

Relationship of the TIMI Myocardial Perfusion Grades, Flow Grades, Frame Count, and Percutaneous Coronary Intervention to Long-Term Outcomes After Thrombolytic Administration in Acute Myocardial Infarction

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Background—Although 90-minute TIMI flow grades (TFGs), corrected TIMI frame counts (CTFCs), and TIMI myocardial perfusion grades (TMPGs) have been associated with 30-day outcomes, we hypothesized that these indices would be related to long-term outcomes after thrombolytic administration.

Methods and Results—As a substudy of the TIMI 10B trial (tissue plasminogen activator versus tenecteplase), 49 centers carried out 2-year follow-up. TIMI grade 2/3 flow (Cox hazard ratio [HR] 0.41, $P=0.001$), reduced CTFCs (faster flow, $P=0.02$), and an open microvasculature (TMPG 2/3) (HR 0.51, $P=0.038$) were all associated with improved 2-year survival. Rescue percutaneous coronary intervention (PCI) of closed arteries (TFG 0/1) at 90 minutes was associated with reduced mortality ($P=0.03$), and mortality trended lower with adjunctive PCI of open (TFG 2/3) arteries ($P=0.11$). In a multivariate model correcting for previously identified correlates of mortality (age, sex, pulse, left anterior descending coronary artery infarction, and any PCI during initial hospitalization), patency (TFG 2/3) (HR 0.32, $P<0.001$), CTFC ($P=0.01$), and TMPG 2/3 remained associated with reduced mortality (HR 0.46, $P=0.02$).

Conclusions—Both improved epicardial flow (TFG 2/3 and low CTFCs) and tissue-level perfusion (TMPG 2/3) at 90 minutes after thrombolytic administration are independently associated with improved 2-year survival, suggesting complementary mechanisms of improved long-term survival. Although rescue PCI reduced long-term mortality, improved microvascular perfusion (TMPG 2/3) before PCI was also related to improved mortality independently of epicardial blood flow and the performance of rescue or adjunctive PCI. Further prospective trials are warranted to re-examine the benefit of early PCI with thrombolysis. (*Circulation*. 2002;105:1909-1913.)

Key Words: perfusion ■ blood flow ■ trials ■ myocardial infarction ■ thrombolysis

Excellent epicardial blood flow, as assessed by use of either the TIMI flow grades (TFGs)¹⁻⁶ or the corrected TIMI frame count (CTFC),^{7,8} and improved microvascular perfusion by use of the TIMI myocardial perfusion grade (TMPG)⁹ have been related to reduced in-hospital and 30-day mortality after administration of thrombolytics. The relationship of these 3 indices to long-term outcomes, however, has not been examined. Furthermore, the relationship of rescue/adjunctive PCI to long-term outcomes in the contemporary era of stenting and adjunctive glycoprotein (GP) IIb/IIIa inhibition is unknown. We hypothesized that both improved epicardial and improved myocardial perfusion would be related to lower long-term mortality and that the assessment of myocardial perfusion would add independent long-term prognostic information to the assessment of epicardial flow.

Methods

Follow-up data at 30 days were obtained in 98% of patients (865/882) in the TIMI 10B trial. A total of 49 centers enrolling 753 patients participated in this substudy and provided 2-year follow-up data in 583 patients (77.4%). TIMI 10B was a randomized comparison of tenecteplase (30, 40, and 50 mg) and 90-minute infusion of recombinant tissue plasminogen activator (Activase or alteplase).¹⁰ Angiography was performed at 90 minutes after administration of thrombolytic drugs.¹⁰ Nitroglycerin was administered every 15 minutes if the systolic blood pressure exceeded 110 mm Hg.¹⁰

Percutaneous coronary intervention (PCI) was performed at the discretion of the clinical investigator and was not mandated by protocol in TIMI 10B. Rescue PCI was defined as PCI performed within 150 minutes of initial thrombolytic treatment for patients with TFG 0 or 1 at 90 minutes ($n=120/150$, 80%). Adjunctive PCI was defined as PCI performed within 150 minutes of thrombolytic treatment for patients with TFG 2 or 3 at 90 minutes ($n=105/668$, 15.7%). Delayed PCI was defined as first PCI performed beyond 150 minutes after thrombolytic treatment ($n=235/593$, 39.6%). Patients

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TABLE 1. Baseline Characteristics and Long-Term Mortality

	Dead	Alive	P
Age, y	68.6±10.3 (n=69)	58.8±11.6 (n=779)	<0.0001
Male sex	69.6% (48/69)	76.7% (596/777)	0.18
Prior MI	23.2% (16/69)	14.6% (112/766)	0.06
History of diabetes	20.3% (14/69)	15.3% (118/771)	NS
History of hypertension	39.1% (27/69)	40.2% (308/766)	NS
Current smokers	27.5% (19/69)	48.9% (378/773)	0.001
LAD infarction	50.75% (34/67)	33.9% (260/766)	0.006
Pulse on admission, bpm	81.9±21.1 (n=68)	75.4±16.7 (n=775)	0.003
Systolic blood pressure on admission	135.9±22.8 (n=69)	134.1±22.0 (n=777)	NS
Time from symptom onset to treatment, h	4.06±2.48 (n=68)	3.45±2.21 (n=774)	0.03

LAD indicates left anterior descending coronary artery.

who experienced a recurrent myocardial infarction (MI) before PCI were analyzed as medically treated patients, because recurrent MI presumably led to their intervention (n=9).

Recurrent MI was defined as in previous TIMI trials, as follows.¹⁰ Within 18 hours of thrombolytic therapy, recurrent ischemic discomfort ≥30 minutes and new or recurrent ST-segment elevation ≥0.1 mV were required. After 18 hours, a criterion of re-elevation of creatine kinase (CK)-MB to above the upper limits of normal (ULN) and increased by ≥50% over the previous value was added. If quantitative CKMB was not available, it was required that the total CK be re-evaluated to more than twice the ULN and increased by ≥25% of ≥200 U/mL over the previous value; if re-elevated to less than twice normal, the CK was required to exceed the ULN by ≥50% and the previous value by 2-fold or ≥200 U/mL. After coronary angioplasty, the definition of recurrent infarction was new Q waves in ≥2 leads and re-elevation of the CKMB (or total CK if CKMB was not available) to at least twice normal and ≥50% above the previous value; after CABG, the latter criterion was set at a CKMB elevation ≥5 times normal.

Visual Assessment of Flow

All angiographic end points were prospectively assessed at 90 minutes. The TFG, as previously defined,¹ was assessed at the TIMI angiographic core laboratory by a single observer (C.M.G.), who was blinded to treatment assignment and clinical outcome. The CTFC was converted when necessary to be based on the most common filming speed in the United States of 30 frames per second.^{7,8} The TMPGs were assessed as previously defined.⁹ In brief, in TMPG 0, there is minimal or no myocardial blush; in TMPG 1, dye stains the myocardium and this stain persists on the next injection; in TMPG 2, dye enters the myocardium but washes out slowly so that dye is strongly persistent at the end of the injection; and in TMPG 3, there is normal entrance and exit of dye in the myocardium so that dye is mildly persistent at the end of the injection.

Statistical Analysis

Analyses were performed with Stata statistical software version 7.0.¹¹ Variables were compared by the Fisher's exact test or χ^2 test for categorical data. Student's *t* test or ANOVA was used for the analysis of normally distributed continuous variables. The nonparametric Wilcoxon rank sum test (for 2-way comparisons) or the Kruskal-Wallis test (for 3-way comparisons) was used to compare continuous variables when the data were not normally distributed or when data were imputed to an occluded vessel. The Cox hazard ratio (HR) model, Kaplan-Meier curves, and log-rank test were used in the survival analysis to test the equality of survival.

Results

Baseline Characteristics by Mortality

Table 1 shows the association between selected baseline characteristics and mortality by 2 years in the TIMI 10B

study. Expected high-risk clinical features were associated with mortality. Median duration of follow-up was 697 days (25th percentile 35, 75th percentile 820); however, for all analyses, data were censored at 730 days (2 years).

Relation of TIMI Flow Indices to Mortality

TFG 2/3 (Cox HR 0.41, *P*=0.001), reduced CTFCs (faster flow) (HR 0.92 per 10-frame decrease, *P*=0.02), and an open microcirculation (TMPG 2/3) (HR 0.51, *P*=0.038) on the 90-minute angiogram were all associated with improved 2-year mortality in univariate analyses (Table 2, Figures 1 and 2), although TFG 3 was not (HR 0.68, *P*=0.12). An open microvasculature was also associated with reduced rates of death/MI (HR 0.64, *P*=0.044), whereas other parameters were not related to the end point of death or MI (Table 3). In a multivariate model correcting for previously identified correlates of death (age, sex, pulse, left anterior descending coronary artery infarction, and any PCI during initial hospitalization), the 90-minute patency (TFG 2/3) (HR 0.32, *P*<0.001), CTFC (HR 0.90 per 10-frame decrease, *P*=0.01), and TMPG 2/3 remained associated with reduced mortality (HR 0.46, *P*=0.02).

TABLE 2. Angiographic Characteristics and Long-Term Mortality

	Mortality Rate	Hazard Ratio	P
TFG			
3	6.91% (34/492)	0.68*	0.12
2	4.91% (8/163)		
1	10.81% (4/37)		
0	15.63% (20/128)		
2/3	6.41% (42/655)	0.41	0.001
0/1	14.55% (24/165)		
CTFC (per 10-frame decrease)		0.92	0.02
CTFC <40 frames	6.99% (33/472)	0.67	0.10
CTFC ≥40 frames	9.91% (33/333)		
TMPG			
2/3	4.76% (12/252)	0.51	0.038
0/1	9.07% (46/507)		

*HR for TFG 3 vs TFG 0/1/2.

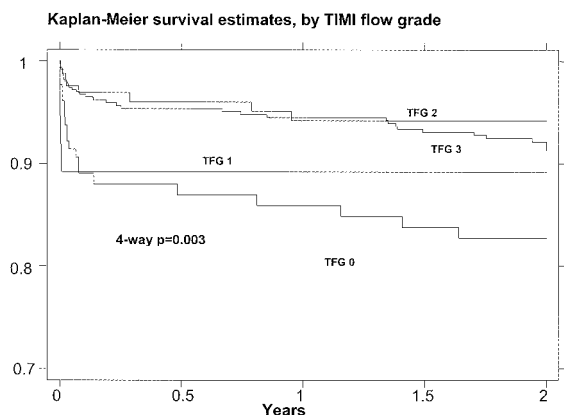


Figure 1. Kaplan-Meier survival curves for 2-year mortality by TFG at 90 minutes. Four-way log-rank $P=0.003$. Mortality trended lower in patients who had TFG 3 at 90-minute angiography (log-rank $P=0.11$).

Relation of PCI and Mortality

On univariate analysis, rescue PCI of closed arteries (TFG 0/1) was associated with improved mortality (log-rank $P=0.031$), whereas adjunctive PCI of open arteries (TFG 2/3) tended to be associated with lower long-term mortality ($P=0.11$), but delayed PCI did not ($P=0.36$) (Figures 3 and 4). The number of patients who received stents was not significantly different for patients who underwent delayed and adjunctive PCI (48% and 38%) but was higher for each of these than in patients who underwent rescue PCI (21%, $P<0.005$). After adjustment for use of stent ($P=NS$), rescue PCI remained associated with 2-year mortality in patients with closed arteries (HR 0.34, $P=0.03$), and a trend was seen for improved mortality in adjunctive (HR 0.31, $P=0.070$) and delayed (HR 0.49, $P=0.15$) PCI.

Discussion

The results presented here indicate that improved epicardial artery perfusion at 90 minutes after administration of thrombolytics is related to reduced long-term mortality by 2 years. Furthermore, independent of epicardial blood flow and the performance of PCI, improved microvascular perfusion as

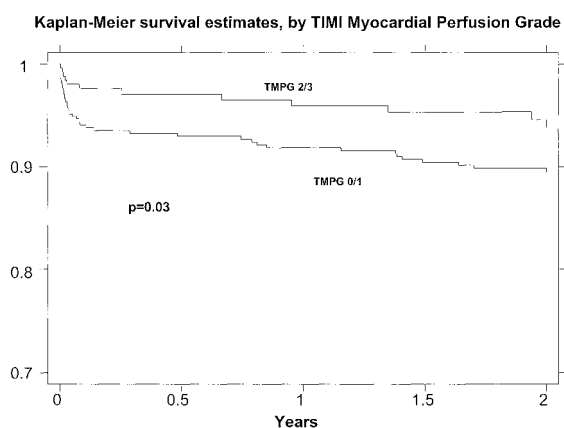


Figure 2. Kaplan-Meier survival curves for 2-year mortality by TMPG at 90 minutes. Mortality was lower in patients who had an open microvasculature (TMPG 2/3) at 90-minute angiography (log-rank $P=0.03$).

TABLE 3. Angiographic Characteristics and Long-Term Mortality/Recurrent MI

	Death/MI Rate	Hazard Ratio	P
TFG			
3	13.91% (68/489)	0.86*	0.44
2	13.04% (21/161)		
1	16.22% (6/37)		
0	18.25% (23/126)		
2/3	13.69% (89/650)	0.74	0.173
0/1	17.79% (29/163)		
CTFC (per 10-frame decrease)		0.97	0.216
CTFC <40 frames	13.86% (65/469)	0.82	0.296
CTFC ≥40 frames	15.81% (52/329)		
TMPG			
2/3	10.71% (27/252)	0.64	0.044
0/1	16.20% (81/500)		

*HR for TFG 3 vs TFG 0/1/2.

assessed by use of the TMPG is also related to reduced long-term mortality at 2 years. Thus, the TMPG adds additional long-term prognostic information to the conventional epicardial TFG and CTFC, again emphasizing that “not all TIMI grade 3 flow is created equally.” To optimize outcomes, both epicardial and microvascular perfusion must be restored to normal. Because all 3 of these angiographic methods can be assessed by visual inspection of the angiogram, without the use of sophisticated equipment, each of these methods could be conveniently and broadly applied in clinical practice as a means of risk stratification of long-term survival on the basis of early angiography.

Long-Term Mortality Benefits of Rescue and Adjunctive PCI

As an adjunct to thrombolysis, PCI might improve flow, relieve residual stenoses, and reduce reocclusion. Despite these intuitive angiographic benefits, early randomized trials of adjunctive PCI in open vessels¹²⁻¹⁴ and nonrandomized trials of rescue PCI in closed vessels¹⁵⁻¹⁷ did not show a clinical benefit of angioplasty routinely performed immediately after thrombolysis over thrombolysis alone, probably because of a higher risk of intramural hemorrhage in the arterial wall and abrupt closure.¹²⁻¹⁷ These trials are now outdated, because they preceded the widespread use of stents, aspirin, ticlopidine/clopidogrel, GP IIB/IIIA inhibitors, and the monitoring of activated clotting times. The recent Primary Angioplasty Alteplase Compatibility Trial (PACT) incorporated these current practice patterns and demonstrated that the 2 strategies (half dose of tissue plasminogen activator plus intervention) can be combined without increased risk of adverse outcomes over intervention alone.¹⁸ Schweiger et al¹⁹ also recently showed that in the TIMI 10B and 14 trials, which incorporated current practice patterns, patients with TFG 0 or 1 who underwent rescue PCI had lower 30-day mortality than those treated without PCI (6% versus 17%, $P=0.01$). The 30-day mortality of adjunctive PCI patients (3%) was similar to that of patients undergoing delayed PCI.¹⁹

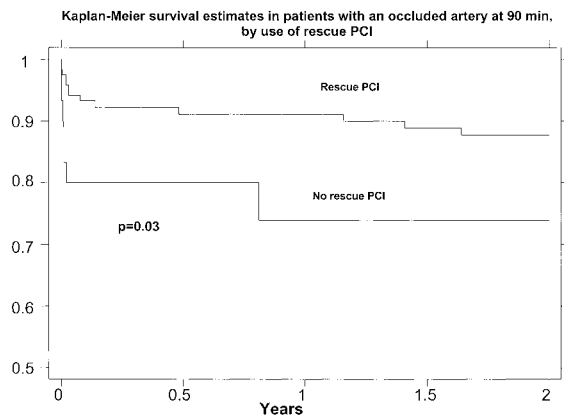


Figure 3. Kaplan-Meier survival curves for 2-year mortality by use of rescue PCI in patients with TFG 0/1 at 90 minutes. Mortality was lower in patients who underwent rescue PCI after 90-minute angiography (log-rank $P=0.03$).

Although previous studies of rescue/adjunctive PCI reported in-hospital or 30-day mortality,^{12–19} the long-term follow-up reported here indicates that in the era of stenting, GP IIb/IIIa inhibition, and newer antiplatelet agents, patients undergoing rescue PCI for a closed vessel (TFG 0/1) have improved 2-year mortality compared with those not treated with a mechanical intervention. Only 3.1% of patients (18/583) were treated with a GP IIb/IIIa inhibitor, and none of these patients died. The favorable outcomes among patients treated with either adjunctive or rescue PCI may obscure differences in clinical outcomes among pharmacological regimens.

The TMPG was related to 2-year mortality independently of whether the patient underwent PCI. Recently, Stone et al²⁰ also reported that myocardial blush provides in-hospital prognostic information in those patients undergoing either primary or rescue PCI. Even among patients with epicardial TFG 3 at the completion of the PCI, there was a significant gradient in in-hospital mortality, depending on the myocardial blush grade in the study by Stone et al.²⁰ Our data now extend these initial observations to show the complementary benefit of complete epicardial flow and myocardial perfusion

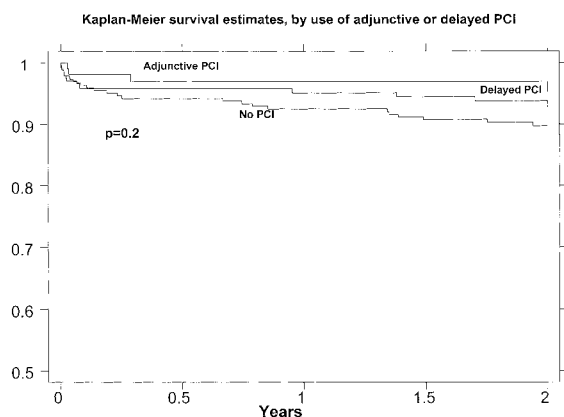


Figure 4. Kaplan-Meier survival curves for 2-year mortality by use of adjunctive and delayed PCI. Mortality trended lower in patients who underwent adjunctive and delayed PCI after 90-minute angiography (log-rank $P=0.2$).

on long-term survival. Taken together, these angiographic data add to a growing body of literature linking impaired tissue-level perfusion on echocardiography or electrocardiography to adverse clinical outcomes in the acute MI setting.^{21–26}

Limitations

The reproducibility of the TMPG remains to be determined. Although 90-minute myocardial perfusion and epicardial coronary blood flow are both related to mortality, there are other causes of death that may be unrelated to 90-minute perfusion, such as intracranial hemorrhage, reinfarction, ventricular arrhythmias, and mechanical complications. Although rescue PCI was related to long-term outcomes, the impact of measured and unmeasured confounders may not have been adequately controlled for.

Conclusions

Three simple, readily available angiographic methods to assess angiographic outcomes are all related to long-term mortality at 2 years. After administration of thrombolytics in patients with acute MI, impaired perfusion of the myocardium on coronary arteriography as assessed by the TMPG is related to a higher risk of mortality that is independent of flow in the epicardial artery. The use of the TMPG permits risk stratification, even among patients with TFG 3 and among those undergoing PCI. Randomized trials are warranted to re-examine the benefit of early PCI with thrombolysis.

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