JACC Vol. 26, No. 4
October 1995:900–7

Prognostic Significance of Nonfatal Reinfarction During 3-Year Follow-Up: Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II Clinical Trial

HILTRUD S. MUELLER, MD, FACC, SANDRA A. FORMAN, MA,*
MARK A. MENEGUS, MD, FACC, LAWRENCE S. COHEN, MD, FACC,†
GENELL L. KNATTERUD, PHD,*
EUGENE BRAUNWALD, MD, FACC,‡ FOR THE TIMI INVESTIGATORS
Bronx, New York; Baltimore, Maryland; New Haven, Connecticut; and Boston, Massachusetts

Objectives. **This study sought to assess the independent contribution of nonfatal reinfarction to the risk of subsequent death in patients with acute myocardial infarction undergoing thrombolytic therapy.**

Background. **A composite of "unsatisfactory outcomes" as an end point has increased statistical power and facilitated evaluation of evolving treatment regimens in acute myocardial infarction. The significance of nonfatal reinfarction as a component of a composite end point has not been evaluated in the thrombolytic era.**

Methods. **Event rate of nonfatal reinfarction over 3-year follow-up was evaluated in patients with acute myocardial infarction entered into the Thrombolysis in Myocardial Infarction Phase II trial. The independent risk of nonfatal reinfarction for subsequent death within various time intervals of follow-up was determined. The mortality rate after nonfatal reinfarction was compared with that of a matched control group.**

Results. **During 3-year follow-up, 349 of 3,339 patients had a nonfatal reinfarction. Univariate predictors were history (antedating the index event) of angina ($p = 0.01$), hypertension ($p = 0.01$), multivessel disease ($p = 0.007$) and not a current smoker ($p = 0.003$); the latter was an independent predictor (relative risk [RR] 1.3, 99% confidence interval [CI] 1.0 to 1.8). Forty-three of the 349 patients with a nonfatal reinfarction died: RR for death (vs. patients without a nonfatal reinfarction) was 1.9 (99% CI 1.1 to 3.2) if reinfarction occurred within 42 days of study entry, 6.2 (99% CI 3.0 to 12.9) if reinfarction occurred between 43 and 365 days and 2.9 (99% CI 0.6 to 13.4) if reinfarction occurred between 366 days and 3 years. The cumulative 3-year death rate was 14.1% in patients with a nonfatal reinfarction compared with 7.9% ($p < 0.01$) in a matched control group. Univariate predictors of death after nonfatal reinfarction were age ≥65 years ($p < 0.001$), not low risk category ($p = 0.015$) and history of heart failure before the index event ($p < 0.001$). Age ≥65 years was the only independent predictor (RR 5.4, 99% CI 2.3 to 12.4).**

Conclusions. **Nonfatal reinfarction is a strong and independent predictor for subsequent death. It represents a powerful component for a composite end point in patients who received thrombolytic therapy after acute myocardial infarction.**

(J Am Coll Cardiol 1995;26:900–7)

The efficacy of thrombolytic therapy of acute myocardial infarction was initially established in placebo-controlled trials in which death was the primary end point (1–4). Subsequently, thrombolytic agents were compared with one another (5–7), as were combinations of thrombolytic agents with other drugs, including anticoagulant agents and aspirin (8,9). Further comparisons of effective treatment strategies with small differences in mortality require strikingly large number of patients. Recent trials, such as GISSI-3 (9), ISIS-4 (8) and GUSTO (7), have required 40,000 to almost 60,000 patients. Largely as a consequence of such trials, the mortality of patients with acute myocardial infarction has declined. Despite this progress, much can be learned with regard to optimizing thrombolytic regimens, in particular the role of emerging thrombolytic agents, specific antithrombins and newer antiplatelet regimens to help establish and maintain patency of the infarct-related artery. The role of primary and adjunctive mechanical reperfusion also requires clarification. These new treatment modes can be administered in an almost infinite number of combinations, but it is not feasible to conduct a megatrial to evaluate the efficacy of every logical new therapeutic regimen. Therefore, to gain statistical power and allow clinically useful information to be obtained in reasonably sized trials, composite end points are being used increasingly. These consist of the

From the Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York; *Maryland Medical Research Institute, Baltimore, Maryland; †Yale University School of Medicine, New Haven, Connecticut; and ‡Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. This study was supported by Research Contracts and Grants from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. A complete list of the TIMI II investigators appears in reference 16.

Manuscript received November 28, 1994; revised manuscript received May 18, 1995, accepted May 22, 1995.

Address for correspondence: Dr. Hiltrud S. Mueller, Division of Cardiology, Montefiore Medical Center, 111 East 210th Street, Bronx, New York 10467.

Address for reprints: TIMI Coordinating Center, Maryland Medical Research Institute, 600 Wyndhurst Avenue, Baltimore, Maryland 21210.

0735-1097/95/$9.50
0735-1097(95)00270-E

combination of mortality with other unsatisfactory outcomes, including nonfatal reinfarction, heart failure, disabling stroke or failure to achieve patency of an occluded infarct-related artery (10,11).

Recurrent myocardial infarction has been a widely used nonfatal end point (12–14) and was identified as a risk factor for subsequent mortality before the thrombolytic era (12–15). However, its significance in patients with thrombolytic therapy, in whom recurrent infarction may represent completion of an interrupted infarction, in particular during the early period after treatment, has not been defined. The present analysis of the Thrombolysis in Myocardial Infarction (TIMI) II (16) data base was undertaken to determine the independent contribution of nonfatal reinfarction to the risk of subsequent death of patients with acute myocardial infarction undergoing thrombolytic therapy.

Methods

Protocol. The TIMI II trial has previously been described in detail (16,17). Briefly, patients <76 years old who presented within 4 h after the onset of ischemic chest pain (>30 min) and who had ST segment elevations on the electrocardiogram (ECG) and no contraindications to thrombolytic therapy were eligible. All patients received intravenous infusion of recombinant tissue-type plasminogen activator (rt-PA [Activase]) and were randomly assigned to either an invasive or a conservative strategy. The former underwent routine catheterization 18 to 48 h after randomization and revascularization, when the anatomy was appropriate. Patients assigned to the conservative strategy underwent these procedures only in response to spontaneous or provoked myocardial ischemia. Antithrombotic therapy with heparin and aspirin was standardized (16). Beta-adrenergic blocking agent therapy was applied according to the design of the TIMI IIB beta-blocker substudy (18). The Mortality and Morbidity Classification Committee (17) reviewed all reported clinical events without knowledge of treatment assignment and classified the events as *definite myocardial reinfarction*, *recurrent ischemia* or *no event*.

Prespecified definitions. *"Not low risk" patient category.* This group demonstrated the presence of one or more of the following: history of myocardial infarction, ST segment elevation in anterior ECG leads, rales extending upward to more than one-third of the lung fields, systolic pressure <100 mm Hg and sinus tachycardia >100 beats/min, atrial fibrillation/flutter, age ≥70 years, pulmonary edema or cardiogenic shock (16).

Recurrent myocardial infarction. In events occurring <18 h after study entry, recurrent myocardial infarction was defined by the development of ischemic chest pain >20 min, either new or markedly worse chest discomfort, new plasma creatine kinase (CK) elevation and appearance of CK-MB isoenzyme. In events occurring ≥18 h after study entry, recurrent myocardial infarction was defined by the development of new ischemic chest pain for >20 min and by one or more of the following: major new Q waves on at least two ECG leads, new left bundle branch block, new plasma CK elevation and appearance of CK-MB isoenzyme (17). A recurrent myocardial infarction was classified as nonfatal if the patient was discharged alive from the hospital after the reinfarction.

Follow-up. Patients were enrolled from April 1986 through June 1988 and followed up through September 1990. Patient status was determined by clinic visit at 6 weeks and 1 year and by telephone contact at 3 months, 6 months and 2 years and, for patients who were enrolled in the study before September 1987, at 3 years. Survival data are based on all-cause mortality (19).

Statistical considerations. Event rates of nonfatal reinfarction and death were calculated by Kaplan-Meier life-table methods (20,21) and compared using the log-rank test.

To identify clinical variables that predict the occurrence of an initially nonfatal reinfarction, a Cox proportional hazards regression technique (22,23) was used. Preselected baseline clinical variables identified in the TIMI II Subgroup Study (24) were entered as predictor variables using nonfatal reinfarction within 3 years as the outcome end point. Similar analyses were performed to identify clinical variables that predict subsequent mortality after a nonfatal reinfarction. Only patients with a nonfatal reinfarction (n = 349) were entered into the model. The same preselected clinical variables were entered as predictor variables with death within 3 years as the outcome end point.

To determine the independent risk of subsequent death from nonfatal reinfarction over the 3-year follow-up period, a time-dependent Cox proportional hazards survival model (22,23) was used, adjusting for clinical baseline characteristics and the variability in time of occurrence of the nonfatal reinfarction.

The mortality rate of patients with nonfatal reinfarction was compared with that of a control group. The control group consisted of a matched control patient for each patient with a nonfatal reinfarction. Matching criteria included clinical center, gender and decade of age. For each patient with an event, a pool of patients was identified who had not experienced an event at that time point. A matched control subject for each patient was randomly selected without replacement from the available pool. To avoid retrospective bias, the matching technique allowed selection of patients with later nonfatal reinfarction as control patients for those with early nonfatal reinfarction. Five independent sets of matched control groups were randomly selected. Comparisons of the mortality over time between the patients with nonfatal reinfarction and each of the five matched control groups were similar. A representative control group was selected for graphical comparison with the nonfatal reinfarction group using a Kaplan-Meier life table.

To adjust for multiple testing, two-sided probability values between 0.01 and 0.001 were considered to provide some evidence, and values <0.001 to provide strong evidence, of differences. Analyses are based on a data file containing information available as of January 1991.

Results

Patients and total clinical events. A total of 3,339 patients were enrolled. Vital status was known for 99.0% at 1 year and for 96.7% at 2 years after study entry. Of the 2,174 patients who were enrolled into TIMI II before September 1987, vital status at 3 years was ascertained to 90.9%. The 2,174 patients enrolled before September 1987 were similar to the 1,165 patients enrolled between October 1987 and June 1988 (19) and may be considered representative of the entire patient cohort. Follow-up for nonfatal events was obtained for 99.8% of patients through 6 weeks, for 98.2% of patients for 1 year, for 95.4% for 2 years and for 90.1% for 3 years.

By the end of the 3-year follow-up, death from all causes occurred in 331 of the 3,339 patients enrolled (9.9%) and death or nonfatal reinfarction in 637 patients (19.1%). There was no difference in the incidence of events between patients randomized to the invasive and conservative strategy (19). Three hundred eighty-one (11.4%) of the 3,339 patients had a reinfarction; in 49 of these patients (1.5%) the reinfarction was fatal, and in 349 (10.4%) it was nonfatal. There were 17 patients who had a nonfatal reinfarction and later a fatal reinfarction; these patients were counted in each category.

Nonfatal reinfarction. Life-table rates of nonfatal reinfarction by specified baseline characteristics over the 3-year follow-up period are presented in Table 1 (univariate analysis), and the rates of nonfatal reinfarction are shown in Figure 1. Fifty-eight percent of the total events occurred within the initial 6 weeks of follow-up. During this time period, nonfatal reinfarction was predicted by age ≥65 years, history (before the index event) of angina or of previous myocardial infarction, by being a never and not a current smoker and, in patients assigned to the invasive strategy, by multivessel coronary artery disease. Over the time course of the 3-year follow-up, the degree of significance of the univariate predictors for nonfatal reinfarction declined, except for history of hypertension. Independent predictors of nonfatal reinfarctions, which occurred within 6 weeks, were history (before the index event) of angina (relative risk [RR] 1.7, 99% confidence interval [CI] 1.1 to 2.5, $p < 0.001$) and not a current smoker (RR 1.9, 99% CI 1.2 to 2.8, $p < 0.001$). For nonfatal reinfarctions that occurred within 3 years, not a current smoker was the only independent predictor (RR 1.3, 99% CI 1.0 to 1.8, $p = 0.01$). In a separate analysis of 42-day survivors free of nonfatal reinfarction, none of the baseline characteristics remained univariate predictors of nonfatal reinfarction between 43 days and 3 years. A patent infarct-related artery tended to occur more often in patients with nonfatal reinfarction: patent artery (n = 1,167) versus occluded artery (n = 204) at 1 year, 2.6% versus 1.0%; at 2 years, 4.9% versus 1.5%; and at 3 years, 5.8% versus 2.1% ($p = 0.05$).

Death after nonfatal reinfarction. Forty-three of the 349 patients with a nonfatal reinfarction died during follow-up. By the end of the 3-year time course, the life-table mortality rate subsequent to nonfatal reinfarction was 14.1% compared with 7.9% ($p < 0.01$) in a matched control group (Fig. 2). The risk for death after nonfatal reinfarction varied during the 3-year follow-up period (Table 2). Within 42 days after study entry, the risk ratio for death was 1.9 higher for patients with a nonfatal reinfarction than for patients without such an event, comparable to the risk ratios of established predictors of death, including advanced age, tachycardia, hypotension, history of previous myocardial infarction, diabetes and female gender. Between 43 and 365 days after study entry, the risk ratio was 6.2, significantly higher ($p < 0.001$) than that for the initial 6 weeks. Subsequent to 1 year of follow-up, the risk of death was not significantly higher for patients with a nonfatal reinfarction than for those without such an event.

For the 3-year follow-up period, univariate predictors of death after nonfatal reinfarction were age ≥65 years, the "not low risk category" (16) during the index infarction and a history of heart failure antedating the index infarction (Table 3). Death rates tended to be higher in patients with an anterior wall myocardial infarction, a history (before the index event) of myocardial infarction and, in patients assigned to the invasive strategy, an ejection fraction <40%. Among these univariate predictors, age ≥65 years was the only independent predictor of death after a nonfatal reinfarction (RR 5.4, 99% CI 2.3 to 12.4, $p < 0.001$).

Discussion

For a nonfatal event to be useful as component of a composite end point, it must occur with sufficient frequency to increase the total event rate substantially, and it must be a marker for an unsatisfactory clinical outcome. For example, the GISSI-2 (25) study used the composite end point of death, new onset of heart failure and extensive left ventricular damage. The TIMI 3 trial (26) on unstable angina applied the composite end point of death, reinfarction and documented recurrent myocardial ischemia. Death and the occurrence of adverse clinical events (stroke, reinfarction, recurrent ischemia, heart failure) and adverse angiographic events (lack of acute patency or reocclusion of the infarct-related artery) was the combined end point in the TAMI 5 trial (27). The TIMI 5 trial (28) used death, reinfarction and lack of complete reperfusion as the primary end point. In the PAMI study (29), the combined end point consisted of death, reinfarction and recurrent ischemia. Among these nonfatal end points, reinfarction is probably the simplest and most reliably obtained.

Incidence of nonfatal reinfarction. The incidence of nonfatal reinfarction does not seem to have changed considerably with the advent of thrombolytic therapy. Before the use of this therapy, the Multicenter Postinfarction Study (12) and the Postinfarction Registry of Gilpin et al. (13) reported incidences of nonfatal reinfarction between hospital discharge and 1 year of 4.3% and 4.7%, respectively. These results are similar to the rate of 3.7% between 2 weeks and 1 year after study entry in TIMI II. In placebo-treated patients of the Multicenter Diltiazem Postinfarction Trial (14), the nonfatal reinfarction rate from study entry to an average follow-up of

Table 1. Nonfatal Reinfarction Life-Table Rate by Specified Baseline Characteristics

	No. of Pts	6 wk (%)	p Value	1 yr (%)	p Value	2 yr (%)	3 yr (%)	p Value
All pts	3,339							
No. of pts with events	349	6.2		8.8		10.6	11.3	—
Gender								
Male	2,742	5.9	0.08	8.5	0.10	10.4	11.1	0.35
Female	597	7.8		10.6		11.6	12.2	
Age								
≥65 yr	859	8.2	0.008	10.8	0.02	12.3	13.0	0.06
<65 yr	2,480	5.5		8.2		10.0	10.7	
Anterior MI								
Yes	1,730	5.7	0.19	8.2	0.20	9.9	10.9	0.12
No	1,609	6.8		9.5		11.3	12.3	
Risk group (TIMI II [ref. 16])								
Low risk	1,113	5.4	0.20	8.3	0.40	9.9	10.0	0.53
Not low risk	2,226	6.6		9.1		10.9	11.5	
History before index MI								
Hypertension								
Yes	1,279	7.3	0.05	10.6	0.007	12.4	13.0	0.01
No	2,059	5.5		7.8		9.5	10.3	
Angina								
Yes	1,798	7.8	< 0.001	10.2	0.003	11.9	12.5	0.01
No	1,539	4.3		7.3		9.0	9.9	
Previous MI								
Yes	468	9.3	0.005	11.7	0.02	13.8	14.2	0.03
No	2,871	5.7		8.4		10.1	10.8	
Diabetes								
Yes	439	7.0	0.47	9.7	0.55	12.5	12.9	0.27
No	2,899	6.1		8.7		10.3	11.1	
CHF								
Yes	92	8.4	0.45	12.3	0.31	15.2	15.2	0.27
No	3,246	6.1		8.8		10.5	11.2	
Ever smoker								
Yes	2,565	5.6	0.007	8.4	0.07	10.0	10.6	0.03
No	768	8.3		10.5		12.6	13.7	
Current smoker								
Yes	1,640	4.2	< 0.001	7.4	0.002	9.0	9.7	0.003
No	1,693	8.1		10.3		12.1	12.9	
SBP <100 mm Hg								
Yes	187	5.4	0.64	7.3	0.47	10.0	11.0	0.82
No	3,152	6.2		8.9		10.6	11.3	
Heart rate >80 beats/min								
Yes	1,122	5.3	0.13	7.7	0.09	9.6	10.1	0.17
No	2,216	6.6		9.5		11.0	11.8	
Invasive strategy*	1,500							
No. of pts with events	157							
Infarct-related artery								
Occluded	225	5.4	0.62	6.3	0.27	6.9	7.4	0.10
Patent	1,272	6.3		8.8		10.9	11.7	
Multivessel CAD								
Yes	473	9.0	0.002	11.7	0.002	13.2	14.3	0.007
No	976	4.8		6.8		8.8	9.5	
Ejection fraction								
<40%	310	7.3	0.54	9.7	0.52	11.9	14.3	0.21
≥40%	1,007	6.2		8.4		10.2	10.7	

*Protocol catheterization performed. CAD = coronary artery disease; CHF = congestive heart failure; MI = myocardial infarction; Pts (pts) = patients; ref. = reference; SBP = systolic blood pressure; TIMI = Thrombolysis in Myocardial Infarction.

25 months was 9.4%, comparable to a rate of 10.8% within 2 years in TIMI II.

The incidence of reinfarction in TIMI II also appears to be similar to that observed in other thrombolytic trials. Nonfatal reinfarction occurred in 2.5% of hospital survivors in GISSI-2 at 6 months (30) and in 4.2% of TAMI 1 patients at 1 year (31),

JACC Vol. 26, No. 4
October 1995:900–7

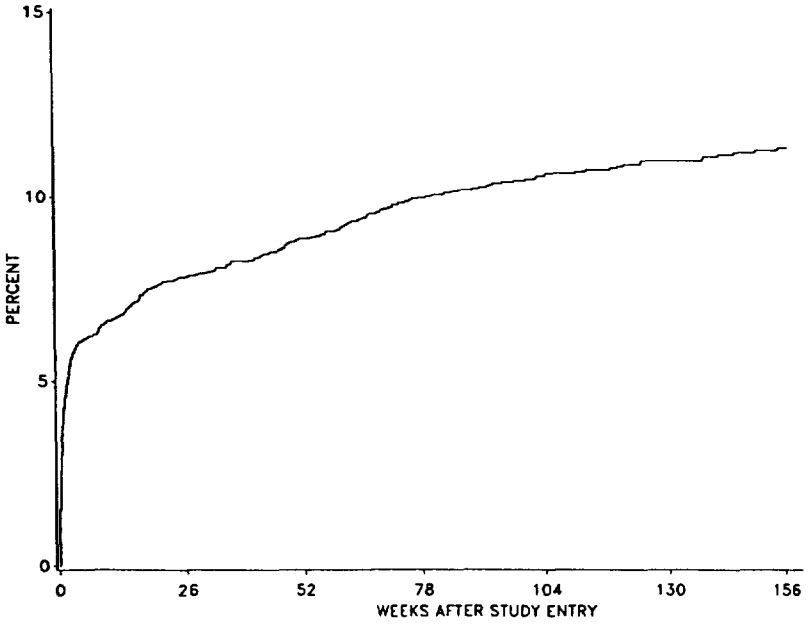

Figure 1. Three-year cumulative rate of nonfatal reinfarction.

similar to the rates in TIMI II, 2.7% between 2 weeks and 6 months and 3.7% between 2 weeks and 1 year. The 2-year follow-up of hospital survivors of patients in the pooled TAMI studies revealed a 5.1% incidence of nonfatal reinfarction (32) compared with the rate of 5.5% in TIMI II between 2 weeks and 2 years. In TIMI II, most of the nonfatal infarctions occurred in the first several weeks after study entry, and the rate then declined markedly (Fig. 1), a pattern that has been observed for a variety of complications occurring after myocardial infarction (19,31–33).

Nonfatal infarction as an independent risk factor. There is considerable information from the prethrombolytic era that recurrent nonfatal myocardial infarction is a risk factor for subsequent mortality. Benhorin et al. (14) reported that nonfatal reinfarction was a significant independent risk factor for subsequent cardiac mortality with a relative risk of 3.0 in patients assigned to the placebo arm of the Multicenter Diltiazem Postinfarction Trial. Indeed, they found that the excess risk contributed by nonfatal reinfarction was greater than that contributed by pulmonary congestion and a de-

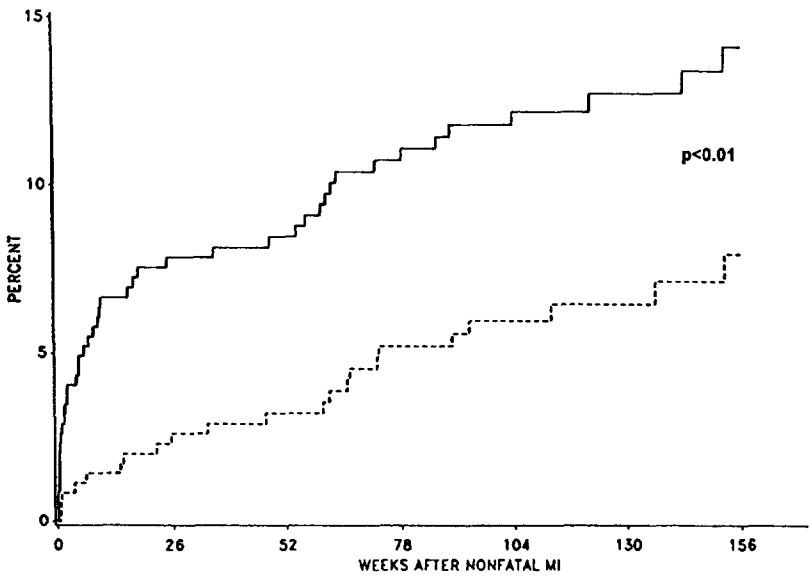

Figure 2. Three-year cumulative rate of death in patients after nonfatal reinfarction (**solid line**) compared with that of a matched control group (**dashed line**). MI = myocardial infarction.

Table 2. Risk Ratios for Death Within 3 Years

Variable	Risk Ratio	99% Confidence Interval
Nonfatal reinfarction		
Within 42 d*†	1.89	1.11–3.23
43 d–1 yr‡	6.22	3.00–12.88
366 d–3 yr	2.90	0.63–13.35
Age ≥65 yr	2.21	1.65–2.98
Not low risk group (TIMI II [ref. 16])	2.00	1.30–3.07
Heart rate >80 beats/min	1.93	1.45–2.57
Hypotension (SBP <100 mm Hg)	1.82	1.15–2.88
MI before index event	1.81	1.30–2.53
Diabetes	1.77	1.26–2.47
Female gender	1.41	1.02–1.95

*$p < 0.001$ versus 43 days (d) to 1 year. †$p = 0.49$. ‡$p = 0.24$ versus 366 days to 3 years. Other abbreviations as in Table 1.

pressed ejection fraction (14). Similarly, Kornowski et al. (34) found reinfarction to be the most powerful predictor of long-term total mortality in the Secondary Prevention Reinfarction Israel Trial (SPRINT) Registry (34), with an adjusted relative risk of 4.7. In the SAVE trial (35), the relative risk of subsequent mortality for patients with nonfatal recurrent myocardial infarction was 3.6.

The present analysis shows that nonfatal reinfarction also has an adverse effect on survival in patients who have received thrombolytic therapy. Nonfatal reinfarction had the greatest prognostic impact within the first year of follow-up, in particular after hospital discharge. The risk ratio for death within the initial 42 days after the index event was 1.9 compared with 6.2 ($p < 0.001$) between 43 days and 1 year. This finding can be considered supportive of the observation that reinfarction early after thrombolysis frequently represents reocclusion of the infarct-related artery and thus completion of an interrupted infarction (36,37), whereas later occurring reinfarction is considered to represent more often progression of coronary artery disease. Myocardial damage caused by completion of an interrupted infarction is likely to be less severe than myocardial damage caused by a new infarction potentially distant from the index event. The risk ratio for death after a nonfatal reinfarction of 1.9 within the initial 42 days of follow-up was comparable to those of baseline variables well known to have an adverse effect on outcome, such as advanced age, diabetes and female gender, as well as of events occurring in the course of the index myocardial infarction, such as heart rate >80 beats/min and hypotension (24).

The adverse prognostic impact of nonfatal reinfarction emphasizes the importance of identifying patients at risk for this event. Prediction of reinfarction (fatal and nonfatal combined) has been difficult in the past (15,24,36–39). In GISSI-2, a history of angina or myocardial infarction before the index infarction and ineligibility for exercise testing as well as the presence of angina at follow-up were predictors of reinfarction (30). In the present analysis of TIMI II, characteristics suggesting the presence of extensive coronary artery disease, such as advanced age, history of angina, hypertension or myocardial infarction before the index infarction, as well as multivessel disease at coronary angiography after the infarction, were

Table 3. Death Life-Table Rate by Specified Baseline Characteristics in Patients With Nonfatal Reinfarction

	No. of Pts	6 wk (%)	1 yr (%)	2 yr (%)	3 yr (%)	p Value
All pts	349					
Pts with events	43	5.2	8.5	12.2	14.1	—
Gender						
Male	283	5.0	8.7	12.1	14.6	0.88
Female	66	6.1	7.7	12.4	12.4	
Age						
≥65 yr	100	14.1	18.2	27.2	29.1	< 0.001
<65 yr	249	1.6	4.5	6.0	7.9	
Anterior MI						
Yes	164	6.7	12.3	15.8	18.5	0.03
No	185	3.8	4.9	8.9	10.2	
Risk group (TIMI II [ref. 16])						
Low risk	115	1.8	1.8	6.0	8.3	0.015
Not low risk	234	6.9	11.7	15.2	17.0	
History before index MI						
Hypertension						
Yes	153	5.2	8.5	13.6	13.6	0.85
No	196	5.2	8.4	10.9	14.6	
Angina						
Yes	209	4.4	8.8	12.6	14.5	0.80
No	140	6.5	8.0	11.7	13.4	
Previous MI						
Yes	60	6.8	17.0	20.8	20.8	0.05
No	289	4.9	6.7	10.3	12.7	
Diabetes						
Yes	50	6.0	14.1	21.1	21.1	0.09
No	299	5.1	7.5	10.6	13.0	
CHF						
Yes	12	0.0	25.0	41.7	51.4	< 0.001
No	337	5.4	7.9	11.0	12.5	
Ever smoker						
Yes	254	5.2	8.8	12.6	15.3	0.54
No	95	5.3	7.5	11.1	11.1	
Current smoker						
Yes	147	4.1	7.6	11.7	14.8	0.98
No	202	6.0	9.1	12.5	13.7	
SBP <100 mm Hg						
Yes	17	5.9	11.8	11.8	22.8	0.49
No	332	5.2	8.3	12.1	13.6	
Heart rate >80 beats/min						
Yes	103	7.8	12.8	16.0	17.8	0.13
No	245	4.1	6.7	10.6	12.5	
Invasive strategy*	157					
Pts with events	21					
Infarct-related artery						
Occluded	16	6.3	12.5	12.5	12.5	0.91
Patent	141	4.3	7.2	12.9	16.0	
Multivessel CAD						
Yes	63	4.8	11.3	16.7	20.2	
No	88	4.6	5.7	9.6	11.6	0.21
Ejection fraction						
<40%	39	5.2	13.2	19.2	29.5	0.03
≥40%	104	3.8	5.8	10.2	10.2	

*Protocol catheterization performed. Abbreviations as in Table 1.

univariate predictors of nonfatal reinfarction (Table 1). The only independent predictors of nonfatal reinfarction were history of angina and not being a smoker at the time of the index infarction. These univariate and independent predictors were strongest for nonfatal reinfarctions that occurred within 6 weeks after the index infarction, when >50% of the events were observed (19,31,32). Not being a current smoker has earlier been reported to be a risk factor for fatal and nonfatal reinfarction combined and to be a risk factor for death in patients with a myocardial infarction who received thrombolytic therapy (24,40). In contrast, before the thrombolytic era, cigarette smoking was an established risk factor for myocardial infarction and reinfarction (41), and continuation of smoking worsened (42), whereas discontinuation of smoking improved, long-term outcome (43). These apparently contradictory findings are difficult to explain. The fact that smokers experience their infarction and recurrent infarction at a younger age and present with a more favorable risk profile compared with not current smokers may, in part, explain the "better" outcome in current smokers (24,40).

It has been observed in both the prethrombolytic and thrombolytic eras that left ventricular failure (7,19,31,36,44,45) and advanced age (19,36,45) are the most powerful predictors of death after myocardial infarction. In the present analysis, advanced age and left ventricular dysfunction were predictors of death subsequent to nonfatal reinfarction as well, but age ≥65 years was the only independent predictor.

Conclusions. Nonfatal reinfarction is an end point that can be documented relatively easily and reliably. The present analysis of a 3-year follow-up of patients enrolled in the TIMI II trial demonstrates that the rate of nonfatal reinfarction is highest within the early period after the index infarction and that nonfatal reinfarction is a strong and independent predictor of fatal outcome, in particular within the first year of follow-up. Therefore, in patients who receive thrombolytic therapy after acute myocardial infarction, nonfatal reinfarction represents a powerful and useful component of a combined end point.

We thank Yolanda Vasquez for assistance in preparation of the manuscript.

References

1. Kennedy JW, Ritchie JL, David KB, Stadium ML, Maynard C, Fritz JK. The Western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. N Engl J Med 1985;312:1073–8.
2. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarcto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–402.
3. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;2:349–60.
4. Wilcox RG, Olsson CG, Skene AM, von der Lippe G, Jensen G, Hampton JR, for the ASSET Study Group. Trial of tissue plasminogen activator for mortality reduction in acute myocardial infarction: Anglo-Scandinavian Study of Early Thrombolysis (ASSET). Lancet 1988;2:525–30.
5. ISIS-3 (Third International Study of Infarct Survival) Collaborative Group. A randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1992;339:753–70.
6. The International Study Group. In-hospital mortality and clinical course of 20,891 patients with suspected acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. Lancet 1990; 336:71–5.
7. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82.
8. ISIS-4. A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. Lancet 1995;345:669–85.
9. GISSI-3. Effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarcto Miocardico. Lancet 1994;343:1115–22.
10. Braunwald E, Cannon CP, McCabe CH. An approach to evaluating thrombolytic therapy in acute myocardial infarction: the "unsatisfactory outcome" end point. Circulation 1992;86:683–7.
11. Califf RM, Harrelson-Woodlief L, Topol EJ. Left ventricular ejection fraction may not be useful as an end point of thrombolytic therapy comparative trials. Circulation 1990;82:1847–53.
12. Dwyer EM, McMaster P, Greenberg H, and the Multicenter Postinfarction Research Group. Nonfatal cardiac events and recurrent infarction in the year after acute myocardial infarction. J Am Coll Cardiol 1984;4:695–702.
13. Gilpin E, Ricou F, Dittrich H, Nicod P, Henning H, Ross J. Factors associated with recurrent myocardial infarction within one year after acute myocardial infarction. Am Heart J 1991;121:457–65.
14. Benhorin J, Moss AJ, Oakes D, and the Multicenter Diltiazem Postinfarction Trial Research Group. Prognostic significance of nonfatal myocardial reinfarction. J Am Coll Cardiol 1990;15:253–8.
15. Norris RM, Barnaby PF, Brandt PWT, et al. Prognosis after recovery from first acute myocardial infarction: determinants of reinfarction and sudden death. Am J Cardiol 1984;53:408–13.
16. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) phase II trial. N Engl J Med 1989;320:618–27.
17. The TIMI Research Group. Immediate versus delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction. JAMA 1988;260:2849–58.
18. Roberts R, Rogers WJ, Mueller HS, et al., and the TIMI Investigators. Immediate versus deferred β-blockade following thrombolytic therapy in patients with acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) II-B study. Circulation 1991;83:422–37.
19. Terrin ML, Williams DO, Kleiman NS, et al., for the TIMI II Investigators. Two- and three-year results of the Thrombolysis In Myocardial Infarction (TIMI) phase II clinical trial. J Am Coll Cardiol 1993;22:1763–72.
20. Kaplan KL, Meier P. Nonparametric estimation from incomplete observations. J Am Statist Assoc 1958;53:457–81.
21. SAS Institute, Inc. SAS/STAT Users Guide: Statistics, version 6, vol. 2. 4th ed. Cary (NC): SAS Institute, Inc., 1990:1027–70.
22. Cox DR. Regression models and life tables (with discussion). J R Statist Soc B 1972;34:187–220.
23. SAS Institute, Inc. SAS Technical Report P-229, SAS/STAT Software: changes and enhancements, release 6.07. Cary (NC): SAS Institute, Inc., 1992:468–74.
24. Mueller HS, Cohen LS, Braunwald E, et al, for the TIMI Investigators. 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. Circulation 1992;85: 1254–64.
25. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto Miocardico. GISSI-2: a factorial randomized trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Lancet 1990;336:65–71.
26. The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non Q-wave myocardial infarction: results of the TIMI IIIB trial. Circulation 1994;89:1545–56.
27. Califf RM, Topol EJ, George BS, et al., and the TAMI Study Group.

One-year outcome after therapy with tissue plasminogen activator: report from the Thrombolysis and Angioplasty in Myocardial Infarction trial. Am Heart J 1990;119:777–85.

28. Cannon CP, McCabe CH, Henry TD, et al., for the TIMI 5 Investigators. A pilot trial of recombinant desulfatohirudin compared to heparin in conjunction with tissue plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis In Myocardial Infarction (TIMI) 5 trial. J Am Coll Cardiol 1994;23:993–1003.
29. Grines CL, Browne KF, Marco J, et al., for the Primary Angioplasty in Myocardial Infarction Study Group. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1993;328:673–9.
30. GISSI-2 Investigators, ANMCO and M. Negri Institute, Italy. Predictors of nonfatal reinfarction in survivors of myocardial infarction after thrombolysis: results from the GISSI-2 data base. J Am Coll Cardiol 1994;24:608–15.
31. Califf RM, Topol EJ, George BS, et al., and the TAMI Study Group. One-year outcome after therapy with tissue plasminogen activator: report from the Thrombolysis and Angioplasty in Myocardial Infarction trial. Am Heart J 1990;119:777–85.
32. Muller DW, Topol EJ, George BS, et al., and the Thrombolysis and Angioplasty Study Group. Two-year outcome after angiographically documented myocardial reperfusion for acute coronary occlusion. Am J Cardiol 1990;66:796–801.
33. Wilcox RG, von der Lippe G, Olsson CG, Jensen G, Skene AM, Hampton JR. Effects of alteplase in acute myocardial infarction: 6-month results from the ASSET study. Lancet 1990;335:1175–8.
34. Kornowski R, Goldbourt U, Zion M, et al., and the SPRINT Study Group. Predictors and long-term prognostic significance of recurrent infarction in the year after a first myocardial infarction. Am J Cardiol 1993;72:883–8.
35. Pfeffer MA, Moye LA, Rutherford J, Braunwald E. More on Survival and Ventricular Enlargement trial [letter]. N Engl J Med 1993;329:1205–6.
36. Ellis SG, Topol EJ, George BS, et al. Recurrent ischemia without warning: analysis of risk factors for in-hospital ischemic events following successful thrombolysis with intravenous tissue plasminogen activator. Circulation 1989;80:1159–65.
37. Ohman EM, Califf RM, Topol EJ, et al. Consequences of reocclusion after successful reperfusion therapy in acute myocardial infarction. Circulation 1990;82:781–91.
38. Rogers WJ, Baim DS, Gore JM, et al. Comparison of immediate invasive, delayed invasive, and conservative strategies after tissue-type plasminogen activator. Results of the Thrombolysis in Myocardial Infarction (TIMI) Phase II-A trial. Circulation 1990;82:1457–76.
39. Reiner JS, Lundergan CF, van den Brand M, et al., for the GUSTO Angiographic Investigators. Early angiography cannot predict postthrombolytic coronary reocclusion: observations from the GUSTO Angiographic study. J Am Coll Cardiol 1994;24:1439–44.
40. Barbash GI, White HD, Modan M, et al., for the Investigators of the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: experience gleaned from the international tissue plasminogen activator/streptokinase mortality trial. Circulation 1993;87:53–8.
41. LaCroix AZ, Lang J, Scherr P, et al. Smoking and mortality among older men and women in three communities. N Engl J Med 1991;324:1619–25.
42. Norris RM, White HD, Cross DB, Wild CJ, Whitlock RML. Prognosis after recovery from myocardial infarction: the relative importance of cardiac dilatation and coronary stenoses. Eur Heart J 1992;13:1611–8.
43. Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. N Engl J Med 1985;313:1511–4.
44. GISSI-2 and International Study Group. Six-month survival in 20,891 patients with acute myocardial infarction randomized between alteplase and streptokinase with or without heparin. Eur Heart J 1992;13:1692–7.
45. Moss AJ, Benhorin J. Prognosis and management after a first myocardial infarction. N Engl J Med 1990;322:743–52.