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**CLINICAL RESEARCH** **Clinical Trials**

# Early and Long-Term Clinical Outcomes Associated With Reinfarction Following Fibrinolytic Administration in the Thrombolysis In Myocardial Infarction Trials

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**OBJECTIVES** We hypothesized that early recurrent myocardial infarction (MI) following fibrinolytic administration would be assessed with higher mortality at both 30 days and 2 years.

**BACKGROUND** Although early recurrent MI after fibrinolytic therapy has been associated with increased early mortality in the acute MI setting, its relation to long-term mortality has not been fully explored.

**METHODS** Mortality data were ascertained in 20,101 patients enrolled in the Thrombolysis In Myocardial Infarction (TIMI) 4, 9, and 10B and Intravenous NPA for the Treatment of Infarcting Myocardium Early (InTIME-II) acute MI trials.

**RESULTS** The frequency of symptomatic recurrent MI during the index hospitalization was 4.2% (836/20,101). Recurrent MI during the index hospital period was associated with increased 30-day mortality (16.4% [137/836] vs. 6.2% [1,188/19,260], $p < 0.001$). Likewise, recurrent MI was associated with a sustained increase in mortality up to two years, even after adjustments were made for covariates known to be associated with mortality and recurrent MI (hazard ratio 2.11, $p < 0.001$). However, this higher mortality at 2 years was due to an early divergence in mortality by 30 days and was not due to a significant increase in late mortality between 30 days and 2 years (4.38% [31/707] vs. 3.76% [685/18,206], p = NS). Percutaneous coronary intervention during the index hospitalization was associated with a lower rate of in-hospital recurrent MI (1.6% vs. 4.5%, $p < 0.001$) and lower two-year mortality (5.6% vs. 11.6%, $p < 0.001$). Performance of coronary artery bypass graft surgery was also associated with a lower recurrent rate of MI (0.7% vs. 4.3%, $p < 0.001$) and lower two-year mortality rate (7.95% vs. 10.6%, $p = 0.0008$).

**CONCLUSIONS** Early recurrent MI is associated with increased mortality up to two years. However, most deaths occur early, and the risk of additional deaths between the index hospital period and two years was not significantly increased among patients with recurrent MI. Percutaneous coronary intervention during the index hospitalization was associated with a lower risk of recurrent MI and a lower risk of two-year mortality. (J Am Coll Cardiol 2003;42:7–16)


The incidence of symptomatic recurrent myocardial infarction (MI) has been reported to be between 2% and 6% by four to six weeks after fibrinolytic administration (1–6).

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Death from recurrent MI remains a limitation of fibrinolytic therapy (1–7). Because recurrent MI is associated with the primary end point of mortality, many recent fibrinolytic trials have adapted death or recurrent MI as a key secondary end point (7). Although recurrent MI has been associated with short-term mortality (7), its relation to long-term mortality in the era of newer fibrinolytic, antithrombotic, and antiplatelet agents, as well as new device technologies, is less well characterized.

Because recurrent MI may be associated with more severe left ventricular dysfunction, we hypothesized that recurrent MI before discharge from the index hospitalization would not only be associated with higher mortality by 30 days but also later, up to 2 years. Furthermore, we hypothesized that early recurrent MI would be associated with an additional increase in late mortality, between 30 days and 2 years. Finally, we hypothesized that performance of a percutaneous coronary intervention (PCI) during the index hospital period would be associated with a lower subsequent risk of recurrent MI and death. The data of over 20,000 patients enrolled in the Thrombolysis In Myocardial Infarc-

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**Abbreviations and Acronyms**

| | |
|---|---|
| CABG | = coronary artery bypass graft surgery |
| CI | = confidence interval |
| CK | = creatine kinase |
| HR | = hazard ratio |
| InTIME-II | = Intravenous NPA for the Treatment of Infarcting Myocardium Early trial |
| IQR | = interquartile range |
| MI | = myocardial infarction |
| PCI | = percutaneous coronary intervention |
| rt-PA | = recombinant tissue-type plasminogen activator |
| TIMI | = Thrombolysis In Myocardial Infarction trial |
| TRS | = Thrombolysis In Myocardial Infarction risk score |
| ULN | = upper limit of normal |

tion (TIMI) 4, 9, and 10B and Intravenous NPA for the Treatment of Infarcting Myocardium Early (InTIME-II, or TIMI 17) trials were analyzed to test these hypotheses.

## METHODS

**Patient population.** Both 30-day and long-term mortality data (up to 2 years) from the TIMI 4, 9, and 10B and InTIME-II acute MI trials were analyzed (n = 20,101). The TIMI 4 trial was a randomized, double-blinded comparison of three fibrinolytic regimens: anistreplase (eminase), front-loaded recombinant tissue-type plasminogen activator (rt-PA) (activase or alteplase), and combination therapy in 416 patients (8). Both TIMI 9A (n = 757) and TIMI 9B (n = 3,002) were multicenter, randomized trials evaluating the safety and efficacy of hirudin as an adjunct to fibrinolytic therapy (rt-PA or streptokinase at the physician's discretion) (9,10). The TIMI 10B study was an 880-patient, randomized trial comparing 30, 40, and 50 mg of tenecteplase, a mutant of rt-PA, with front-loaded alteplase (11). The TIMI 17 (InTIME-II) study was an

**Table 2.** Incidence of Recurrent MI by In-Hospital Medication Use

| Medication | Recurrent MI (n = 836) | p Value |
|---|---|---|
| Fibrinolytic (%) | | 0.010 |
| tPA | 4.5 | |
| SK | 3.3 | |
| TNK | 3.9 | |
| nPA | 3.9 | |
| APSAC | 8.8 | |
| APSAC + tPA | 4.6 | |
| Beta-blocker (%) | | 0.792 |
| Yes | 4.1 | |
| No | 4.2 | |
| Calcium channel blocker (%) | | < 0.001 |
| Yes | 6.8 | |
| No | 3.8 | |
| Nitrate (%) | | < 0.001 |
| Yes | 4.6 | |
| No | 2.6 | |
| ACE inhibitor (%) | | 0.001 |
| Yes | 4.6 | |
| No | 3.7 | |

APSAC = anisoylated plasminogen streptokinase activator complex; nPA = lanoteplase; SK = streptokinase; tPA = tissue-type plasminogen activator; TNK = tenecteplase; other abbreviations as in Table 1.

**Table 1.** Baseline Characteristics

| Variable | Recurrent MI (n = 836) | No Recurrent MI (n = 19,265) | p Value |
|---|---|---|---|
| Age (yrs) | 63.4 ± 11.6 | 60.7 ± 12.0 | < 0.001 |
| Male gender (%) | 71.4 | 75.3 | 0.012 |
| White (%) | 92.8 | 92.1 | 0.435 |
| Hypertension (%) | 37.5 | 31.6 | < 0.001 |
| Diabetes (%) | 14.5 | 14.3 | 0.872 |
| Angina (%) | 31.0 | 23.5 | < 0.001 |
| CHF* (%) | 3.5 | 2.9 | 0.390 |
| Current smoker (%) | 35.8 | 45.3 | < 0.001 |
| Previous MI (%) | 22.4 | 15.9 | < 0.001 |
| Anterior infarct location (%) | 43.5 | 41.8 | 0.314 |
| Heart rate (beats/min) | 73.9 ± 16.8 | 75.9 ± 17.7 | 0.002 |
| Blood pressure (mm Hg) | | | |
| Systolic | 136.2 ± 21.3 | 136.8 ± 21.9 | 0.444 |
| Diastolic | 80.8 ± 13.7 | 81.1 ± 13.8 | 0.573 |
| Weight (kg) | 77.3 ± 15.2 | 78.4 ± 14.8 | 0.042 |
| Symptom onset to treatment (h) | 2.5 (1.8–3.75) | 2.85 (2–4) | < 0.001† |
| Pre-admission medication (%) | | | |
| Aspirin | 29.0 | 20.3 | < 0.001 |
| Beta-blocker | 23.1 | 14.7 | < 0.001 |
| Calcium channel blocker | 22.6 | 15.7 | < 0.001 |
| Nitrate | 24.6 | 18.7 | < 0.001 |
| ACE inhibitor | 12.8 | 11.7 | 0.334 |

*History of CHF not collected in TIMI 4. †Wilcoxon rank-sum. Data are presented as the mean value ± SD, percentage of subjects, or median value (interquartile range).
ACE = angiotensin-converting enzyme; CHF = congestive heart failure; MI = myocardial infarction.

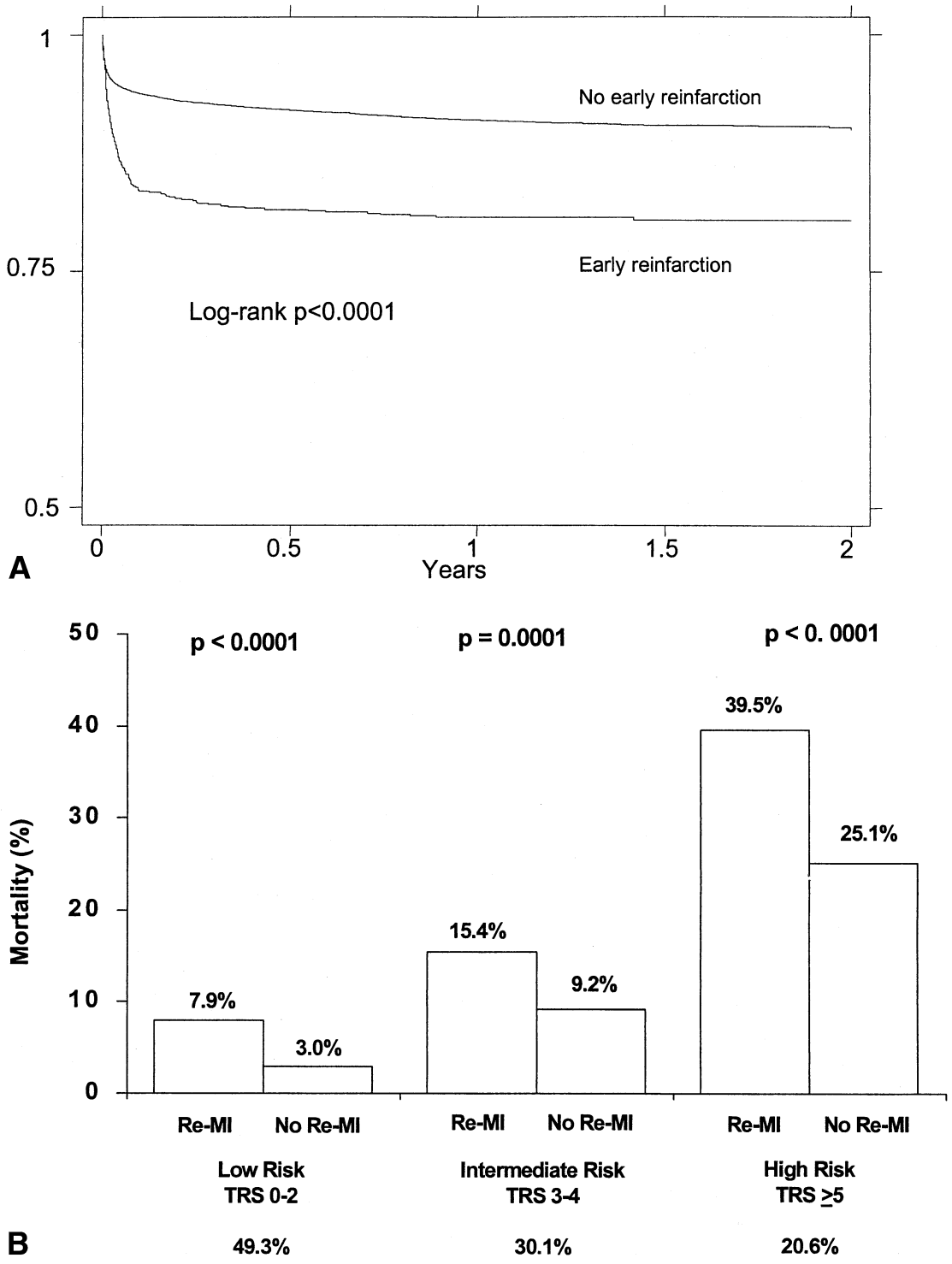


**Figure 1.** **(A)** Kaplan-Meier curves relating short-term and long-term outcomes to recurrent myocardial infarction (MI). Most deaths among patients with early reinfarction occurred early, and the curves did not shift between 30 days and 2 years of follow-up. **(B)** Kaplan-Meier estimated mortality rates up to two years by in-hospital reinfarction, stratified by Thrombolysis In Myocardial Infarction risk score (TRS). Mortality was higher in patients with reinfarction in the low, intermediate, and high TRS groups. In the analysis adjusting for age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment, the p value was <0.001 in each of the TRS groups.

noninferiority trial (n = 15,078) that compared single-bolus intravenous lanoteplase with front-loaded alteplase (12).

**End points and definitions.** Recurrent MI was adjudicated by a Clinical Events Committee in TIMI 4, TIMI 9, and InTIME-II and was prospectively assessed by the local investigators in TIMI 10B. In all trials, reinfarction within 18 h of the index MI was defined as recurrent chest pain lasting at least 30 min, associated with new or recurrent

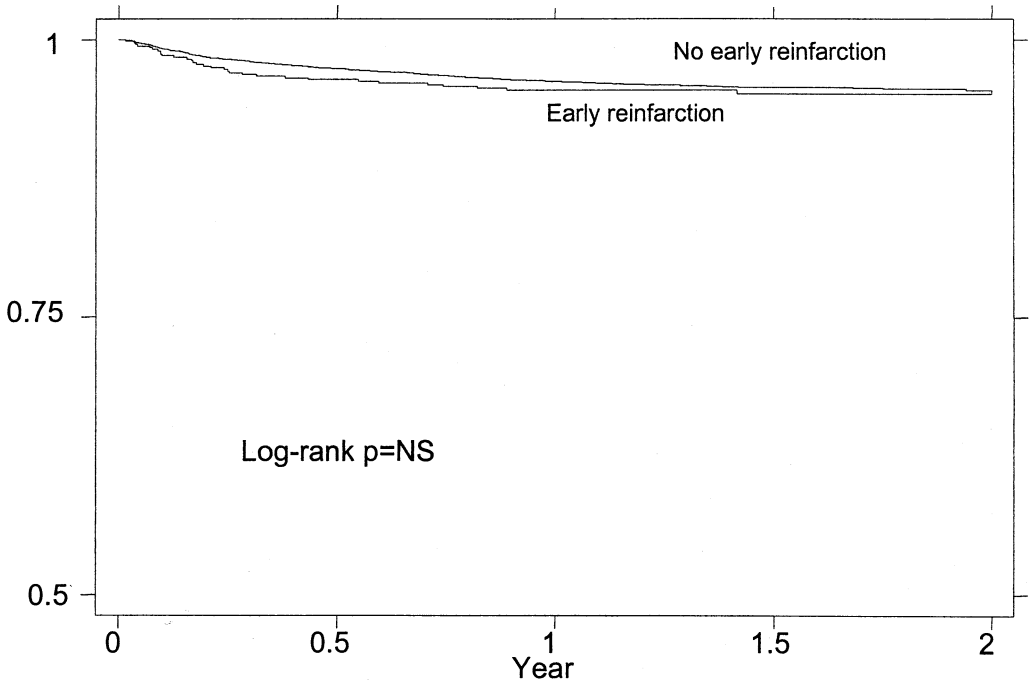


**Figure 2.** Kaplan-Meier curves relating long-term outcomes (up to two years) to recurrent myocardial infarction in patients who were alive at hospital discharge. There was no difference in mortality in patients with an early reinfarction when the analysis was restricted to patients who survived the index hospitalization (p = 0.45 by log-rank).

ST-segment elevation ≥0.1 mV in at least two contiguous electrocardiographic leads. After 18 h of fibrinolytic administration, there had to be enzyme or electrocardiographic evidence of MI in addition to recurrent chest pain. In TIMI 4, 9, and 10B, the requirement was creatine kinase-MB fraction (CK-MB) greater than the upper limit of normal (ULN). In TIMI 9 and 10B, the value also had to be >50% increased over the previous value. In TIMI 9 and 10B, after coronary angioplasty, the definition of recurrent MI was new Q waves in two or more leads and re-elevation of CK-MB (or total CK if CK-MB was not available) to at least twice the ULN and ≥50% above the previous value; after coronary artery bypass graft surgery (CABG), the latter criterion was set at CK-MB elevation to at least five times the ULN with new Q waves. In InTIME-II, two of the following conditions were required for reinfarction: chest pain lasting ≥20 min not relieved by nitroglycerin, new ST-segment elevation ≥0.1 mV or new abnormal Q waves, and serum CK >2 times the ULN and >50% above the lowest CK level from the index MI.

Performance of PCI and CABG was assessed through index hospitalization discharge in all trials. Use of PCI or CABG was left to the discretion of the investigator and was not protocol-mandated. Patients who experienced recurrent MI before their delayed PCI (n = 288) or CABG (n = 76) were analyzed as medically treated patients, because their recurrent MI presumably led to the intervention. Patients with PCI or CABG and recurrent MI on the same day but with a missing time of MI (n = 11) or revascularization (n = 45) were excluded from the revascularization analysis, as the sequence of the events (whether the MI preceded or followed revascularization) could not be ascertained. Recurrent MIs that developed after revascularization were counted among the MIs that occurred in the revascularization strategy.

The distribution of the TIMI risk score (TRS) for ST-segment elevation acute MI, as previously reported, was used to assess the effect of recurrent MI and revascularization on mortality in low-risk (TRS 0 to 2), intermediate-risk (TRS 3 and 4), and high-risk (TRS 5 to 7) patients (13). The TRS was developed to identify the patients' risk of 30-day mortality.

**Statistical analysis.** All analyses were performed using Stata Statistical Software (version 7.0, Stata Corp., College Station, Texas). All continuous variables are reported as the mean value ± SD. The Student *t* test or analysis of variance was utilized for the analysis of continuous variables. The nonparametric Wilcoxon rank-sum test was used when the data were not normally distributed, according to the skewness/kurtosis tests for normality by D'Agostino et al. (14). The chi-square test was used for the analysis of categorical variables. Kaplan-Meier curves were generated, and the log-rank test was used to test the equality of the survivor function across groups. The Cox proportional hazards model was used to estimate maximum-likelihood proportional hazard ratios.

## RESULTS

**Patient characteristics.** The median duration of follow-up was 456 days (interquartile range [IQR]: 361 to 580 days).

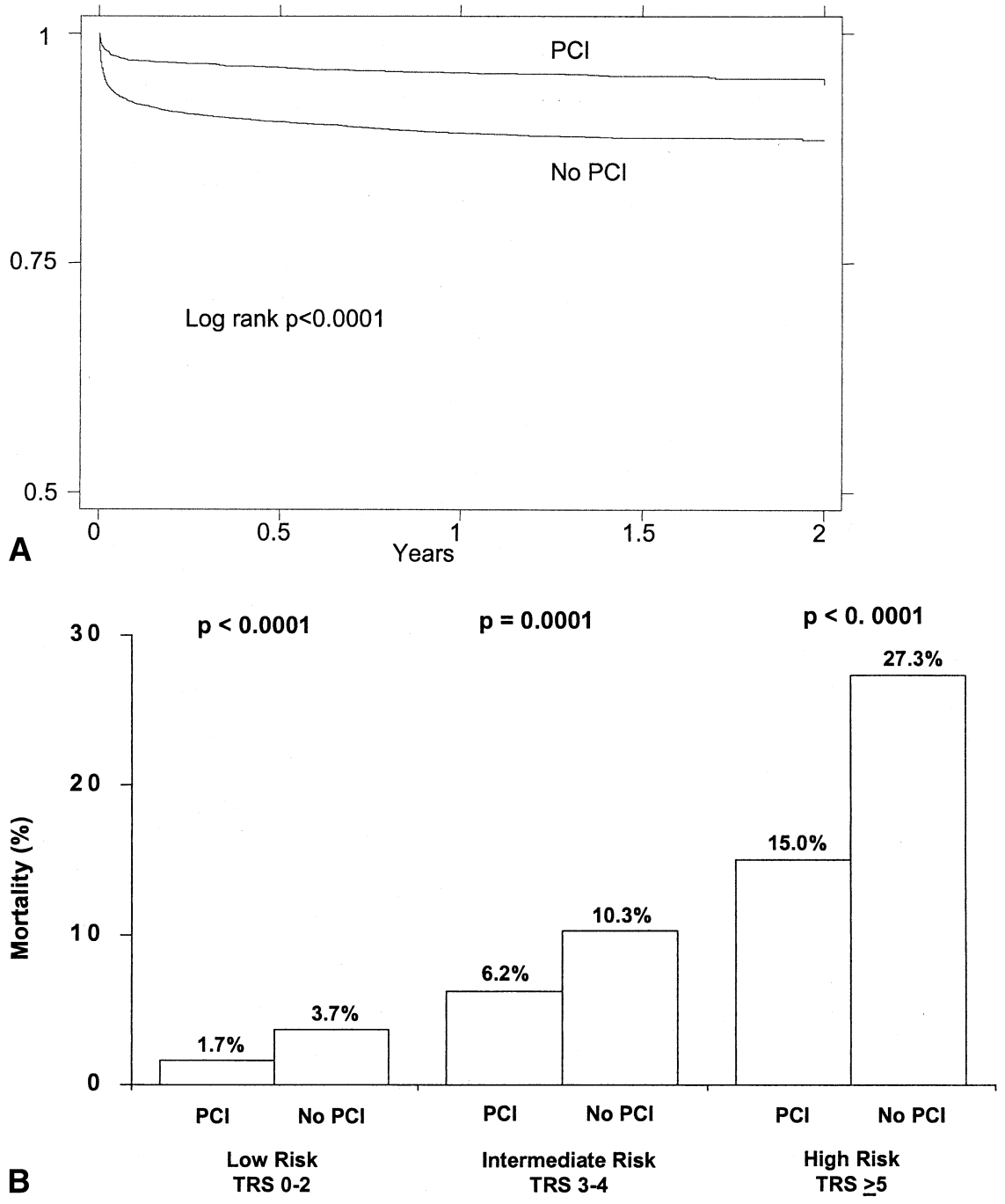


**Figure 3.** **(A)** Kaplan-Meier curves relating short-term and long-term outcomes (up to two years) to percutaneous coronary intervention (PCI) use during the index hospitalization. In the analysis adjusting for age, gender, anterior myocardial infarction (MI), pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment, the p value was <0.001. **(B)** Kaplan-Meier estimated mortality rates up to two years by in-hospital PCI, stratified by Thrombolysis In Myocardial Infarction risk score (TRS). Mortality was lower in patients who underwent PCI in the low, intermediate, and high TRS groups. In the analysis adjusting for age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment, the p value was <0.001 in each of the TRS groups.

Of the 20,105 patients enrolled in the five trials, 4 patients did not have follow-up through 30 days. At 6 months, follow-up was available in 16,180 patients. A total of 5,122 patients had follow-up for <1 year. For the majority of patients (n = 14,379), follow-up occurred for between 1 and 2 years, and 598 patients had >2 years of follow-up. All data after two years were censored at two years.

Recurrent MI during the hospitalization for the index MI occurred in 836 (4.2%) of the 20,101 patients at a median of 2.2 days (IQR 0.2 to 4.7). Patients who sustained

**Table 3.** Mortality by In-Hospital Reinfarction and Use of PCI

| | Recurrent MI Absent | | Recurrent MI Present | | | |
|---|---|---|---|---|---|---|
| | No PCI (n = 15,051) | PCI (n = 4,212) | Treated With PCI (n = 288) | Not Treated With PCI (n = 423) | PCI Complicated by Reinfarction After PCI (n = 69) | p Value (5-way) |
| In-hospital mortality | 6.31% | 2.61% | 5.21% | 23.64% | 11.59% | < 0.001 |
| 30-day mortality | 7.10% | 2.83% | 5.56% | 25.06% | 11.59% | < 0.001 |
| 2-year mortality* | 10.38% | 4.25% | 6.60% | 29.55% | 11.59% | < 0.001 |
| 2-year mortality† | 11.15% | 5.52% | 7.23% | 29.88% | 11.59% | < 0.001 |

*Raw percentages. †Kaplan-Meier estimates.
MI = myocardial infarction; PCI = percutaneous coronary intervention.

a recurrent MI were more likely to have had a previous MI and a history of hypertension and were older and more likely to be female (Table 1). There were differences in the frequency of recurrent MI in patients who received a calcium channel blocker, nitrate, and angiotensin-converting enzyme inhibitor during the index hospitalization (Table 2).

**Reinfarction and mortality.** The frequency of symptomatic recurrent MI during the index hospitalization was 4.2% (836/20,101). Among patients who sustained a recurrent MI during the index hospitalization, 30-day mortality was increased (16.4% [137/836] vs. 6.2% [1,188/19,260], $p < 0.001$). This association persisted after adjustment for covariates known to be associated with 30-day mortality and covariates associated with recurrent MI ($p < 0.05$ on univariate analysis) (Table 1), including age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment (hazard ratio [HR] 2.55, 95% confidence interval [CI] 2.12 to 3.06; $p < 0.001$).

Mortality remained higher during follow-up among patients with recurrent MI, as compared with those without recurrent MI, even after adjustment for age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment (HR 2.11, 95% CI 1.79 to 2.50; $p < 0.001$) (Fig. 1A). The unadjusted six-month mortality rates for the two groups by reinfarction status were 18.5% (re-MI) and 8.0% (no re-MI). The corresponding mortality rates at 12, 18, and 24 months were 19.3% vs. 9.0%, 19.6% vs. 9.6%, and 19.6% vs. 10.1%, respectively. Similar results were seen across the low, intermediate, and high TRS categories (Fig. 1B).

In an analysis restricted to patients who survived the index hospitalization, long-term mortality up to two years was not significantly higher in patients who had a reinfarction during the index hospital period ($p = 0.45$ by log-rank) (Fig. 2). The unadjusted two-year mortality rates in this analysis were 4.9% (re-MI) and 4.9% (no re-MI) ($p = NS$). At one year, these values were 4.5% (re-MI) and 3.7% (no re-MI) ($p = NS$).

**Mortality and in-hospital reinfarction by performance of revascularization.** Percutaneous coronary intervention was performed in 4,281 (21.4%) of 20,043 patients during the index hospitalization at a median of four days after fibrinolytic administration (IQR 1 to 8). Reinfarction occurred less frequently among patients treated with PCI (1.6% vs. 4.5%, $p < 0.001$). Similar results were seen across the low, intermediate, and high TRS categories ($p < 0.001$ for each). In patients treated with PCI, mortality was lower during the index hospitalization (2.76% vs. 6.75%, $p < 0.001$), at 30 days (2.97% vs. 7.56%, $p < 0.001$), and up to 2 years (5.62% vs. 11.59%, $p < 0.001$) (Fig. 3A). Similar results were seen across the low, intermediate, and high TRS categories (Fig. 3B). Mortality was highest among patients with recurrent MI who were not treated with PCI (in-hospital mortality rate of 23.6%) and lowest (2.6%) among patients without recurrent MI who were treated with PCI (Table 3). Both PCI and recurrent MI remained associated with mortality in a model adjusting for age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment (PCI-related HR 0.52, 95% CI 0.44 to 0.61, $p < 0.001$; recurrent MI-related HR 1.98, 95% CI 1.66 to 2.36, $p < 0.001$).

Coronary artery bypass graft surgery was performed in 1,048 (5.2%) of 20,092 patients during the index hospitalization at a median of eight days after fibrinolytic administration (IQR 4 to 13). Reinfarction occurred less frequently among patients treated with CABG (0.7% vs. 4.3%, $p < 0.001$), and mortality was lower ($p = 0.0008$) (Fig. 4A). When stratified by TRS, mortality was lower in CABG-treated patients in the high-risk group ($p = 0.0021$), with a trend toward being lower in the intermediate-risk group ($p = 0.0933$), but showed no difference in the low-risk group ($p = 0.7845$) (Fig. 4B). Both CABG and recurrent MI remained associated with mortality in a model adjusting for age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment (CABG-related HR 0.63, 95% CI 0.48 to 0.81, $p < 0.001$; recurrent MI-related HR 2.06, 95% CI 1.75 to 2.44, $p < 0.001$).

Use of any revascularization (PCI or CABG) occurred in 5,238 (26.1%) of 20,039 patients during the index hospitalization at a median of five days after fibrinolytic administration (IQR 2 to 9). Reinfarction occurred less frequently among patients treated with revascularization (1.4% vs.

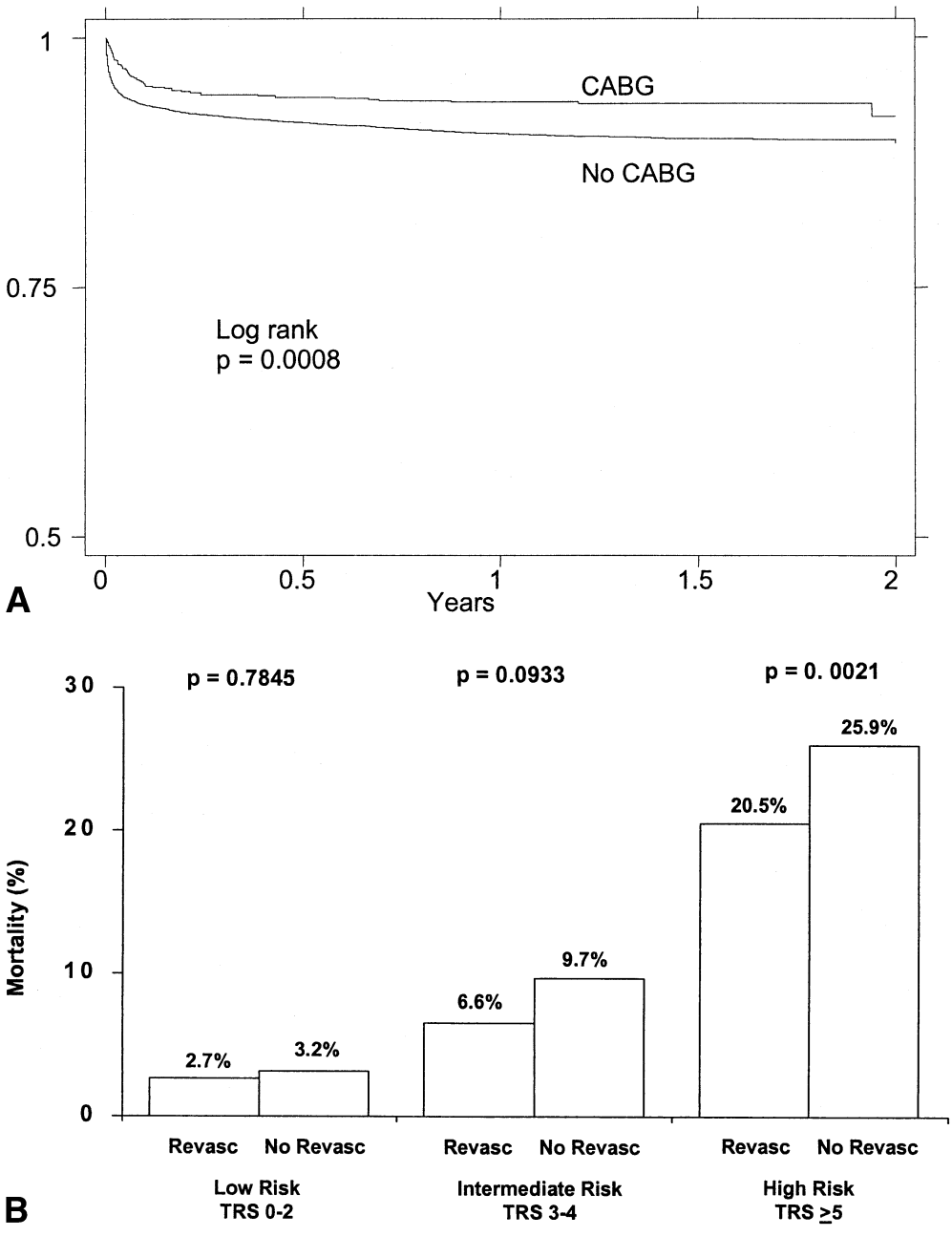


**Figure 4.** **(A)** Kaplan-Meier curves relating short- and long-term outcomes (up to two years) to coronary artery bypass graft surgery (CABG) use during the index hospitalization. **(B)** Kaplan-Meier estimated mortality rates up to two years by in-hospital CABG, stratified by Thrombolysis In Myocardial Infarction risk score (TRS). Mortality was lower in patients who underwent CABG in the high TRS groups, with a trend toward being lower in the intermediate-risk group, but showed no difference in the low-risk score group.

4.7%, $p < 0.001$), and mortality was lower ($p < 0.0001$) (Fig. 5A). Similar results were seen across the low, intermediate, and high TRS categories (Fig. 5B). Both revascularization and recurrent MI remained associated with mortality in a model adjusting for age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, and time from symptom onset to treatment (revascularization-related HR 0.51, 95% CI 0.44 to 0.59, $p < 0.001$; recurrent MI-related HR 1.92, 95% CI 1.61 to 2.30, $p < 0.001$).

## DISCUSSION

This analysis demonstrates that in-hospital recurrent MI following fibrinolytic administration is associated with an increased risk of long-term mortality up to two years, but this risk appears to be attributable primarily to an increase in early mortality during the index hospitalization. After adjustment for other known correlates of mortality, reinfarction remained significantly associated with long-term mortality for up to two years after the index MI. However,

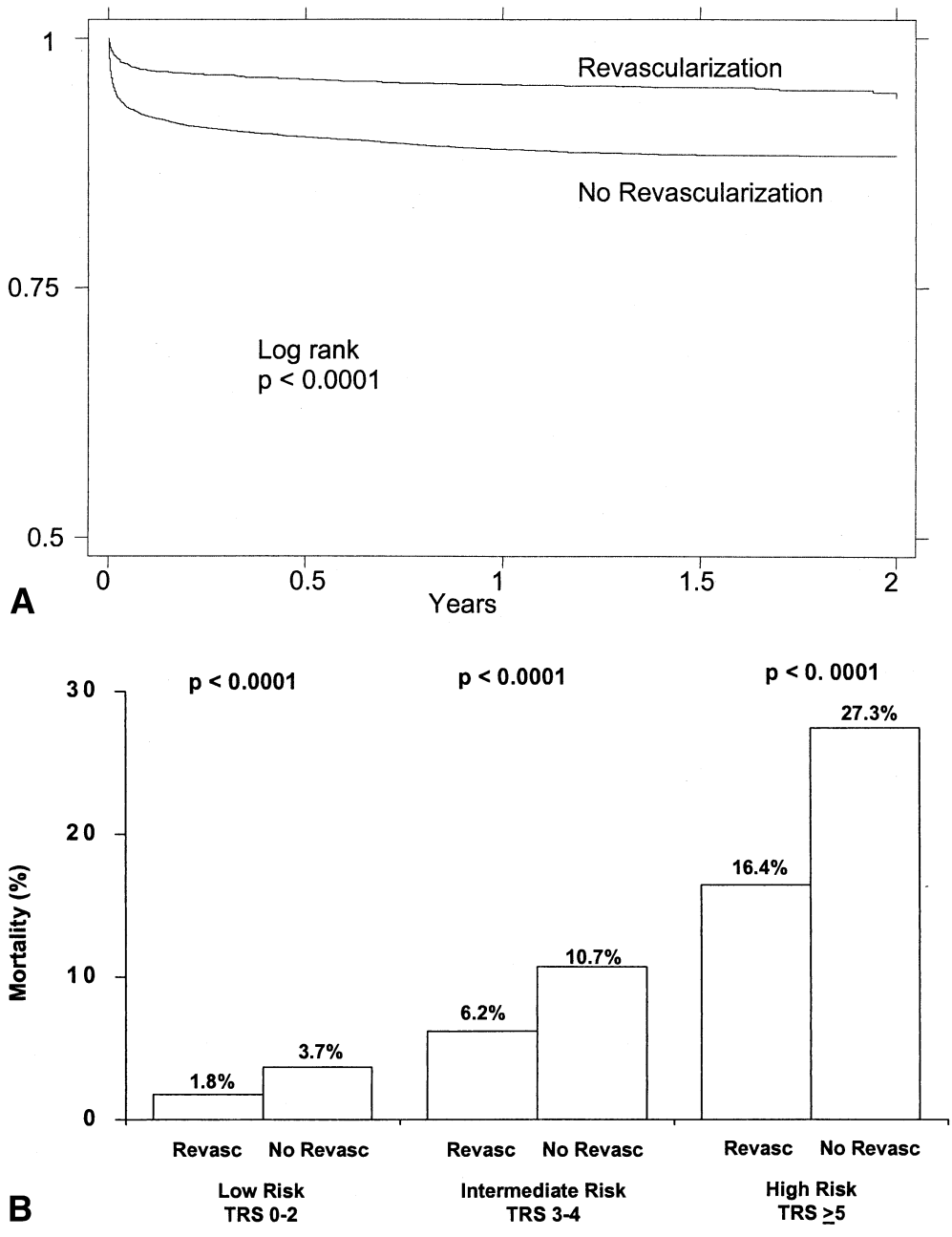


**Figure 5.** **(A)** Kaplan-Meier curves relating short- and long-term outcomes (up to two years) to revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]) use during the index hospitalization. **(B)** Kaplan-Meier estimated mortality rates up to two years by in-hospital revascularization (PCI or CABG), stratified by Thrombolysis In Myocardial Infarction risk score (TRS). Mortality was lower in patients who underwent revascularization in the low, intermediate, and high TRS groups.

long-term mortality up to two years among patients who survived the index hospital period was not significantly increased among patients with versus without reinfarction.

Our findings complement and expand on previous studies that have associated increased long-term mortality with in-hospital reinfarction (4–7,15,16). The 4.2% incidence of reinfarction in this cohort of patients is similar to the 2.1% to 6.1% incidence reported in other large fibrinolytic trials (1,2,17,18). An analysis of the TIMI II trial demonstrated an increased relative risk (RR) of death at three-year follow-up in patients with early reinfarction following fibrinolysis, as compared with patients without reinfarction (RR 1.9, 99% CI 1.1 to 3.2) (19). Pooled results from the Global Utilization of Streptokinase and tPA (alteplase) for Occluded arteries (GUSTO I) and Global Use of Strategies To Open occluded arteries (GUSTO III) trials showed a similar trend toward late mortality among patients with nonfatal reinfarction compared with those without reinfarction (adjusted HR 1.25, 95% CI 0.97 to 1.61) (7).

One potential strategy to reduce the risk of recurrent MI after fibrinolytic administration, as suggested by our data, might be the performance of revascularization during the

index hospitalization. Although early randomized trials failed to demonstrate a benefit in the performance of conventional angioplasty soon after fibrinolytic administration, these trials preceded the use of stents, thienopyridines, platelet glycoprotein IIb/IIIa inhibitors, and the monitoring of activated clotting times (20–22). More recent observational studies that incorporate these current practices have demonstrated the safety and potential efficacy of performing PCI after fibrinolytic administration (23–25).

In the present study, performance of revascularization during the index hospital period was associated with a lower rate of in-hospital recurrent MI and lower rates of early and long-term mortality up to two years. This association was observed in multivariate models adjusting for potential confounders and was also observed among patients at varying risk, as assessed using TRS. The timing of recurrent MI and performance of revascularization were carefully evaluated to ensure that the events were assigned to the appropriate strategy.

These retrospective observational findings are consistent with the hypothesis that performance of PCI after fibrinolytic administration during the index hospitalization is associated with a reduced risk of in-hospital recurrent MI, and a reduction in the risk of recurrent MI may, in turn, confer a favorable long-term prognosis. Prospective, randomized studies are warranted to validate this finding.

**Study limitations.** Several limitations of this study should be considered. This is a retrospective, observational analysis based on several trials. Although we controlled for variables previously identified as associated with mortality and recurrent MI (e.g., age, gender, anterior MI, pulse rate on admission, history of hypertension, previous angina, current smoker, previous MI, weight, time from symptom onset to treatment), unidentified confounders may have contributed to these findings. Recurrent MI was adjudicated in 19,255 (95.8%) of the 20,101 patients. Multiple definitions were used for recurrent MI. Data were unavailable as to which definition was used for each specific case of recurrent MI. As such, it is undetermined whether each definition of MI had the same effect on mortality and whether PCI affected the types of reinfarction and subsequent mortality.

**Conclusions.** Recurrent MI after fibrinolytic administration during the index hospitalization is associated with increased mortality up to two years. However, most of these deaths occur early, and the risk of additional deaths between the index hospitalization and two years did not appear to be increased. Performance of adjunctive PCI or CABG is associated with a lower rate of recurrent MI and death.

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