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Relationship Between Corrected TIMI Frame Counts at Three Weeks and Late Survival After Myocardial Infarction

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OBJECTIVES To evaluate the corrected Thrombolysis in Myocardial Infarction (TIMI) frame count (CTFC) as a predictor of late survival after myocardial infarction.

BACKGROUND Thrombolysis in Myocardial Infarction flow grades predict late survival after myocardial infarction. The CTFC provides a more reproducible measurement of infarct-related artery blood flow than the TIMI flow grade, and has been linked to 30-day outcomes, but it has not yet been established how the CTFC correlates with late survival.

METHODS Of 1,001 patients with acute myocardial infarction presenting within 4 h of symptom onset, 882 underwent angiography at approximately three weeks. Infarct artery flow was assessed, blinded to clinical outcomes, according to the CTFC and TIMI flow grade. Late cardiac mortality and survival were determined in 97.5% of patients.

RESULTS The mean CTFC was 40 ± 29 in 644 patent infarct arteries (median, 34 [interquartile range, 24 to 47]). The CTFC, assessed as a continuous univariate variable, was found to be a predictor of five-year survival, as was the TIMI flow grade (both $p < 0.001$). On multivariate analysis, factors associated with five-year survival included the ejection fraction or end-systolic volume index (both $p < 0.001$), exercise duration ($p = 0.005$), age ($p = 0.008$), diabetes ($p = 0.02$) and CTFC ($p = 0.02$) or TIMI flow ($p = 0.02$). The same factors, except for the CTFC and TIMI flow grade, were predictors of 10-year survival.

CONCLUSIONS The CTFC three weeks after myocardial infarction was an independent predictor of five-year survival, but not 10-year survival. Although the CTFC provided additional prognostic information within TIMI flow grades, its superiority was not demonstrated. (J Am Coll Cardiol 2000;35:1516–24) © 2000 by the American College of Cardiology

Administration of thrombolytic therapy increases reperfusion, preserves left ventricular function and increases survival (1–5). Differences in infarct-related artery blood flow, assessed by Thrombolysis in Myocardial Infarction (TIMI) flow grading (6) at 90 min, correlated with 30-day mortality in the Global Use of Strategies to Open Occluded Arteries (GUSTO-I) trial (2), and may provide a conceptual basis for determining the relative efficacy of reperfusion therapies for testing in large clinical trials (7,8).

However, the reproducibility of TIMI flow assessments, particularly TIMI grade 2 (incomplete reperfusion), has been questioned (9). The corrected TIMI frame count (CTFC) is more reproducible than TIMI flow grading (9). This technique counts the number of cineangiographic frames from initial contrast opacification of the proximal coronary artery to opacification of distal arterial landmarks, and corrects for the length of the left anterior descending artery and saphenous vein grafts (9,10).

The mean CTFC in the arteries of patients without infarction is 21 (SD 3) (9,10). Among patients with TIMI grade 3 flow in the infarct-related artery (i.e., similar flow to nonculprit arteries), only 50% to 60% have a CTFC of ≤27, and 10% to 20% have a CTFCs of ≥40, as assessed in core laboratories (9–11). Lower CTFCs at 90 min and four weeks after the administration of thrombolytic therapy has been shown to correlate with better ventricular function (9,11,12), but to our knowledge, there are no data relating the CTFC to late survival.

In this study, we determined the value of the CTFC and TIMI flow grade, assessed at three weeks after myocardial infarction, as predictors of late survival.

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Abbreviations and Acronyms

CASS = Coronary Artery Surgery Study
CTFC = corrected TIMI frame count
GISSI = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries
HEAP = Heparin in Early Patency
IQR = interquartile range
TIMI = Thrombolysis in Myocardial Infarction

METHODS

Patient population. Patients enrolled in three randomized controlled trials (4,13,14) of thrombolytic and adjunctive therapies for acute myocardial infarction were scheduled to have angiography at three weeks. Patients were eligible if they presented ≤4 h after the onset of ≥30 min of chest pain with ≥1 mm of ST-segment elevation in two contiguous electrocardiographic leads or ≥2 mm in two of leads V_1 to V_3 (15). The patients were aged ≤70 years in two trials (4,13) and ≤75 years in the third; the exclusion criteria were as described previously (4,13–16). The trials were approved by the local ethics committees and written informed consent was obtained from all patients.

Treatment regimen. Details of the thrombolytic regimens have been reported previously (4,13,14). In brief, 135 patients received recombinant tissue plasminogen activator (10-mg bolus followed by 50 mg over 1 h and 40 mg over the next 2 h); 754 patients received intravenous streptokinase (1.5 mU over 30 to 60 min); and 112 received a matching placebo infusion. The intravenous heparin and antiplatelet regimens used have been described previously (4,13,14).

In all three studies, treatment with oral beta-adrenergic blocking agents was commenced on days 2 to 3 in patients without contraindications and, in the first study, intravenous propranolol was recommended. In the third study, patients were randomized to receive captopril or a matching placebo 2 h after commencing streptokinase therapy. Other medications such as calcium-channel blockers and nitrates were prescribed only for postinfarction angina. All patients were advised to stop smoking, lose weight, exercise regularly and consume a low-fat diet.

Cardiac catheterization. In the absence of medically uncontrolled ischemia, angiography was performed three weeks after infarction so as to minimize the confounding effects of myocardial stunning (16) on ventricular volumes and the ejection fraction (4,13,14). All patients received sublingual nitrate before the procedure. Core laboratory assessment (17) of infarct artery flow, blinded to treatment and clinical outcome, was performed according to TIMI flow grading (6) and the CTFC (9). The reproducibility of the CTFC in our laboratory has been reported previously (12). We prospectively determined CTFC cutpoints at 21, 15 and 27 (normal ± 2 SDs) and 40 ("quantitative" TIMI grade 3) (18). Coronary artery stenoses and the number of diseased vessels were determined according to the Coronary Artery Surgery Study (CASS) criteria (19).

Follow-up. Patients underwent exercise testing using the Bruce protocol at three weeks. Patients were reviewed every three months for one year in the first two studies (4,13,14). Late follow-up was performed either by recall to the clinic or by telephone or mail contact with the patient or family physician. End points were verified by source documentation. Deaths were classified as cardiac or noncardiac (20). Reinfarction was defined as two of the following: prolonged ischemic chest pain, an elevation in creatine kinase concentration to more than two times normal or development of new Q-waves on the electrocardiogram. Revascularization was performed for severe angina not controlled by medical therapy or ≥50% left mainstem stenosis detected by angiography.

Statistical analysis. Baseline characteristics are expressed as means ± SDs or percentages. Continuous variables were compared by one-way analysis of variance, and discrete variables were compared by the chi-square test for independence. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. When indicated, imputations for patients not undergoing angiography were performed. The CTFC of occluded arteries was assigned to patients dying early and the median CTFC was assigned to surviving patients not undergoing angiography. When indicated, the TIMI flow grades were imputed for thrombolytic-treated patients with early death based on GUSTO-I (2) and Heparin in Early Patency (HEAP) studies (21) for those receiving heparin and aspirin only. Using a conservative analytical approach, the highest CTFC in a patent artery in this study (244) was assigned to occluded arteries. Arteries graded TIMI 0 or 1 were analyzed as occluded arteries. Univariate and multivariate predictors of survival were identified using Cox proportional-hazards regression methods, and the assumption of proportional hazards was satisfied for variables in the final models.

RESULTS

A total of 1,001 patients (mean age 57 ± 9 years) were randomized in the three trials to receive recombinant tissue plasminogen activator (135), intravenous streptokinase (754) or a matching placebo (112). Angiography was performed on 882 patients (88%) at a median of 23 days (interquartile range [IQR], 20 to 28).

The late mortality status was determined in 97.5% of patients at a median of 6.3 years (IQR, 4.9 to 8.7 years). There were 182 cardiac and 67 noncardiac deaths, and 86 nonfatal infarctions. Actuarial survival was 91% at one year, 82% at five years and 75% at 10 years (Fig. 1). Five-year survival for the first two studies (1984 to 1988) was 81%,

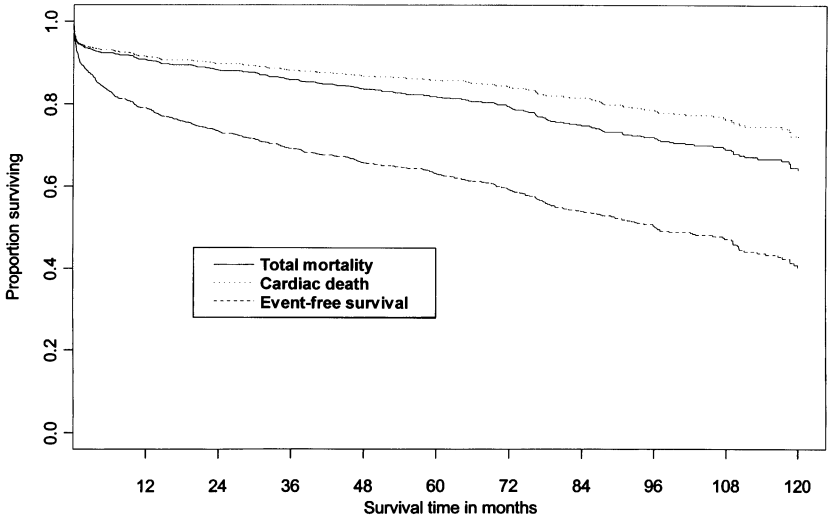

Figure 1. Late actuarial outcome after myocardial infarction.

and the third (1989 to 1994), 83% (p = 0.40). Revascularization at one, five and 10 years postinfarction was performed in 12%, 19% and 23% of patients (133 surgical, 81 percutaneous), respectively. The event-free survival rates (freedom from death, recurrent infarction or revascularization) at five and 10 years were 64% and 55%, respectively (Fig. 1).

Baseline clinical and angiographic characteristics are shown in Tables 1 and 2. Of the 119 patients who did not undergo angiography, 49 had died, 40 did not consent and 30 had significant comorbidity precluding angiography; these patients are not further described herein, except where indicated.

Infarct artery flow at three weeks. Seventy-four percent of patients (644/882) had patent infarct-related arteries (TIMI 2 to 3 flow) at three weeks. The mean CTFC in patent arteries was 40 ± 29 (95% confidence interval, 38 to 42; median 32 [IQR, 24 to 47]). Thirty-four percent of patients had a CTFC of ≤27, 31% between 27 and 40, 30% between 40 and 100 (inclusive) and 4.4% had >100 (Fig. 2 and Table 3).

The CTFC was a predictor of five-year survival, as did TIMI flow grades (both p < 0.001) (Fig. 2). Survival curves were similar for cardiac and total mortality and when only those patients (786) receiving thrombolytic therapy were analyzed (data not shown). Assessed as a continuous variable, CTFCs correlated with cardiac death at one year (chi-square = 4.5; p = 0.03) and five years (chi-square = 6.5; p = 0.01), but not at 10 years (chi-square = 2.3; p = 0.13) (Fig. 3).

Table 1. Baseline Characteristics

	Angiogram* (n = 882)	No Angiogram (n = 119)	p Value	Total (n = 1,001)
Age (mean ± SD)	56.7 ± 9.2	61.3 ± 9.8	<0.001	57.2 ± 9.3
Male gender	706 (80%)	77 (65%)	0.001	783 (78%)
Hypertension	228 (26%)	37 (35%)	0.055	265 (27%)
Diabetes mellitus	73 (8%)	14 (13%)	0.099	87 (9%)
Smoking	391 (44%)	42 (39%)	0.089	433 (44%)
Beta-blockers	127 (14%)	21 (21%)	0.068	148 (15%)
Cholesterol (mmol/liter)	6.2 ± 1.2	6.14 ± 1.1	0.65	6.2 ± 1.2
LDL cholesterol (mmol/liter)	4.3 ± 0.99	4.2 ± 0.86	0.32	4.3 ± 0.98
HDL cholesterol (mmol/liter)	0.97 ± 0.31	0.99 ± 0.31	0.012	0.99 ± 0.31
Treatment				
Streptokinase	662 (75%)	92 (77%)		754 (75%)
Tissue plasminogen activator	124 (14%)	11 (9%)	0.29	135 (14%)
Placebo	96 (11%)	16 (13%)		112 (11%)

*Four patients had further intracoronary thrombolytic therapy with tissue plasminogen activator and four patients had angioplasty on the day of hospital admission.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 2. Angiographic Characteristics*

	Placebo (n = 96)	Thrombolysis (n = 786)	Total (n = 882)
CTFC			
≤27	22 (23%)	198 (25%)	220 (25%)
27 to 40	16 (17%)	184 (23%)	200 (23%)
≥40 to 244	20 (21%)	202 (25%)	222 (25%)
Occluded	37 (39%)	201 (26%)	238 (27%)
TIMI flow grade			
0–1	37 (39%)	201 (26%)	238 (27%)
2	20 (21%)	142 (18%)	163 (18%)
3	39 (41%)	443 (56%)	481 (55%)
Infarct-related artery			
Right coronary	54 (56%)	345 (44%)	399 (47%)
Left anterior descending	35 (36%)	326 (42%)	361 (42%)
Left circumflex	7 (7%)	107 (14%)	114 (13%)
Left ventricular function			
Ejection fraction (%)	50.7 ± 13.8	57.2 ± 13.1	56.5 ± 13.3
ESVI (ml/m^2)	42.6 ± 25.2	35.3 ± 18.9	36.1 ± 19.9
EDVI (ml/m^2)	81.9 ± 31.3	79.4 ± 25.0	79.7 ± 25.8
LVEDP (mm Hg)	16.0 ± 8.4	15.3 ± 8.0	15.4 ± 8.0

*Comparisons between placebo and thrombolysis with respect to the CTFC, TIMI flow and infarct-related artery were $p = 0.044$, $p = 0.008$ and $p = 0.05$, respectively, and between ventricular function characteristics EF, ESVI, EDVI and LVEDP: $p < 0.001$, $p = 0.007$, $p = 0.44$ and $p = 0.49$, respectively.

CTFC = corrected TIMI frame count; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; LVEDP = left ventricular end-diastolic pressure; TIMI = Thrombolysis in Myocardial Infarction.

Patients with TIMI 3, TIMI 2 and TIMI 2 or 3 flow were divided sequentially into groups at CTFC cut-points of 15, 21, 27 and 40, respectively. There were no differences in survival at one, five or 10 years in any group except for the 10-year survival of patients with TIMI 2 flow using a CTFC cut-point of 21 ($p = 0.008$). Among patients with TIMI 3 flow, a CTFC cut-point of 21 was associated with differences in the composite end point of death and recurrent myocardial infarction at 10 years ($p = 0.01$). Among patients with TIMI 2 or 3 flow, CTFC cut-points of 15 and 40 (three categoric groups) influenced the composite end points of death or myocardial infarction and death or myocardial infarction or revascularization ($p < 0.01$ for both). Following imputations for deaths prior to angiography, the CTFC (cut-point 40) in patients with TIMI 2 and TIMI 2 or 3 flow predicted one-year survival ($p < 0.05$ for both).

Ventricular function and the corrected TIMI frame count. There was an association between an increasing CTFC and an ejection fraction of <50% (chi-square = 8.6; $p = 0.04$). Similarly, an increased CTFC was associated with an end-systolic volume index of ≥40 ml/m^2 (chi-square = 10.7; $p = 0.014$) (Table 3). Patients with occluded arteries and either an ejection fraction of <50% or an end-systolic volume index of ≥40 ml/m^2 had a lower five-year survival rate than those with patent arteries (both $p < 0.05$).

Predictors of late survival. On univariate analysis, the predictors of survival at five years were age, ejection fraction, end-systolic volume index, end-diastolic volume index, treadmill exercise time, CTFC, TIMI flow grade (all $p < 0.001$), diabetes and the number of stenosed vessels (both $p = 0.002$) and female gender ($p = 0.008$) (Table 4). On multivariate analysis, the end-systolic volume index or the ejection fraction (both $p < 0.001$), treadmill exercise time ($p = 0.005$), diabetes ($p = 0.02$) and the CTFC ($p = 0.02$) or TIMI flow grade ($p = 0.02$) were predictors of five-year survival (Table 5). The CTFC and TIMI flow grade cosegregated in the multivariate model, and each factor, when inserted separately in the five-factor model, had a p value of 0.02. Imputations performed for patients dying prior to angiography did not increase the p values for the CTFC or TIMI flow grade. Factors predictive of 10-year survival on multivariate analysis were the ejection fraction (or end-systolic volume index), exercise time and age, but not the CTFC or TIMI flow grade (Table 5).

DISCUSSION

In this study the CTFC, assessed at three weeks after myocardial infarction, was an independent predictor of five-year survival but not superior to TIMI flow grading. Neither measure of infarct artery flow was a predictor of 10-year survival.

The TIMI flow grading after reperfusion therapy has been accepted as the standard method of assessing infarct-related artery blood flow (7). However, Gibson et al. (9) highlighted discrepancies between infarct-related artery flow assessments done at an angiographic core laboratory

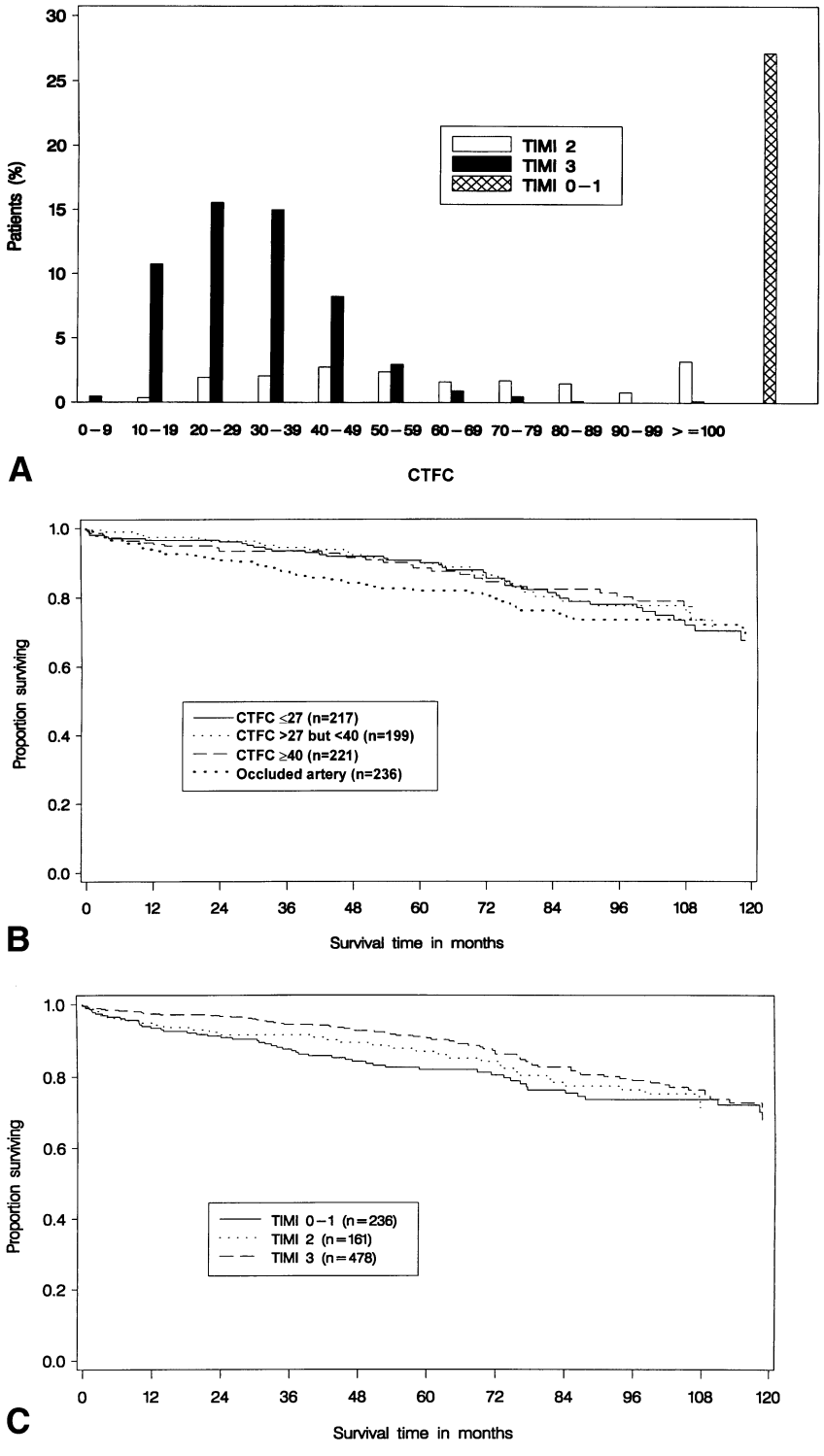

Figure 2. Infarct-related artery flow in patients who underwent angiography at three weeks without imputation for early death. **(A)** Comparison of CTFCs and TIMI flow grades. **(B)** Influence of CTFC on late survival. The log rank comparisons (four-way) at one, five and 10 years were p = 0.06, p = 0.002 and p = 0.26, respectively. **(C)** Influence of TIMI flow grades on late survival. The log rank comparisons (three-way) at one, five and 10 years were p = 0.03, p = 0.0003 and p = 0.14, respectively. The log rank comparisons (two-way) between TIMI 3 and TIMI 0 to 1 and between TIMI 3 and TIMI 0 to 2 at one, five and 10 years were p = 0.009, p = 0.0001 and p = 0.049; and p = 0.025, p = 0.004 and p = 0.49, respectively. The log rank comparisons between TIMI 2 and TIMI 0 to 1 at one, five and 10 years were p = 0.25, p = 0.047 and p = 0.25, respectively. The log rank comparisons between TIMI 0 to 1 and TIMI 2 to 3 at one, five, and 10 years were p = 0.012, p = 0.0001 and p = 0.049, respectively. There were no significant differences in survival between patients with TIMI 2 and TIMI 3 flow. The results were similar when only thrombolytic-treated patients were analyzed (data not shown). CTFC = corrected TIMI frame count; TIMI = Thrombolysis in Myocardial Infarction.

Table 3. Comparison Between Corrected TIMI Frame Counts, TIMI Flow and Ventricular Function at Three Weeks

					Ventricular Function			
	TIMI Flow*				ESVI (ml/kg/m^2)†		Ejection Fraction‡	
CTFC	3	2	0–1	Total	≤40	≥40	<50%	≥50%
≤27	205	15	—	220	152 (71%)	63 (29%)	50 (23%)	170 (77%)
27 to 40	174	26	—	200	138 (70%)	58 (30%)	47 (24%)	151 (76%)
≥40 to 244	102	120	—	222	146 (67%)	72 (33%)	69 (31%)	152 (69%)
Occluded arteries	—	—	238	238	135 (58%)	98 (42%)	76 (32%)	158 (68%)
Total	479	161	238	880§	571	291	243	631

Data represent the number of patients in each category. *Comparison of CTFC (four categories) with TIMI flow chi-square = 1099.5; $p < 0.001$. †Comparison of CTFC (four categories) and end-systolic volume index chi-square = 10.7; $p = 0.014$. ‡Comparison of CTFC (four categories) and ejection fraction chi-square = 8.6; $p = 0.04$. §CTFC could not be assessed in two patients with coronary artery dissection.

CTFC = corrected TIMI frame count; ESVI = end-systolic volume index (ml/kg/m^2); TIMI = Thrombolysis in Myocardial Infarction.

and those done by local investigators, especially in patients with TIMI 2 flow, where there was only 52% concordance. To enhance reproducibility, these investigators developed the CTFC as a more quantitative assessment of infarct-related artery flow (9). We also found this method highly reproducible (12).

In the present study, the CTFCs of patent infarct-related arteries three weeks after infarction were prolonged (median, 32 [IQR, 24 to 47]), extending earlier observations that have found the CTFC of patent arteries to be prolonged at both 24 and 48 h after intravenous thrombolytic therapy (9,11).

Infarct-related artery flow and outcome. The mechanism of the early benefits of thrombolytic therapy has been attributed to prompt restoration of blood flow in the infarct-related artery, as measured by TIMI flow grading at 90 min (2,22). By 3 h, most thrombolytic regimens achieve patency (TIMI 2 or 3 flow) in 70% to 80% of patients, and the patency rate remains similar at one and three weeks (2,4,22,23). In the current study, the CTFC at three weeks, assessed as a continuous variable, independently predicted total and cardiac mortality at five years, but not at 10 years. The TIMI flow grade was also independently predictive ($p = 0.02$) and cosegregated with the CTFC. However, CTFC, examined as a categoric variable in patients with TIMI 2 or 3 flow, did influence the composite end points of death or myocardial infarction and death or myocardial infarction or revascularization. The TIMI group (18) has also recently shown that the CTFC at 90 min, analyzed as a categoric variable, was a predictor of one-month mortality, and the composite end point of death, nonfatal infarction, shock, heart failure or an ejection fraction of ≤40%.

The velocity of infarct artery flow needed to provide sufficient myocyte nutrition to influence prognosis is unclear. We recently reported that survival in patients with TIMI 2 flow may be interpreted as intermediate between that of patients with TIMI 0 to 1 and TIMI 3 flow after adjustment for baseline risk (24). In the current study, patients with TIMI 2 flow had significantly better survival rates than those with TIMI 0 to 1 flow, but not statistically different than those with TIMI 3 flow. The TIMI flow grade was a univariate predictor of five-year survival ($p < 0.001$). The GUSTO investigators reported that the unadjusted two-year survival of patients with TIMI 2 flow at 90 ± 45 min was not significantly better than that of patients with TIMI 0 to 1 flow (25). In the European Cooperative Study (26), patients with TIMI 3 (but not those with TIMI 2) flow at 10 to 22 days had a higher survival rate at five years than patients with TIMI 0 to 1 flow.

The lack of influence of infarct artery flow on 10-year survival may be due to several factors. These may include progression of coronary artery disease in the infarct or non–infarct-related arteries (as evidenced by the univariate prognostic significance of the number of stenosed arteries), plaque rupture or fissuring in non–infarct-related arteries, late reocclusion with or without infarction, or the effect of late revascularization. The possibility of beta error, the increased incidence of late noncardiac deaths after five years, the smaller numbers of patients followed up for 10 years, or other unrecognized factors may also have influenced this result.

Patency, ventricular function and survival. Left ventricular function was the most powerful determinant of survival at both five and 10 years, with the ejection fraction and end-systolic volume index having similar influence. Two studies have reported a relationship between the CTFC at 90 min and the ejection fraction, assessed either by predischarge radionuclide ventriculography or by 48-h contrast ventriculography (9,11). At these times ejection fraction may be influenced by myocardial stunning (16). We assessed left ventricular function at three weeks after infarction when myocardial stunning was likely to have resolved (11).

Other factors. The Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto Miocardico (GISSI) group (27) has reported that exercise duration and inability to perform an exercise test were powerful predictors of mortality at six months. We found that exercise duration was independently associated with both five- and 10-year outcomes. Lenderink

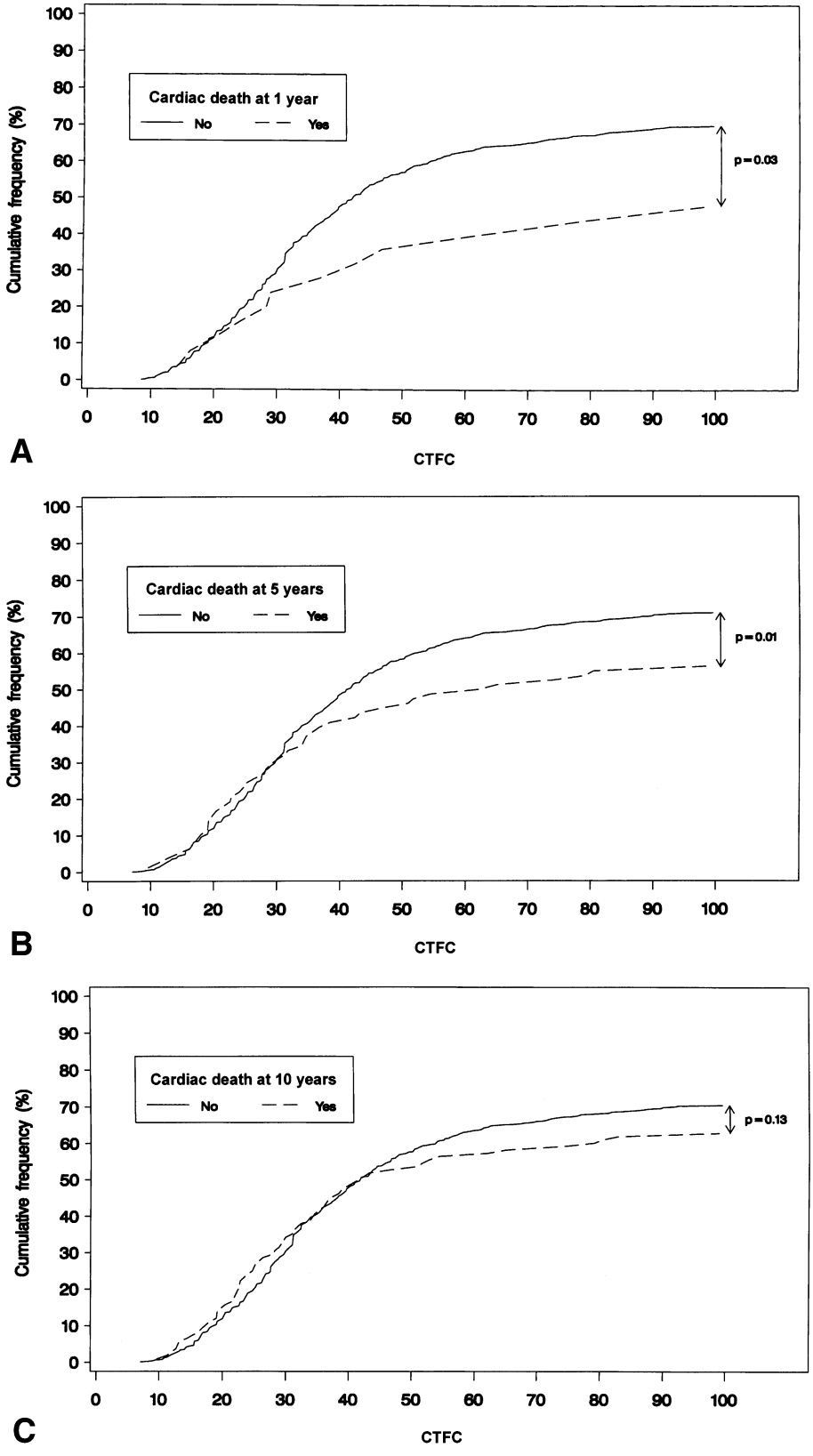

Figure 3. Influence of the CTFC on cardiac death. **(A)** At one year. **(B)** At five years. **(C)** At 10 years. The cumulative frequency is the percentage of patients with a CTFC not exceeding the X-value. CTFC = corrected TIMI frame count; TIMI = Thrombolysis in Myocardial Infarction.

Table 4. Univariate Predictors of Late Mortality

	5 y		10 y	
	Chi-square	p* Value	Chi-square	p* Value
Clinical factors				
Age	33.7	<0.001	49.6	<0.001
Female gender	7.3	0.008	6.0	0.01
Diabetes	10.1	0.002	11.0	<0.001
Hypertension	3.6	0.06	1.4	0.25
Smoking	1.12	0.29	3.5	0.06
Total cholesterol (mmol/liter)	0.82	0.36	2.3	0.13
HDL cholesterol (mmol/liter)	2.3	0.13	0.1	0.75
Exercise time	23.7	<0.001	25.6	<0.001
Angiographic factors				
Ejection fraction	29.4	<0.001	63.9	<0.001
ESVI	31.9	<0.001	49.8	<0.001
EDVI	16.7	<0.001	19.8	<0.001
TIMI flow	14.9	<0.001	3.6	0.06
CTFC†	13.9	<0.001	2.6	0.11
No. of stenosed vessels	9.3	0.002	13.2	<0.001
IRA=LAD	0.9	0.35	0.17	0.68

*No adjustments have been made for multiple comparisons. †CTFC of occluded arteries imputed at the maximum value of patent arteries (244).

CTFC = corrected TIMI frame count; EDVI = end-diastolic volume index; ESVI = end-systolic volume index; HDL = high-density lipoprotein; IRA=LAD = infarct related artery-left anterior descending coronary artery; TIMI = Thrombolysis in Myocardial Infarction.

et al. (26) also found that exercise duration at hospital discharge influenced five-year survival. Neither baseline total nor high density lipoprotein cholesterol levels influenced late outcome, possibly due to beta error, the effects of dietary advice or pharmacologic therapy.

Study limitations. The effect of the CTFC, measured in the early hours and days postinfarction, was not examined in the present study. The CTFC measured at 90 min may have had a greater effect on late mortality than has been reported herein, as approximately 20% of deaths occurred prior to angiography, although imputation of infarct artery flow for these early deaths did not influence these findings. While CTFC provided additional prognostic information within the TIMI flow grade, our study may have been underpowered to determine whether the CTFC was a better predictor of late survival than the TIMI flow grade.

The CTFC at three weeks represented the net effects of

Table 5. Multivariate Predictors of Late Mortality

Variables	p (Coefficient)	Chi-square (Model)	df (Model)	p (Model)
5-yr mortality				
Age	0.008	65	5*	<0.001
Exercise time	0.005			
Ejection fraction†	<0.001			
CTFC‡	0.02			
Diabetes	0.02			
10-yr mortality				
Age	<0.001	99	5	<0.001
Exercise time	0.01			
Ejection fraction†	<0.001			
CTFC‡	0.82			
Diabetes	0.02			

*Number of diseased vessels (p = 0.1) in six-factor model. †p and chi-square values were similar for the model if end-systolic volume index was substituted for ejection fraction. The end-systolic volume index was the most powerful predictor of five-year survival, and the ejection fraction was more powerful at 10 years. ‡p = 0.02 and 0.78 for TIMI flow if this factor was substituted for CTFC as a predictor of five- and 10-year mortality, respectively. Insertion of CTFC as a three-way categoric variable (similar to TIMI flow grades) did not increase the p value.

CTFC = corrected TIMI frame count; df = degrees of freedom; TIMI = Thrombolysis in Myocardial Infarction.

reperfusion and reocclusion in patients treated with aspirin (with or without dipyridamole), intravenous heparin administered for 48 h, and either streptokinase (administered over 30 to 60 min) or recombinant tissue plasminogen activator (administered over 3 h) or a placebo.

A conservative approach to revascularization was undertaken in the absence of left main stenosis or limiting symptoms. In the present study, only 12% of patients had undergone revascularization at one year and 23% at 10 years, compared with approximately 20% at one year in the European Cooperative Study (26). The value of the CTFC as a predictor of late survival may be different with higher or lower rates of revascularization.

CONCLUSIONS

The CTFC at three weeks after infarction is an independent predictor of five-year mortality, and provides a more reproducible assessment of flow in patent infarct arteries than the TIMI flow grade. Further studies are necessary to determine whether the CTFC should influence prognostic decisions regarding revascularization or medical therapies.

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REFERENCES

1. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–402.
2. Simes RJ, Topol EJ, Holmes DR, Jr, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. Circulation 1995;91:1923–8.
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. White HD, Norris RM, Brown MA, et al. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. N Engl J Med 1987;317:850–5.
5. French JK, Hyde TA, White HD. Left ventricular function following thrombolytic therapy for myocardial infarction. J Interven Cardiol 1998;11:9–18.
6. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. Circulation 1987; 76:142–54.
7. White CW. Simplicity's virtue scorned: precision comes to TIMI flow grading and the results are . . . surprising [editorial]. Circulation 1996; 93:853–6.
8. Bode C, Smalling RW, Berg G, et al. Randomized comparison of coronary thrombolysis achieved with double-bolus reteplase (recombinant plasminogen activator) and front-loaded, accelerated alteplase (recombinant tissue plasminogen activator) in patients with acute myocardial infarction. Circulation 1996;94:891–8.
9. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. Circulation 1996;93:879–88.
10. Dodge JT, Jr., Gibson CM, Nykiel M, et al. Impact of injection rate on the Thrombolysis in Myocardial Infarction (TIMI) trial frame count. Am J Cardiol 1998;81:1268–70.
11. French JK, Straznicky IT, Webber BJ, et al. Angiographic frame counts 90 minutes after streptokinase predict left ventricular function at 48 hours following myocardial infarction. Heart 1999;81:128–33.
12. French JK, Ellis CJ, Webber BJ, et al. Abnormal coronary flow in infarct arteries 1 year after myocardial infarction is predicted at 4 weeks by corrected Thrombolysis in Myocardial Infarction (TIMI) frame count and stenosis severity. Am J Cardiol 1998;81:665–71.
13. White HD, Rivers JT, Maslowski AH, et al. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction. N Engl J Med 1989;320:817–21.
14. French JK, Amos DJ, Williams BF, et al. Effects of early captopril administration after thrombolysis on regional wall motion in relation to infarct artery blood flow. J Am Coll Cardiol 1999;33:139–45.
15. French JK, Williams BF, Hart HH, et al. Prospective evaluation of eligibility for thrombolytic therapy in acute myocardial infarction. BMJ 1996;312:1637–41.
16. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982;66:1146–9.
17. White HD, Aylward PE, Frey MJ, et al. Randomized, double-blind comparison of hirulog versus heparin in patients receiving streptokinase and aspirin for acute myocardial infarction (HERO). Circulation 1997;96:2155–61.
18. Gibson CM, Murphy SA, Rizzo MJ, et al. The relationship between the TIMI frame count and clinical outcomes following thrombolytic administration. Circulation 1999;99:1945–50.
19. The Principal Investigators of CASS and Their Associates. The National Heart, Lung, and Blood Institute Coronary Artery Surgery Study (CASS): a multicenter comparison of the effects of randomized medical and surgical treatment of mildly symptomatic patients with coronary artery disease, and a registry of consecutive patients undergoing coronary angiography. Circulation 1981;63:I-1–I-81.
20. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998;339:1349–57.
21. Liem A, Zijlstra F, Ottervanger JP, et al. High dose heparin as pretreatment for primary angioplasty in acute myocardial infarction: the Heparin in Early Patency (HEAP) Randomised Trial. J Am Coll Cardiol 2000;35:600–4.
22. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction [published erratum appears in N Engl J Med 1994;330:516]. N Engl J Med 1993;329:1615–22.
23. Reiner JS, Lundergan CF, Fung A, et al. Evolution of early TIMI 2 flow after thrombolysis for acute myocardial infarction. Circulation 1996;94:2441–6.
24. French JK, Hyde TA, Patel H, et al. Survival 12 years after randomization to streptokinase: the influence of Thrombolysis in Myocardial Infarction flow at three to four weeks. J Am Coll Cardiol 1999;34: 62–9.
25. Ross AM, Coyne KS, Moreyra E, et al. Extended mortality benefit of early postinfarction reperfusion. Circulation 1998;97:1549–56.
26. Lenderink T, Simoons ML, van Es G-A, et al. Benefit of thrombolytic therapy is sustained throughout 5 years and is related to TIMI perfusion grade 3 but not grade 2 flow at discharge. Circulation 1995;92:1110–6.
27. Villella A, Maggioni AP, Villella M, et al. Prognostic significance of maximal exercise testing after myocardial infarction treated with thrombolytic agents: the GISSI-2 data-base: Gruppo Italiano per lo Studio della Sopravvivenza Nell'Infarto. Lancet 1995;346:523–9.