaction Terms

<table>
<thead>
<tr>
<th>Event</th>
<th>Variables</th>
<th>Relative risk</th>
<th>99% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 42 days or earlier</td>
<td>No prior AMI, no diabetes, conservative strategy*</td>
<td>1.0</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>No prior AMI, no diabetes, invasive strategy</td>
<td>1.2</td>
<td>0.7–2.1</td>
</tr>
<tr>
<td></td>
<td>No prior AMI, diabetes, conservative strategy</td>
<td>1.2</td>
<td>0.4–3.5</td>
</tr>
<tr>
<td></td>
<td>No prior AMI, diabetes, invasive strategy</td>
<td>4.3</td>
<td>2.0–9.0</td>
</tr>
<tr>
<td></td>
<td>Prior AMI, conservative strategy</td>
<td>3.0</td>
<td>1.4–6.0</td>
</tr>
<tr>
<td></td>
<td>Prior AMI, invasive strategy</td>
<td>1.5</td>
<td>0.6–3.4</td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction.

*Reference category for relative risk estimation.

**FIGURE 2. Graph shows cumulative rates of fatal and nonfatal reinfarction according to strategy assignment from study entry to 42 days. With initiation of invasive strategy, incidence of reinfarction increased sharply. At 42 days, reinfarction rates were similar in both assigned treatment strategies.**

### TABLE 5. Univariate Analysis, Baseline Characteristics, and Early Treatment Variables According to Fatal and Nonfatal Reinfarction at 42 Days or Earlier

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes ((n=221))</td>
</tr>
<tr>
<td>Male sex</td>
<td>76.5</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>59.3</td>
</tr>
<tr>
<td>Age ≥70 years</td>
<td>16.2</td>
</tr>
<tr>
<td>Not low risk</td>
<td>71.5</td>
</tr>
<tr>
<td>History of AMI</td>
<td>21.3</td>
</tr>
<tr>
<td>Anterior AMI</td>
<td>49.3</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>1.8</td>
</tr>
<tr>
<td>or cardiogenic</td>
<td></td>
</tr>
<tr>
<td>shock</td>
<td></td>
</tr>
<tr>
<td>History of</td>
<td>44.3</td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>History of diabetes</td>
<td>15.8</td>
</tr>
<tr>
<td>History of angina</td>
<td>65.2</td>
</tr>
<tr>
<td>History of CHF</td>
<td>3.6</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>34.4</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>34.8</td>
</tr>
<tr>
<td>Never-smoker</td>
<td>30.8</td>
</tr>
<tr>
<td>Dramatic relief</td>
<td>37.1</td>
</tr>
<tr>
<td>of chest pain</td>
<td></td>
</tr>
<tr>
<td>(rt-PA infusion)</td>
<td></td>
</tr>
</tbody>
</table>

AMI, acute myocardial infarction; CHF, congestive heart failure; rt-PA, recombinant tissue-type plasminogen activator.
the never-smokers to the current smokers, they more often were women, older, more frequently had an anterior AMI, pulmonary edema, or cardiogenic shock, and more often had a history of hypertension, diabetes, and congestive heart failure. Angiographic findings obtained in the patients assigned to the invasive strategy did not differ between the groups except in the distribution of the infarct artery. Never-smokers had the highest and current smokers the lowest incidence of the left descending coronary artery as infarct vessel.

The mortality at 42 days (Table 6) was highest in the never-smokers, and the rates of fatal and nonfatal reinfarction were highest in the never-smokers and ex-smokers. "Not current smoker" was an independent correlate with fatal and nonfatal reinfarction (Table 3).

**Discussion**

Predictors of outcome after AMI have been described over several decades. Early treatment with a thrombolytic drug has altered the pathophysiology of infarct evolution and decreased mortality but increased the incidence of recurrent ischemia. Because of its favorable impact on survival, thrombolytic therapy is used on an increasing number of patients, necessitating early and quick risk stratification. Therefore, reevaluation of conventional predictors of outcome and identification of new predictors is appropriate. In a retrospective analysis, clinical characteristics on admission and early responses to thrombolytic therapy of 3,339 patients of the TIMI II study were used to examine subgroups for predictors of mortality and morbidity and for guidelines of subsequent treatment.

**Death**

As observed in the prethrombolytic era, pulmonary edema or cardiogenic shock was the strongest independent correlate with death in the TIMI II study. There was no difference in the incidence of pump failure related to death between patients assigned to the invasive or conservative strategy. Most of these deaths
occurred early during the infarct period when according to protocol, treatment in the two assigned strategies was the same. The inability of thrombolytic therapy alone to improve survival of patients with cardiac pump failure has been shown in previous studies. In contrast, early establishment of recanalization of the infarct artery in cardiogenic shock by PTCA or a combination of thrombolysis and PTCA was associated with survival rates of 55–70%.

Although there were no control groups (i.e., patients not receiving PTCA or a combination of thrombolysis and PTCA), such results have not been reported before in this patient population. Based on the results discussed above, it appears that early aggressive management should be considered in certain patients with cardiogenic shock to improve survival.

Two subgroups were associated with different outcome in the two treatment strategies: 1) patients with history of AMI and 2) patients with diabetes mellitus without history of AMI.

In the conservative strategy, patients with prior AMI had a significantly higher 6-week mortality than those without prior AMI, whereas in the invasive strategy, the mortalities were essentially the same in the two patient categories (Figure 1A). The benefit of invasive management is probably related to the high incidence of multivessel disease and impaired left ventricular function in this patient population. Angiographic data in the patients with prior AMI assigned to the invasive strategy revealed, not surprisingly, a higher prevalence of multivessel disease in patients with prior AMI (59.9%) compared with those without a prior event (28.4%). Furthermore, mean ejection fraction was lower in these patients (42.1%) compared with those with first infarction (48.3%). The preference for invasive management of this group is consistent with the results of three large trials demonstrating improved survival with surgical revascularization in patients with advanced chronic coronary artery disease despite these trials did not include either patients treated with thrombolytic drugs or patients who had very recently experienced a myocardial infarction. Although we are aware of the hazard of overinterpreting subgroup analyses, based on these observations, the invasive strategy of the TIMI II protocol might be advisable (e.g., early cardiac catheterization followed by early revascularization) in patients similar to those in this trial who have experienced a recurrent AMI and received thrombolytic therapy.

Conversely, patients with diabetes mellitus without prior AMI had a higher mortality in the invasive than in the conservative strategy (Figure 1B). Several factors might contribute to these results in diabetic patients. Numerous studies have identified diabetic cardiomyopathy as an independent risk factor for this patient group. Further, the more extensive coronary artery disease observed in diabetic compared with nondiabetic patients in the TIMI II study and by other investigators might have increased the risk of procedures. In a study on multivessel angioplasty, diabetes mellitus and the severity of the underlying coronary artery disease were the only independent predictors for poor procedural outcome and for major ischemic complications such as death, infarction, and emergency CABG. Thus, diabetics, especially those without prior AMI, appear to be not well suited for an invasive strategy after receiving thrombolytic therapy. Based on the observations in the TIMI II trial, and again, recognizing the hazards of subgroup analyses, it may be prudent to avoid an early invasive protocol in patients with diabetes mellitus who have not suffered a prior AMI and who do not display the indications used for catheterization in the conservative arm of TIMI II (e.g., recurrent ischemia at rest or a positive predischARGE exercise test).

Reinfarction

The rate of fatal and nonfatal reinfarction during the 6-week study period was similar in patients assigned to the invasive (6.7%) or conservative (6.5%) strategy and was comparable with the rates reported in other recent trials of thrombolytic therapy. The high incidence of recurrent AMI and ischemia during the early period after thrombolytic therapy reemphasizes the need for early identification of patients at risk of this complication. Clinical characteristics at admission and early responses to treatment were not helpful for risk stratification in the TIMI II study, as has been observed by other investigators. A history of angina preceding the TIMI infarct and not currently smoking were the only independent correlates with recurrent AMI. Angiographic data, obtained in patients in the invasive strategy, could not be used for risk stratification because two thirds of these patients underwent protocol PTCA or CABG. It might be noted, however, that 18–48 hours after thrombolytic therapy, 85% of the infarct arteries had TIMI perfusion grade 2 or 3 both in patients with and without subsequent reinfarction. Similar results were reported in the Trial of Acute Myocardial Infarction studies. Angiographic variables of 192 patients including TIMI perfusion grade 2 or 3 of the infarct artery immediately after thrombolysis without subsequent interventions did not predict recurrent ischemic events.

Cigarette Smoking

The finding in the TIMI II study that smokers fared better than nonsmokers was unexpected. Current smokers and ex-smokers had a lower mortality than never-smokers, and current smokers had a lower incidence of reinfarction than ex-smokers and never-smokers. These data, however, must be interpreted with caution. They are in contrast to the unequivocal evidence from numerous studies that smoking represents a significant risk factor for ischemic heart disease. The apparent paradoxical finding in the current smokers of the TIMI II study is probably related to the lower-risk profile of this patient group (Table 6) and thus to an a priori better prognosis. The fact that current smoker is not an independent correlate with death after adjustment for other confounding variables supports this suggestion. A lower incidence of cardiac risk factors in smokers with AMI has been observed previously. 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the TIMI II study might have tolerated the AMI better than nonsmokers.

More complicated is the finding that not current smoker remained an independent correlate with reinfarction, even after accounting for many (but perhaps not all) of the known risk factors in the logistic regression analysis. These data are difficult to interpret. They are in contrast to those of Kelly et al., who did not find a difference in the rate of reinfarction between nonsmokers and smokers 1 month after AMI; the number of events, however, was small. Results of other investigators about smoking status and reinfarction are related to follow-up data. In the TIMI II study, however, smoking status was evaluated only at hospital admission, and no subsequent information is available. Sudden cessation of smoking at the time of the TIMI infarct might have decreased the risk for reinfarction, as was observed in other studies. Rivers et al. reported an increased incidence of reinfarction after thrombolytic therapy in patients who continued to smoke after the acute event.

Although the apparently better outcome of smokers compared with nonsmokers in the TIMI II study is of interest and should receive attention prospectively in future studies, the hazards of subgroup analyses should be emphasized. It is possible that current smoker might have served as a surrogate for a lower overall symptomatology and risk. However, the coronary anatomy, which was not different between current and not-current smokers, did not seem to account for the results.

**Study Limitations**

The TIMI II study reports evidence that the effect of invasive versus conservative strategy on mortality may vary among patient subgroups defined by prior AMI, diabetes mellitus without prior AMI, and the absence of both prior AMI and diabetes mellitus. These findings in the TIMI II study must be regarded as an exploratory result requiring evaluation for biological plausibility and confirmation from other clinical trials. The subgroups were identified in a stepwise procedure involving repeated tests for interactions between treatment and 20 baseline variables. Although a nominal probability value of less than 0.01 was required at each step to state that any evidence for interaction existed, the Bonferroni inequality shows that if 20 tests were performed at the first step, the probability may be as high as 0.18 that at least one probability value of less than 0.01 will be observed when no differences in fact exist. In a recent editorial, Yusuf et al. warned that random variation is to be expected in the magnitude of treatment differences among subgroups in a clinical trial, and that the treatment differences in the most extreme subgroups observed in a prior trial will almost always be closer to the overall result on replication.

Patients of the TIMI II study received varied pharmacological regimens with respect to rt-PA, aspirin, and β-blockers, which might have affected the outcome in the various subgroups. As a result of randomization, reasonable balance was obtained for the invasive and conservative strategies. The use of these agents was also comparable in subgroups of current and not-current smokers as well as among the smallest subgroups of diabetic patients without prior AMI assigned to invasive or conservative strategy. Thus, it is reasonable to assume that these different regimens did not significantly influence results.

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**Appendix**

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Steering committee. Members of the steering committee are the study chairman and principal investigators from TIMI clinical centers, Core Laboratories, Coordinating Center, and NHLBI Program Office.

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Predictors of early morbidity and mortality after thrombolytic therapy of acute myocardial infarction. Analyses of patient subgroups in the Thrombolysis in Myocardial Infarction (TIMI) trial, phase II.

H S Mueller, L S Cohen, E Braunwald, S Forman, F Feit, A Ross, M Schweiger, H Cabin, R Davison and D Miller

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