Two-Year Outcome After Angiographically Documented Myocardial Reperfusion for Acute Coronary Occlusion

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Reperfusion therapy has been clearly shown to de-
crease the early mortality after acute myocardial
infarction, but the impact of this therapy on long-
term survival has been less extensively evaluated.
This study reports the extended follow-up of a
large cohort of 810 patients treated with intrave-
nous thrombolytic therapy combined, when consid-
ered necessary to maintain or augment infarct ves-
sel patency, with mechanical reperfusion therapies.
Each patient underwent coronary angiography
within 2 hours of the initiation of the thrombolytic
infusion. Coronary angioplasty was performed in
62% of the patients before hospital discharge and
21% underwent coronary artery bypass graft sur-
gery. Follow-up was obtained in 96% to a mean of
18.8 months (range, 1.5 to 48 months). All-cause
mortality over this period was 3.3%; 2.1% died
from cardiac causes. Nonfatal reinfarction occurred
in 5.1%. Although the low event rate limits the va-
lidity of statistical comparisons, the patients who
survived the follow-up period tended to be younger
(56 ± 10 vs 65 ± 7 years), to have better predis-
charge left ventricular function (left ventricular
ejection fraction, 52 ± 11 vs 46 ± 13%) and to
have a lower prevalence of multivessel coronary ar-
tery disease (45 vs 67%). This excellent long-term
survival may, in part, reflect the exclusion of high-
risk patients from enrollment in the Thrombolysis
and Angioplasty in Myocardial Infarction (TAMI)
studies. It may also be attributable, however, to the
frequent use of combined thrombolysis and me-
chanical revascularization in this population.
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During the past 2 decades, the in-hospital mortality rate from acute myocardial infarction has decreased progressively. This has been due, firstly, to the impact of cardiac monitoring and the rapid treatment of cardiac arrhythmias and, secondly, to the shift in emphasis from therapeutic strategies aiming to decrease myocardial work and oxygen demand to therapies that actively restore myocardial oxygen supply. Several randomized, controlled trials have reported 30-day mortality rates ranging from 5.0 to 10.7%[1-4] after reperfusion therapy. This compares with early fatality rates of 16% for hospitalized men and 28% for women in the Framingham Study,[5] a study performed before the widespread use of antiplatelet and β-adrenergic blocking therapy and before the use of thrombolytic therapy, direct coronary angioplasty and emergency coronary artery bypass graft surgery.

Since January 1985, the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group has evaluated myocardial reperfusion strategies using intravenous thrombolysis and adjunctive medical therapies combined, when considered appropriate, with coronary angioplasty. The impact of these strategies on left ventricular functional recovery and on in-hospital mortality,[6-11] and the 1-year outcome of the 386 patients in the first TAMI study[12] have been previously reported. This study examines the clinical outcome over a more extended follow-up period of the larger cohort of patients enrolled in the first 4 TAMI studies.

METHODS

Patient selection: Between January 1985 and March 1988, 810 patients were enrolled in 4 phases of the TAMI study. The study protocols were similar for each phase and have been previously published.[7-11] Patients were eligible for enrollment if they presented within 6 hours of the onset of chest pain and had ≥0.1 mV ST-segment elevation in ≥2 contiguous electrocardiographic leads or ST-segment depression in the precordial leads consistent with posterior wall infarction. Patients were ineligible if they had contraindications to thrombolytic therapy, were ≥76 years of age, had a history of prior coronary artery bypass graft surgery or Q-wave myocardial infarction in the same territory as the acute event or were in cardiogenic shock (defined as a systolic blood pressure <85 mm Hg that was unresponsive to the administration of intravenous fluids).

TABLE I Baseline Demographic and Angiographic Characteristics of the Hospital Survivors with Complete Follow-Up Data (n = 727)	
Sex (% men)	82
Age (yrs)	56 ± 10
Risk factors (%)	
Diabetes mellitus	14%
Systemic hypertension	40%
Hyperlipidemia	12%
Cigarette smoking	65%
Vascular disease	
Cerebral	2%
Peripheral	5%
Time to therapy	176 ± 66 min
Infarct-related artery	
Left anterior descending	39%
Right coronary artery	48%
Left circumflex	12%
Other	0.3%
Acute angiography	
Left ventricular ejection fraction	51 ± 11%
Multivessel disease	45%

TABLE II Predischarge Treatment of Hospital Survivors with Complete Follow-Up	
Thrombolytic agent	
Tissue plasminogen activator	69%
Urokinase	13%
Tissue plasminogen activator + urokinase	18%
Predischarge coronary angioplasty	
Acute	42%
Emergency	8%
Elective	25%
Predischarge coronary artery bypass surgery	
Emergency	6%
Urgent	6%
Elective	10%
Infarct vessel patency at discharge	
Patent (TIMI 2,3)	63%
Occluded (TIMI 0,1)	8%
Surgically bypassed	22%
Unknown	7%
TIMI = Thrombolysis in Myocardial Infarction trial.	

Treatment regimen: The thrombolytic agents used were recombinant tissue plasminogen activator (tPA) and urokinase, given alone or in combination.[7-10] In 1 phase, tPA was combined with intravenous prostacyclin.[11] All patients received oral aspirin and intravenous heparin for ≥4 days after admission and the majority received intravenous nitroglycerin and prophylactic intravenous lidocaine. Oral diltiazem and β-adrenergic blocking agents were given as clinically indicated for hypertension, arrhythmias or recurrent myocardial ischemia. Cardiac catheterization was performed within 90 minutes of the initiation of the thrombolytic therapy to document baseline global and regional left ventricular function and to determine the patency status of the infarct vessel. Rescue angioplasty was performed if the infarct vessel remained occluded (Thrombolysis in Myocardial Infarction [TIMI] flow grade 0 or 1). Patients with TIMI 2 or 3 flow in the infarct vessel and suitable anatomy were randomized in the first phase to either immediate or to deferred angioplasty of residual infarct vessel stenoses. In subsequent phases, angioplasty of the infarct vessel was performed acutely only if it remained occluded 90 minutes after the initiation of the thrombolytic therapy. Cardiac catheterization was repeated before hospital discharge to evaluate changes in global and regional left ventricular function and infarct vessel patency. Coronary angioplasty of residual stenoses in the infarct-related artery was performed at the time of the predischarge cardiac catheterization if submaximal exercise thallium testing showed evidence of reversible ischemia in the infarct territory and the coronary anatomy was deemed suitable for the procedure. Intercurrent coronary angiography was also performed for symptoms of recurrent myocardial ischemia or hemodynamic instability. Emergency coronary artery bypass graft surgery was performed for ongoing myocardial ischemia when the infarct vessel subserved a large myocardial territory and was either unsuitable for coronary angioplasty because of the presence of left

main (or equivalent) coronary artery disease or extreme tortuosity or if patency of the infarct vessel could not be achieved and maintained after intravenous thrombolytic therapy and balloon dilatation.[13] Urgent coronary artery graft surgery was performed for recurrent myocardial ischemia and elective surgery for provocable ischemia when the coronary anatomy precluded coronary angioplasty.

Follow-up: Regular follow-up was performed after hospital discharge by telephone and mailed questionnaire. The events recorded included death, nonfatal myocardial infarction, functional class (Canadian Heart Association Classification) and postdischarge coronary angioplasty or coronary artery bypass graft surgery. The timing and cause of death were determined when possible by examination of death certificates and reports of postmortem studies. Events leading to rehospitalization were determined by the study nurse during follow-up contact and by examination of hospital records.

Statistics: All values are quoted as mean ± 1 standard deviation unless otherwise stated. A Kaplan-Meier estimate was used to construct a curve of long-term out-of-hospital survival. Statistical comparisons of baseline characteristics and outcomes between groups were not made because of the low event rate and the observational nature of the data.

RESULTS

Patient characteristics: Baseline characteristics of the patients surviving to hospital discharge are listed in Table I. The use of thrombolytic therapy, predischarge coronary angioplasty and bypass graft surgery, and the patency status of the infarct-related artery are listed in Table II. Of the 810 patients, 757 were discharged from the hospital alive. Follow-up has been obtained on 727 (96%) of these to a mean of 18.8 months (25th, 75th percentiles; 13.3, 24.4 months). The age of the patients surviving to hospital discharge was 56 ± 10 years; 82% were men. Mean predischarge global left ventricular ejection fraction was 51%; 25% of the patients had an

TABLE III Baseline Characteristics of Patients Alive at Last Follow-Up Compared with Non-Survivors.

	Survivors (n = 703)	Non-Survivors (n = 24)
Sex (% men)	82	79
Age (yrs)	56 ± 10	65 ± 7
Infarct vessel status at discharge		
Coronary artery bypass graft	22%	20%
TIMI 2 or 3	63%	67%
TIMI 0 or 1	8%	0%
Unknown	7%	13%
No. of diseased vessels (acute catheterization)		
0 to 1	55%	33%
2 to 3	45%	67%
Predischarge left ventricular ejection fraction	52 ± 11%	46 ± 13%

TIMI = Thrombolysis in Myocardial Infarction trial.

ejection fraction <43%. The infarct vessel was patent at discharge or had been surgically bypassed in 85%, was occluded in 8% and its status was unknown in the remaining 7%.

During the follow-up period, 24 deaths occurred. Figure 1 shows the survival curve, projected to 2 years, of patients discharged from the hospital alive. The cause of out-of-hospital death was cardiac in 15 patients (2.1%) and noncardiac, predominantly due to disseminated malignancy, in 9 patients (1.2%). Nonfatal recurrent myocardial infarction occurred in 5.1%, coronary angioplasty was performed after hospital discharge in 7.4% and 5.4% underwent elective coronary artery bypass graft surgery (Figure 2). Comparison of the patients surviving the follow-up period with the non-survivors (Table III) shows that there was no apparent difference in sex distributions or infarct vessel patency status between the 2 groups. However, the non-survivors tended to be older, to have worse left ventricular function and more extensive coronary artery disease. Subgroup analysis of out-of-hospital events according to the patency status of the infarct-related artery is listed in Table IV. Surprisingly, no deaths were recorded in the group of 54 patients with non-patent infarct vessels. The mortality rate for patients with patent infarct vessels was 3% and for those with unknown patency status was 5%.

DISCUSSION

The principal finding of this study is that an aggressive strategy of early intravenous thrombolysis combined with mechanical revascularization for residual or
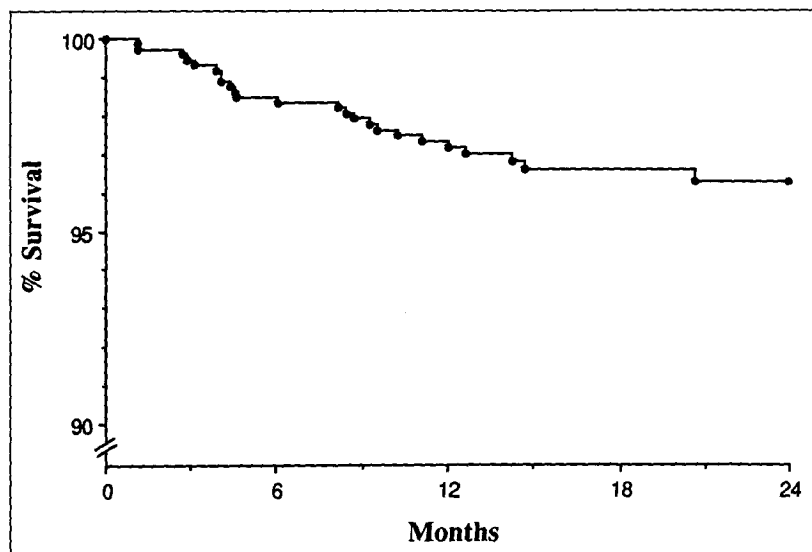

FIGURE 1. Kaplan-Meier survival curve for patients discharged from hospital alive (n = 757).
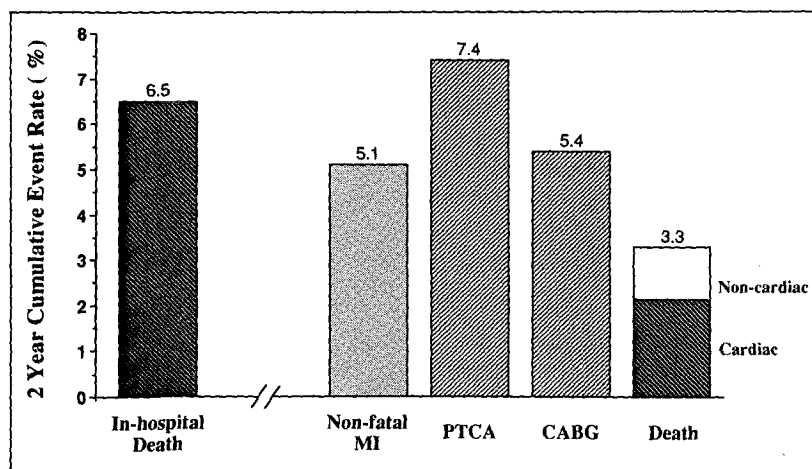

FIGURE 2. Bar graphs showing in-hospital mortality for total population (n = 810), and out-of-hospital mortality, nonfatal reinfarction rate and need for revascularization procedures during follow-up period in population of hospital survivors (n = 757). CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

TABLE IV Baseline Characteristics and Outcome According to Patency of Infarct-Related Artery (IRA) at Hospital Discharge

	Patent IRA (n = 610)	Non-Patent IRA (n = 58)	Unknown Status (n = 57)
Sex (% men)	83	84	68
Age (yrs)	56 ± 10	55 ± 9	54 ± 11
Left ventricular ejection fraction			
Acute (%)	51 ± 11	55 ± 10	49 ± 13
Day 7 (%)	52 ± 11	52 ± 10	51 ± 14
Infarct zone regional wall motion			
Acute (SD/chord)	−2.56 ± 1.07	−2.59 ± 1.00	−2.36 ± 1.21
Day 7 (SD/chord)	−2.12 ± 1.24	−2.69 ± 1.05	−2.02 ± 1.26
Events after discharge (%)			
Death	3	0	5
Nonfatal myocardial infarction	5	9	2
Coronary angioplasty	8	6	7
Coronary artery bypass surgery	5	13	4
Time to follow-up (months) (mean ± SD)	19 ± 8	20 ± 8	18 ± 7

SD = standard deviation.

recurrent myocardial ischemia was associated with excellent long-term survival and a low incidence of late recurrent ischemic events. A progressive decline in the incidence of death from coronary artery disease has been documented over the past 2 decades[5,14,15] and has been attributed to both the primary prevention of coronary artery disease and a decrease in periinfarction mortality.[14,15] Our results suggest that early reperfusion therapy has not only further decreased periinfarction mortality but has also substantially improved long-term postinfarction survival. The patients in this study do represent a relatively low-risk cohort since elderly patients, those in cardiogenic shock and patients presenting late after the onset of their symptoms were excluded from enrollment. Nonetheless, the out-of-hospital survival of this TAMI population compares favorably with that of similar cohorts of patients treated with less aggressive therapeutic regimens.

Mortality after thrombolysis: Two large, placebo-controlled thrombolytic trials have used conservative postlytic strategies. In the Gruppo Italiano per lo Studio della streptochinasi nell'infarto miocardico (GISSI) study,[16] streptokinase therapy was associated with a 10% decrease in cumulative 1-year mortality from 19.0 to 17.2% (p = 0.008). The decrease in mortality was particularly striking for patients treated within 1 hour of the onset of symptoms (12.9 vs 21.2%, p = 0.00001, relative risk = 0.6). A similar decrease in cumulative 2-year mortality was noted in each subgroup of the second International Study of Infarct Survival (ISIS-2),[2] from 19.0% in the control group to 13.5% in the group receiving streptokinase and aspirin. In both studies, the survival curve of the patients treated with thrombolytic therapy paralleled that of the respective control groups suggesting that the principal impact of thrombolytic therapy on survival occurred during the acute, hospital phase.

Combined pharmacologic and mechanical reperfusion therapy: In contrast to the above 2 trials in which predischarge coronary angioplasty or bypass graft surgery were rarely performed, the TAMI study protocol evaluated a strategy of intravenous thrombolysis, acute-phase coronary angiography and, in a large proportion of the patient population, urgent coronary angioplasty and/or coronary artery bypass surgery. Elective revascularization procedures were also performed in a relatively high proportion of the patients before hospital discharge. This strategy has the theoretical advantages of maximizing infarct vessel patency and the extent of myocardial salvage, of decreasing the likelihood of infarct vessel reocclusion and reinfarction, and of preserving function of the non-infarct zone in patients with multivessel disease. Using this intensive revascularization strategy, the out-of-hospital mortality in this study was only 3.3% at a mean follow-up of 18.8 months, with a cardiovascular mortality of 2.1%. The incidence of nonfatal reinfarction was 5.1% which is comparable to that of other studies.[16-18] Similar postlytic strategies were used by Stack[19] and Kander[20] and their colleagues. The 1-year survival was 94% in the former study and, in the latter, the 2-year survival was 93.6% and correlated with infarct vessel patency, left ventricular ejection fraction and the absence of prior myocardial infarction. Comparable 1-year survival rates have also been reported after direct coronary angioplasty.[21]

Three randomized trials have directly compared an "invasive" postlytic revascularization strategy with a more conservative approach.[22-24] Cumulative 1-year mortality was 6.9% in the invasive group of the TIMI 2B study compared with 7.5% in the conservative group.[22] It should be noted, however, that elective revascularization procedures were performed in a relatively high proportion of the conservative strategy group (37%) during the follow-up period. Low 90-day mortality rates have also been reported for both groups of the "Should We Intervene Following Thrombolysis?" trial (3.2 vs 4.8%).[23] Patients enrolled in this study were ≤70 years old, presented within 3 hours of the onset of symptoms of their first myocardial infarction and required 24 hours of clinical stability to be eligible for randomization. Thus, they also represent a low-risk population and any difference in long-term survival between the 2 postlytic strategies is likely to be small. In the European Cooperative Study,[24] 1-year mortality was actually

somewhat higher after tPA with immediate PTCA (9.6%) compared with thrombolysis alone (5.5%) but the difference did not reach statistical significance.

Surgical reperfusion: Perhaps the most direct method of rapidly achieving myocardial revascularization is by emergency coronary artery bypass graft surgery. A long-term study of surgical reperfusion therapy for acute myocardial infarction was recently reported by DeWood et al.[25] When compared with a similar group of patients treated with conventional medical therapy, the overall 13-year actuarial mortality rate was significantly decreased (27 vs 41%, p = 0.0007).

Mechanisms of improved survival after reperfusion therapy: Several mechanisms are likely to contribute to the improved survival after reperfusion therapy. Patency of the infarct-related artery has been associated with significant improvement in long-term survival even in the absence of an improvement in left ventricular function.[19,26-28] Possible explanations for this observation include a decreased incidence of left ventricular aneurysm formation independent of the extent of myocardial salvage,[29] greater electrical stability of the injured myocardium,[30,31] a decrease in left ventricular mural thrombus formation[32] and the provision of a conduit for later recruitment of a collateral vascular supply to the contralateral myocardium. Somewhat surprisingly, in this study there were no deaths during the follow-up period in the group of patients discharged from hospital with an occluded infarct vessel. In comparison, although they had significantly better regional infarct zone wall motion and an improvement rather than deterioration in global left ventricular function, the group with patent infarct-related arteries had a 3% mortality. The cause of this discrepancy is unclear. One final mechanism should be considered. It has been suggested[33] that the improved out-of-hospital survival in patients treated aggressively may be due to the accelerated and premature death of high-risk patients before hospital discharge. In this study, however, the overall in-hospital mortality was only 6.5% which is comparable to that of other large thrombolytic trials including those with conservative postthrombolysis protocols.

Study limitations: All long-term follow-up studies are limited by incomplete data collection and the possibility of underreporting of event rates during the follow-up period. The survival status of 30 patients of the original cohort discharged from hospital is unknown. Theoretically, therefore, the actual mortality rate could be as high as 7%. This problem is not unique to this study and the 96% follow-up obtained is comparable to that achieved in other large, multicenter studies. A second limitation is the absence of a control population that may have permitted more definite conclusions about the value of this therapeutic approach. Finally, conclusions drawn from this study cannot be applied to the large proportion of the myocardial infarction population excluded from eligibility from this trial because of advanced age, late presentation or contraindications to thrombolysis. Further systematic evaluation is required to better define optimal treatment strategies and the prognosis for long-term postinfarction survival of these important groups of patients.

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