Clinical Investigation

TIMI Perfusion Grade 3 but Not Grade 2 Results in Improved Outcome After Thrombolysis for Myocardial Infarction

Ventriculographic, Enzymatic, and Electrocardiographic Evidence From the TEAM-3 Study

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Background. **Coronary patency has been used as a measure of thrombolysis success after acute myocardial infarction. The Thrombolysis in Myocardial Infarction (TIMI) Study Group perfusion grades have gained wide acceptance, with grades 0 (no distal flow) and 1 perfusion (minimal flow) being designated as thrombolysis failures and grades 2 (partial perfusion) and 3 (complete perfusion) as thrombolysis successes. However, the significance of the individual TIMI grades on clinical outcome has not been adequately assessed.**

Methods and Results. **To evaluate the functional significance of TIMI perfusion grades, we compared 1-day coronary patency status with ventriculographic, enzymatic, and ECG indexes of acute myocardial infarction in 298 patients treated with anistreplase or alteplase within 4 hours of myocardial infarction symptom onset. Radionuclide ejection fraction was determined at 1 week and at 1 month. Perfusion grades for the entire study population were distributed as 12% (n=37) grades 0/1, 13% (n=40) grade 2, and 74% (n=221) grade 3. Patency profile did not differ between the two thrombolytic regimens. Further coronary interventions were performed after the 1-day patency determination in 43% of patients (43%, 48%, 42%, respectively, in grades 0/1, 2, and 3 patients). The outcome of grade 2 patients did not differ from grades 0/1 patients in ejection fraction, enzyme peaks, ECG markers, or morbidity index. In contrast, grade 3 patients, compared with grades 0–2 patients, showed 1) a greater global ejection fraction at 1 week (54% versus 49%, p=0.006) and at 1 month (54% versus 49%, p=0.01), 2) a greater infarct zone ejection fraction at 1 week (41% versus 33%, p=0.003) and at 1 month (42% versus 32%, p=0.003), 3) smaller enzyme peaks, significant for lactate dehydrogenase, and shorter times to enzyme peaks, significant for all four enzymes, 4) a smaller QRS score at discharge and at 1 month, and 5) a trend toward a lower morbidity index.**

Conclusions. **Grade 3 flow predicts significantly better outcomes than lesser grades of flow and represents an important measure of reperfusion success. (*Circulation* 1993;87:1829–1839)**

KEY WORDS • clinical trials • reperfusion • myocardial infarction

Reestablishment of coronary blood flow is believed to be the primary mechanism of benefit of thrombolytic therapy in acute myocardial infarction.[1–7] The Thrombolysis in Myocardial Infarction (TIMI) Study Group grading scale[8] has gained wide acceptance as a semiquantitative measure of coronary perfusion. TIMI perfusion grades 0 and 1 have been designated as perfusion failures, and grades 2 and 3 have traditionally been viewed as reperfusion successes. However, the clinical significance of the individual TIMI grades on outcome has been inadequately tested and has not been firmly established. Specifically, it is uncertain whether grade 2 perfusion is sufficient to achieve adequate myocardial salvage.

Thus, the purpose of the present study was to examine the predictive value of the TIMI perfusion grades achieved by thrombolytic therapy on outcome after acute myocardial infarction as assessed by ventriculographic, enzymatic, and ECG indexes in the study data base of the Third Thrombolysis Trial of Anistreplase (Eminase®) in Acute Myocardial Infarction (TEAM-3).[9] (TEAM-3 was a blinded, randomized multicenter comparison of anistreplase and alteplase. The primary, drug-specific results of TEAM-3 were published recent-

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ly[9] and showed that convalescent rest ejection fraction was high after both therapies but favored alteplase; other clinical outcomes were favorable and were comparable after anistreplase and alteplase, including exercise function, morbidity index, and 1-day coronary artery patency.)

Our hypothesis in the present study was that TIMI grade 2 perfusion, achieved by either "fibrin-specific" (alteplase) or non–fibrin-specific thrombolysis (anistreplase), is not sufficient to optimize myocardial salvage and that only grade 3 perfusion results in substantial improvement in functional outcomes distinguishable from lower perfusion grades. This hypothesis was generated prospectively, based on observations in a previous study.[10,11]

See p 2055

Methods

Study Design

The data base for the present study was the TEAM-3 trial.[9] TEAM-3 was a double-blind, randomized, active controlled trial in which patients with acute myocardial infarction received standard doses of either intravenous anistreplase (APSAC; 30 units over 2–5 minutes) or alteplase (tissue-type plasminogen activator [t-PA]; 100 mg over 3 hours). Conjunctive therapy included aspirin (160 mg) immediately and then daily and intravenous heparin, begun with a 5,000-unit bolus during the t-PA infusion and maintained with an infusion of 1,000 units/hr, adjusted as required to keep the activated partial thromboplastin time at approximately twice the upper normal limit, at least until angiography was completed. Coronary angiography was performed at 1 day to assess thrombolysis-mediated coronary patency rates. Patients were followed for 1 month to evaluate clinical outcome, with radionuclude ventriculography being measured at 1 week and at 1 month.

Patient Entry Criteria

Entry criteria included ischemic chest pain of less than 4 hours' duration, ECG ST segment elevation in two or more contiguous leads of ≥0.1 mV in at least one limb lead or ≥0.2 mV in at least one precordial lead, and age of less than 76 years. Patients were excluded if they had contraindications to thrombolysis, were in cardiogenic shock, had previous bypass surgery or recent (within 1 month) coronary angioplasty, or had received streptokinase or anistreplase within 6 months.

Patency Groups

Because 1-day patency rates were similar for the two treatment groups, both overall and among individual TIMI perfusion grades,[9] the groups were pooled, and an overall analysis of outcome versus TIMI perfusion grade was made. For purposes of statistical comparisons, three patency groups were defined: Grades 0 and 1 were considered together the perfusion failure group, group 2 was considered the partial perfusion group, and group 3 was considered the complete perfusion group.[8]

Outcome Measures

Outcome assessments included radionuclide ventriculography, cardiac enzyme determinations, ECG, and clinical morbidity. The primary ventriculographic measures of interest, specified prospectively,[9] were predischarge (7–10 days) and 1-month (3–6 weeks) rest radionuclide ejection fraction. (Both global and infarct zone ejection fraction measurements were of interest.) Measurements of serum creatine kinase (CK) and lactate dehydrogenase (LDH) enzymes and their cardiac isoenzymes CK-MB and LDH-1 were measured before dosing and at the time intervals indicated after dosing. ECG was performed at study entry, 8 hours, before discharge, and 1 month. Clinical morbidity was assessed for in-hospital and out-patient events up to the 1 month evaluation.

Angiographic Determinations of Patency

Coronary angiography was to be performed 1 day (18–48 hours) after thrombolytic therapy and included multiple orthogonal views of the infarct-related artery. Angiography, angioplasty, surgery, and other coronary interventions were not permitted, except for a medical emergency, before the 1-day (18–48 hours) window for angiography; thereafter—until the 1-month follow-up—interventions were to be done only for patients with inadequate coronary perfusion (i.e., grades 0/1 or "inadequate" grade 2 flow) and with clinical indications (i.e., recurrent ischemia). The actual mean time to angiography was 31 hours (median, 26 hours; 10–90% confidence intervals, 13–49 hours). Angiography was performed earlier (within 12 hours) in 30 patients for clinical indications; of these, 14 underwent early ("rescue") procedures. All patients with patency determinations were retained in the analyses, regardless of the actual time to angiography.

Angiographic determination of patency status was made centrally for the entire study population by one experienced, validated reader[12,13] who was blinded to patients' treatment assignment and clinical status. TIMI definitions of perfusion were used: Grade 0 is complete occlusion, characterized by absence of contrast flow distal to the infarct-related occlusion site. Grade 1 is minimal perfusion; contrast penetrates around the site of obstruction, but minimal distal perfusion is present. Grade 2, called partial perfusion, is defined by a reduced rate of entry and clearance of contrast into and from the distal coronary bed. Grade 3, called complete perfusion, is defined by normal entry and clearance rates of contrast to and from the distal coronary bed.

Of the 325 patients entered into TEAM-3, 298 (92%) had angiograms available for analysis and thus formed the primary study population for patency associations with outcome. Reasons for missing angiographic information included death (n=8), nonfatal stroke (n=1), hemodynamic instability precluding angiography (n=4), indeterminate infarct-related artery (n=5), film lost or report missing (n=5), and procedure not done for other reasons (e.g., patient refusal) (n=4).

Radionuclide Ventriculography

An initial study was undertaken within 4 hours of starting thrombolytic therapy. Convalescent radionuclide ventriculography was performed at 7–10 days after dosing or at the time of hospital discharge, whichever came first, and at 1 month (3–6 weeks after dosing). Gated blood pool scans were performed on the same equipment for each individual patient on all studies at each center. A standardized procedure[14–16] enabled centralized reading of ejection fractions at the study's

core radionuclide laboratory.[9] Individual studies were copied onto floppy computer disks by the study centers and sent to the core radionuclide laboratory, where blinded assessment was made. End-systolic and end-diastolic frames were automatically selected, and regions of interest then were manually drawn around the left ventricle in each frame. Subtraction of background counts was performed by using as a region of reference an automatically selected area just lateral and inferior to the left ventricular apex in the end-systolic frame. Corrected end-systolic and end-diastolic counts were then used to calculate ejection fraction as: end-diastolic minus end-systolic counts/end-diastolic counts multiplied by 100.

Regional wall motion was determined in the left anterior oblique view using a 16-sector (22.5° per sector) display automatically generated from fixed center points in the end-systolic and end-diastolic frames. Ischemic zone sectors were identified on the baseline study by the blinded observer, and an ischemic zone regional ejection fraction was calculated from the regional end-systolic and end-diastolic counts. Similarly, sectors showing normal or best wall motion outside of the ischemic zone were selected on the baseline study, and a normal zone regional ejection fraction was calculated. These same sectors were then analyzed on the discharge and 1-month studies to determine convalescent ischemic zone and normal zone ejection fraction.

ECG and Cardiac Enzyme Determinations

Standard 12-lead ECGs were obtained at entry, 8 hours after dosing, at 7–10 days (or discharge, whichever came first), and at the 1-month visit. Analysis of QRS score[17] was performed centrally by a single experienced observer[18] blinded to drug treatment and clinical outcome measures.

Blood samples were taken for CK and its cardiac isoenzyme (CK-MB) before dosing and at 4, 8, 12, 24, and 36 hours after dosing and for LDH and its cardiac isoenzyme (LDH-1) before dosing and at 12, 24, 36, and 72 hours. Assays were performed by certified biochemistry laboratories at the individual study sites by technicians blinded to clinical characteristics and outcomes and were reported in standard international units (IU).

Combined Morbidity Index

Overall clinical outcome was assessed using a combined morbidity index, modified[9] after the method of Califf et al.[19] Analysis used both standard nonparametric testing (Mann-Whitney, Kruskal-Wallis) and specific testing for determination of the relative odds of events by perfusion group with ordinal logistic regression (JMP Statistical Software, SAS Institute Inc., Cary, N.C.). Perfusion group was used as the independent variable. This analysis ranked the worst event for each patient during hospitalization and the 1-month follow-up using five ordered levels: 1, death; 2, hemorrhagic *or* thrombic *or* embolic stroke; 3, global ejection fraction <30% *or* reinfarction *or* heart failure within 1 month *or* ventricular fibrillation; 4, emergency bypass surgery *or* ischemic pain *or* ventricular tachycardia; and 5, none of these events (see Table 4).[9,19]

Study Hypothesis and Statistical Analysis

The hypothesis tested was that the degree of patency was related to outcome as defined by the convalescent ventriculographic, enzymatic, ECG, and morbidity index variables. Specifically, we postulated that achievement of TIMI grade 2 (partial) perfusion at the 1-day patency determination was not sufficient to achieve optimal functional improvement compared with results in patients achieving TIMI grades 0/1 patency (negative controls) and grade 3 (complete) perfusion (positive controls), whereas grade 3 perfusion could be distinguished by functional outcome from the other patency grades. The hypothesis was generated prospectively, before analysis of the TEAM-3 data base was undertaken, and was based on observations in a previous study (TEAM-2).[10,11]

The primary variables of interest were convalescent ventriculographic global ejection fraction and infarct zone (regional) ejection fraction. Secondary variables of interest included cardiac enzyme peaks and ECG QRS scores, based on the method of Wagner Selvester and colleagues.[17] ANOVA was used to assess the dependence of outcome (i.e., ejection fraction) on patient characteristics according to patency group, acute myocardial infarction location, and intervention status. When the effect of patency on the dependent variable was found to be statistically significant in the ANOVA, the method of orthogonal contrasts of the mean[20,21] was applied to assess where differences resided among the three perfusion groups. Patency groups were prospectively ranked by desirability of patency result (i.e., grade 3>grade 2>grades 0/1), the contrast coefficients were chosen prospectively, and the following two a priori contrasts performed: contrast 1, defined as the comparison of patients with grades 0 or 1 with those with grade 2 perfusion; and contrast 2, defined as the comparison of grade 0, 1, or 2 with grade 3.

LDH and LDH-1 were designated as the primary enzymatic variables because their kinetics are less influenced by reperfusion than CK and CK-MB and because they have been correlated with infarct size measures after thrombolysis.[3,22–24] Repeated-measures ANOVA was applied to compare enzyme kinetics of LDH and LDH-1 with the TIMI perfusion grade as the between-group factor.

Results for continuous variables are presented as mean±SEM or together with SD values, as indicated. ANOVA was used to assess baseline differences among groups in continuous variables, and contingency table analysis was used to test for differences in categorical variables. Morbidity index was analyzed as previously described. A two-tailed $p \leq 0.05$ was considered significant for the principal hypothesis comparisons; for other comparisons, $p \leq 0.01$ was used.

Results

Baseline Characteristics of the Study Groups

The study comprised 298 patients who were randomized to blinded thrombolytic therapy, underwent coronary angiography at 1 day, and had angiograms evaluable for perfusion (patency) grade. An additional 27 patients (8%) were not evaluable for patency status (see "Methods"). Entry characteristics of evaluable patients, grouped by 1-day TIMI perfusion grade, are presented

TABLE 1. Characteristics of Patients at Entry and of Evaluation and Treatment

A. Characteristics of patients at entry	Grade			
Characteristic	0/1	2	3	*p*
Patency-evaluable patients (No.)	37	40	221	...
Age (mean±SEM years)	57±1.7	59±1.6	59±0.7	0.61
Sex (%, No. male)	81 (30)	68 (27)	77 (171)	0.31
Previous myocardial infarction (%, No.)	14 (5)	24 (9)	16 (34)	0.41
Hypertension history (%, No.)	59 (22)	40 (16)	38 (84)	0.05
Previous angina (%, No.)	43 (16)	43 (17)	36 (80)	0.58
Diabetes (%, No.)	30 (11)	15 (6)	16 (35)	0.12
Heart failure (%, No.)	0 (0)	3 (1)	1 (2)	0.52
B. Characteristics of patient evaluation and treatment				
Variable				
Time from symptom onset to therapy (mean±SEM hours)	2.7±0.2	2.8±0.1	2.7±0.1	0.83
Time from entry to angiography (mean±SEM hours)	30.9±5.0	28.5±3.3	32.1±2.0	0.76
Anterior myocardial infarction (%, No.)	30 (11)	58 (23)	33 (73)	0.01
Mechanical interventions* (%, No.)	43 (16)	48 (19)	42 (93)	0.82

*Percutaneous transluminal coronary angioplasty; coronary artery bypass graft surgery.

in Table 1A. Groups were similar for age, sex, history of acute myocardial infarction, history of previous angina, diabetes, and heart failure. Differences in hypertension history bordered on significance.

The time from symptom onset to thrombolytic therapy was identical in the three patency groups (Table 1B). Also, the three groups were similar in time from study entry to angiography and in the percent eventually undergoing mechanical interventions during the interval from the 1-day angiogram to the 1-month follow-up. Because a greater percentage of patients experienced anterior acute myocardial infarction in the TIMI grade 2 group, *p* values for the primary statistical assessments of outcome were adjusted for acute myocardial infarction location (anterior versus inferior/other).

At study entry, the three groups had similar serum levels of CK, CK-MB, LDH, and LDH-1 enzymes (Table 2). ECG measures also did not differ significantly, including summed ST segment elevations, summed Q wave amplitudes, and summed R waves in infarct-related leads (Table 2).

Patency grades for the entire study population at 1 day were distributed as 8% (n=24) grade 0, 4% (n=13) grade 1, 13% (n=40) grade 2, and 74% (n=221) grade 3.

Effect of Perfusion Grade and Acute Myocardial Infarction Location on Global and Regional Ejection Fraction at 1 Week

Global ejection fraction at discharge by TIMI grade is shown in Figure 1A and averaged 50% in patients with grades 0/1, 48% with grade 2, and 54% with grade 3 perfusion, a significant difference even after adjusting for acute myocardial infarction location (p=0.02). Contrast 1 (the comparison of grades 0/1 with grade 2) was not significant, whereas contrast 2, comparing grade 3 with combined grades 0/1 and 2, was highly significant (mean ejection fractions, 54% versus 49%; p=0.006).

To explore the relation of infarct site to outcome, global ejection fraction at discharge was evaluated by TIMI grade and acute myocardial infarction location. Acute myocardial infarction location did not influence the effect of perfusion grade on ejection fraction (p=0.59 for interaction term). In the inferior/other (nonanterior) acute myocardial infarction subgroup (n=175), ejection fraction for grade 2 patients was similar to grades 0/1 patients (p=0.72, contrast 1), whereas outcome for grade 3 patients was better (p=0.02, contrast 2; overall p=0.03) (Figure 2A). In the

TABLE 2. Selected Baseline Enzymatic and ECG Measures

	Grade			
Measure	0/1	2	3	*p**
Creatine kinase (IU/L)	138±21 (34)	138±18 (38)	152±20 (214)	0.81
Creatine kinase-MB (IU/L)	4.1±1.2 (22)	4.7±1.6 (27)	10.3±5.1 (149)	0.85
Lactate dehydrogenase	246±27 (34)	257±27 (35)	248±11 (201)	0.73
Lactate dehydrogenase-1	68±15 (20)	63±13 (18)	77±8 (133)	0.74
ΣST (mV)	1.05±0.12 (36)	1.31±0.12 (40)	1.10±0.06 (217)	0.53
ΣQ (mV)	0.94±0.16 (36)	1.03±0.18 (40)	0.73±0.06 (217)	0.39
ΣR (mV)	6.6±0.5 (36)	6.6±0.5 (40)	7.1±0.2 (217)	0.42

*p values adjusted for acute myocardial infarction location. Values given as mean±SEM with No. of patients in parentheses.

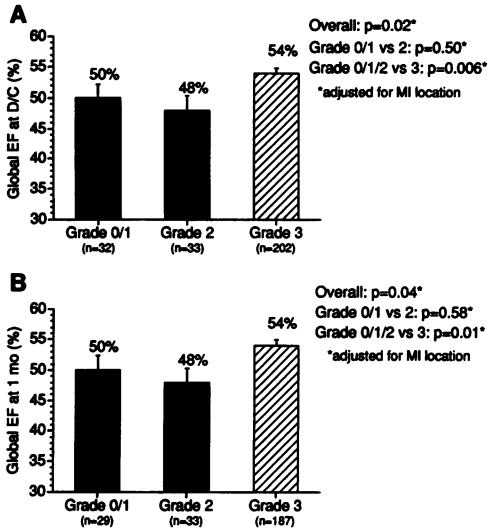

FIGURE 1. *Bar graphs of global ejection fraction (EF) by Thrombolysis in Myocardial Infarction grade, (panel A) at discharge and (panel B) at 1 month. MI, myocardial infarction.*

smaller anterior acute myocardial infarction subgroup (n=92), ejection fraction in grade 2 patients was intermediate between grades 0/1 and grade 3, but only the comparison of grade 3 with other grades approached significance (p=0.25 for contrast 1, p=0.08 for contrast 2, overall p=0.29) (Figure 2B).

Because global ejection fraction can be influenced by compensatory hyperkinesis and other factors unrelated to myocardial salvage, effects of perfusion grade on infarct zone ejection fraction were examined. A significant overall effect of patency on infarct zone ejection fraction was observed (p=0.008). This difference was found to reside in contrast 2, the comparison of grade 3 with grades 0/1/2 (regional ejection fraction, 41.5% versus 33%, respectively; p=0.003). Acute myocardial infarction location did not influence the effect of perfusion grade on infarct zone ejection fraction (p=0.83 for interaction term). Shown in Figure 3 is infarct zone ejection fraction at discharge by TIMI grade and acute myocardial infarction location. In inferior acute myocardial infarction patients (n=165), the pattern was similar to that of global ejection fraction (see Figure 2A): Grade 2 patients showed an infarct zone ejection fraction that was similar to or less than that of grades 0/1 patients (p=0.36, contrast 1), and grade 3 patients showed an infarct zone ejection fraction greater than that of grades 0/1 and 2 patients (p=0.009, contrast 2;

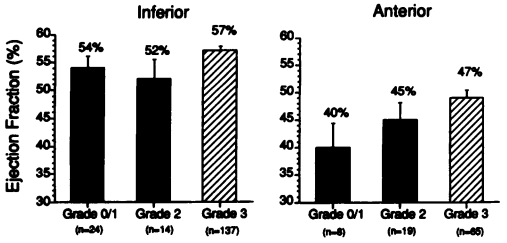

FIGURE 2. *Bar graphs of global ejection fraction by Thrombolysis in Myocardial Infarction grade and infarct location, (panel A) at discharge and (panel B) at 1 month. (See text for statistical summary.)*

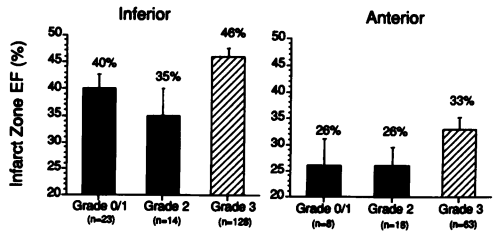

FIGURE 3. *Bar graphs of infarct zone ejection fraction (EF) by Thrombolysis in Myocardial Infarction grade and acute myocardial infarction location at discharge. (See text for statistical summary.)*

overall p=0.03). In the smaller (n=89) anterior acute myocardial infarction subgroup (see Figure 2B), grade 2 patients showed results no better than those for grades 0/1 patients (p=0.99) and less than that for grade 3 patients (p=0.07 for contrast 1; overall p=0.19).

Effect of Perfusion Grade on Global and Regional Ejection Fraction at 1 Month

Global ejection fraction at 1 month by TIMI grade is presented in Figure 1B and parallels results at discharge. Overall, a significant difference among grades is noted, with p=0.04, adjusted for acute myocardial infarction location. There was no difference in comparing grades 0/1 with grade 2 patients, but again, a significant difference resulted when grade 3 was compared with grades 0–2 patients (mean ejection fraction, 54% versus 49%), with an adjusted p=0.01.

The differences among patency groups noted at 1 month for global ejection fraction were maintained or augmented when infarct zone ejection fraction at 1 month was compared by TIMI grade (Figure 4). ANOVA among the groups gave an adjusted p=0.01. Again, there was no difference in comparing the results of grades 0/1 with grade 2 patients (contrast 1), but a highly significant difference emerged when comparing grade 3 with grades 0–2 patients (contrast 2; p=0.003).

Effect of Perfusion Grade on Cardiac Enzyme Kinetics

As has been noted in several other investigations, CK and CK-MB peaks were not useful in separating groups of patients by TIMI perfusion grade (Table 3), although time to peak shortened progressively for both CK and CK-MB with increasing perfusion grade. In contrast, LDH and LDH-1 did show differences in enzyme peaks that were significant for LDH, with a lower peak in grade 3 patients than in grades 0/1 and 2 patients (p=0.05). Both LDH and LDH-1 showed significant

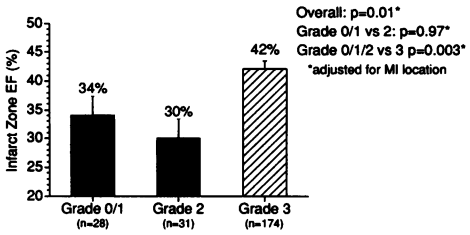

FIGURE 4. *Bar graph of infarct zone ejection fraction (EF) by Thrombolysis in Myocardial Infarction grade at 1 month.*

TABLE 3. Cardiac Enzyme Responses

A. Individual patient enzyme peaks	Grade			
Enzyme	0/1	2	3	p^*
Creatine kinase (IU/L)	2,153±230 (35)	3,013±327 (40)	2,418±134 (220)	0.24
Creatine kinase-MB (IU/L)	197±23 (35)	286±29 (40)	250±17 (210)	0.18
Lactate dehydrogenase (IU/L)	985±179 (35)	1,092±197 (39)	759±43 (217)	0.05
Lactate dehydrogenase-1 (IU/L)	465±105 (28)	482±99 (31)	354±26 (184)	0.08
B. Individual times from treatment to enzymatic peaks				
Enzyme				
Creatine kinase (hours)	20.8±1.8 (35)	15.5±1.0 (40)	13.4±0.4 (220)	0.0001
Creatine kinase-MB (hours)	17.8±1.3 (35)	14.4±0.8 (40)	12.7±0.3 (210)	0.0001
Lactate dehydrogenase (hours)	40.3±3.0 (35)	34.6±2.5 (39)	32.5±1.2 (217)	0.04
Lactate dehydrogenase-1 (hours)	38.8±2.9 (28)	35.2±2.5 (31)	30.0±1.0 (184)	0.003

*p values adjusted for acute myocardial infarction location. Values given as mean±SEM with No. of patients in parentheses.

shortening in time to peak with increasing perfusion grade (Table 3).

Comparisons of enzyme kinetics by grade were limited by the smaller proportion of patients with complete data sets (as required for the repeated-measures ANOVA). Nevertheless, when these patients were compared and time-release curves were generated, differences in the overall time-concentration interaction (or shapes) of the curves were observed by TIMI grade for LDH (n=148, p<0.001) and LDH-1 (n=81, p=0.003) (Figure 5). These differences were due to differences in contrast 2, comparing grade 3 with grades 0/1 and 2 (p=0.0001 and p=0.0002 for LDH and LDH-1, respectively).

The interaction of individual drug assignment (APSAC versus t-PA) with ventriculographic outcome by patency grade was evaluated at discharge and 1 month and did not achieve significance.

Effect of Patency Grade on ECG QRS Score

The mean QRS score on the discharge ECG by TIMI grade is shown in Figure 6. A higher score indicates more extensive infarction. Each point is estimated to represent infarction of approximately 3% of the left ventricle.[17] Overall, the three groups differ at an adjusted p=0.01. Although the score for grade 2 patients is slightly less than that of grades 0/1, the difference does not achieve significance. In contrast, grade 3 patients show a significantly lower QRS score than those with grades 0/1 or 2 perfusion, with a p=0.008. A difference in grade 3 versus grades 0–2 perfusion was also observed at 1 month ($p \leq 0.02$).

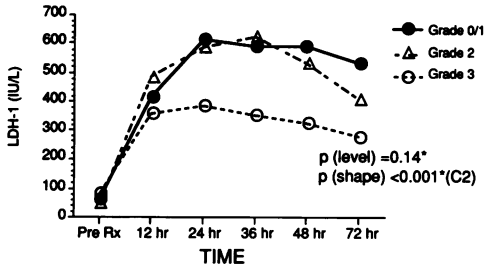

FIGURE 5. *Time-activity curves for lactate dehydrogenase-1 (LDH-1) by Thrombolysis in Myocardial Infarction grade in patients with complete data sets* (n=*8, 8, 65 patients for Thrombolysis in Myocardial Infarction grades 0/1, 2, 3, respectively). A significant difference in time-concentration interaction (shape of curves) by Thrombolysis in Myocardial Infarction grade is present* (p=*0.001).*

Effect of Patency Grade on In-Hospital and 1-Month Clinical Morbidity

The patency groups are too small to allow an adequately powered comparison of mortality or comparisons of individual nonfatal adverse clinical events among study groups. Therefore, to explore trends in adverse clinical outcomes, an overall clinical morbidity index, as previously described,[9,19] was constructed and compared using nonparametric testing and stepwise ordinal logistic regression (Table 4). Overall significance was not achieved; however, based on the difference trend in morbidity by patency grade (p<0.15, Table 4), exploratory subset comparisons were made using the same strategy as for the orthogonal contrasts (i.e., comparisons of groups 0/1 with 2 and groups 0–2 with 3). The comparison of 0/1 with 2 was not significant (p=0.49), whereas the comparison of 0–2 with 3 did approach significance (p=0.07, Mann-Whitney). The odds ratio for an adverse event was 1.51 (95% confidence interval, 0.97 to 2.52) for patients with patency grades 0–2 versus grade 3 using ordinal logistic regression (p=0.065). The morbidity index result by patency grade is consistent with that of the more powerful discriminator, ejection fraction, and suggests that addi-

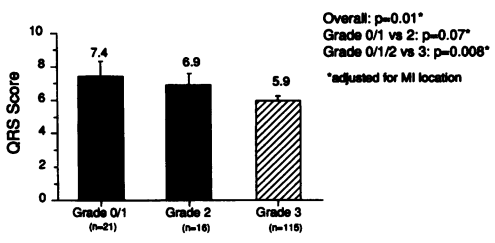

FIGURE 6. *Bar graph of mean QRS score on discharge ECG by Thrombolysis in Myocardial Infarction grade. MI, myocardial infarction.*

TABLE 4. Clinical Morbidity Analysis

Ordered end points* (worst event per patient)	Grade 0/1 (n=37)	Grade 2 (n=40)	Grade 3 (n=221)
Death (%, No.)	5 (2)	5 (2)	3 (7)
Stroke (hemorrhagic, thrombotic, embolic) (%, No.)	3 (1)	0 (0)	0 (1)
EF <30% or reinfarction or CHF or VF (%, No.)	27 (10)	33 (13)	21 (47)
Emergency CABG or ischemic pain or VT (%, No.)	27 (10)	38 (15)	36 (80)
None of these (%, No.)	38 (14)	25 (10)	39 (86)
Summed rank (No. of patients)*	5,785 (37)	6,843 (40)	31,924 (221)
Mean rank of patients*	156.3	171.1	144.5

*Death was given a score of 4 (worst); stroke, 3; ejection fraction (EF)<30% or reinfarction or congestive heart failure (CHF) or ventricular fibrillation (VF), 2; emergency coronary artery bypass graft surgery (CABG) or ischemic pain or ventricular tachycardia (VT), 1; and none, 0. Each patient was then ranked from 0 to 298 (with adjustment made for tied ranks), and the summed rank and mean rank in each of the groups (higher rank equals worse event status) calculated and compared.

†p=0.14 (Kruskal-Wallis). Similar p also obtained by ordinal logistic regression.

tional evaluations of this index in larger study populations will be of interest.

Coronary Interventions

Overall, coronary interventions (angioplasty, surgery) were performed within 1 month in 43% (n=128) of patients: 43%, 48%, 42%, respectively, of grade 0, 1, 2, and 3 patients (p=0.82 for intervention by patency grade). However, interventions were performed more frequently within the 48-hour window of angiographic assessment in patients with lower grades of flow (30% [11 of 37] of grades 0/1, 12% [five of 40] of grade 2, and 6% [14 of 221] of grade 3 patients), whereas later (>48 hours to 1 month) interventions were performed more frequently in those with initial grades 2/3 perfusion and clinically significant stenoses (14% [five of 37] of grades 0/1, 35% [14 of 40] of grade 2, and 36% [79 of 221] of grade 3 patients).

The influence of interventions on the effect of patency grade on ejection fraction was tested with three-way ANOVA, which included acute myocardial infarction location, and was found to be not significant. Ejection fractions at 1 week and 1 month were unaffected by interventions performed anytime (p=0.84 and p=0.41 at 1 week and 1 month, respectively) or within 48 hours (p=0.58, p=0.66).

Discussion

In the TEAM-3 study population, acute myocardial infarction patients were given standard thrombolytic therapy within 4 hours of symptom onset. Patients in whom treatment led to TIMI perfusion grade 2 at the 1-day determination of patency were difficult to distinguish from patients with grades 0/1 perfusion by ventriculographic, enzymatic, and ECG indexes of infarct size. In contrast, patients with grade 3 flow differed significantly from those with grades 0/1 and 2, suggesting that a significantly smaller infarct occurred in those patients who achieved "complete" perfusion. These findings complement those from an earlier study (TEAM-2[10,11]) in which patency was assessed within 2 hours of therapy and that showed that patients with grade 2 perfusion experienced enzymatic and ECG outcomes closer to those of patients with occluded (grades 0/1) than with patent (grade 3) arteries. In both studies, these differences were achieved despite the frequent use of "rescue" and elective procedures, performed as clinically directed, subsequent to angiography. Thus, neither 1–2-hour nor 1-day TIMI grade 2 perfusion appears to be sufficient to optimize myocardial salvage but rather results in functional outcomes closer to those of grades 0/1 than of grade 3 patients. Therefore, grade 3 perfusion, which was clearly distinguished from the other perfusion grades, may be the best measure of the relative functional outcome after thrombolytic therapy, whether assessed at 1–2 hours or 1 day, and therefore should be the goal of reperfusion strategies.

Considerations Relating Patency Grade to Outcome

The semiquantitative visual grading system of coronary "perfusion" devised by the TIMI investigators to characterize the flow of injected radio contrast in infarct-related arteries[8] has rapidly become a gold standard for visual grading of patency outcome. The underlying assumptions in relating the TIMI grades to myocardial functional outcome are that the intensity of radio contrast flow parallels the rate of native blood flow as well as the rate of myocardial tissue perfusion. Although the system is simple and intuitively appealing, these assumptions have not been rigorously validated. Also, differences among TIMI patency grades have not been systematically related to differences in outcome. These concerns are of special interest in relation to grade 2 perfusion: Does it represent more closely a reperfusion success, as commonly stated, or a reperfusion failure? The general correlation observed in this study between angiographic patency grade and noninvasively measured infarct size lends support to the concept that TIMI score generally represents a semiquantitative index of tissue perfusion, but it also indicates that grade 2 flow is more akin to reperfusion failure than to success.

Reasons for Poor Outcome With TIMI Grade 2 Patency

Grade 2 patency may have failed to achieve significant myocardial salvage compared with grades 0/1 because blood flow was inadequate or too delayed to meet the metabolic demands of jeopardized myocardium[25–29] or because of a greater tendency of vessels with grade 2 flow to rethrombose.[30] Grade 2 flow also may occur

secondary to loss of microvascular integrity in the infarct zone ("no reflow" phenomenon).[30,31]

Subsequent reocclusion may occur in a greater percentage of patients who are left with a very high-grade residual stenosis after thrombolysis (e.g., those with grade 2 versus grade 3 perfusion).[28,30,32] Some reports have also related reocclusion risk[30,32] and functional outcome[28,32] to minimal residual cross-sectional area of the culprit coronary lesion, whereas others have emphasized the unpredictability of reocclusion based on the angiographic characteristics of the lesion.[31,33] Because our patients with "inadequate flow" frequently received rescue procedures (angioplasty, bypass surgery), differences in reocclusion risk or late perfusion status appear to be less likely mechanisms in explaining the poor results in the grade 2 group than inadequate early perfusion.

Comparison With Other Studies

In a previous thrombolysis study of anistreplase and streptokinase by our group in 370 acute myocardial infarction patients,[10] the influence of different TIMI patency grades determined at 90–240 minutes (median, 130 minutes) on cardiac enzyme and ECG indexes of myocardial infarct size were evaluated.[11] In that study, as in the present one, the behavior of TIMI grade 2 patency was difficult to distinguish from grades 0/1 in most comparisons, whereas grade 3 contrasted significantly with the others: Perfusion grade 2 patients did not differ significantly from those with grades 0/1 in enzymatic peaks; times to peaks; and evolution of summed ST segments, Q waves, and R waves. In contrast, grade 3 patients showed significantly better outcomes for enzymatic peaks, times to peaks (three of four enzymes), and ECG indexes.

Several other studies have shown the importance of infarct artery patency in predicting convalescent left ventricular ejection fraction and short- and long-term survival,[1–7,28,32] but few have addressed outcome by TIMI grade or addressed the specific issue of grade 2 ("incomplete") flow. In the Western Washington Study, mortality reductions at 1 month and at 1 year were dependent on achieving patency, not just on the receipt of thrombolytic therapy.[34] Patients achieving "partial reperfusion" (probably grade 2 flow) in the Western Washington Study fared no better than controls or unsuccessfully treated patients. Unfortunately, patency correlations are not available for the subsequent, larger mortality prevention thrombolysis studies.[35–38]

Influence of Timing of Patency Determinations

Controversy has developed regarding the optimal end point for coronary patency assessments in clinical thrombolysis trials. Perfusion rates measured at various times after therapy represent the result of the temporally dynamic, opposing processes of reocclusion and ongoing thrombolysis/recanalization, which continue for several hours to days after thrombolysis. Traditionally, results at 90 minutes have been used for comparative and predictive purposes based on the rationale that early reperfusion should best predict myocardial salvage. However, 90-minute patency results have failed to predict relative mortality outcomes among regimens associated with differing reperfusion/patency rates.[7,39] Sherry and Marder[40] have observed that patency rates measured somewhat later than 60–90 minutes, but within a few hours to 1 day, appear to better predict mortality benefit than patency assessed at 90 minutes. This suggests that 1-day patency rates, as used in this study, also are of interest as predictors of outcome.

In the present study, the time for angiographic assessment of patency was chosen to be 1 day to avoid the confounding by early interventions of the left ventricular functional outcome end points. (Increased use of angioplasty and surgery has been found inevitably to follow angiographic assessments—a phenomenon referred to as the "oculostenotic reflex" or "reperfusion momentum."[41]) Moreover, it was recognized that 90-minute patency (averaging 70–75%)[7,8,13,42–45] had already been determined for the two treatment regimens and that 1-day assessments would add information complementary to the data on earlier perfusion[10,11] and of potential predictive value.

Combining the results of the present study, which assessed 1-day patency and evaluated ventriculographic end points, with those of our previous study (TEAM-2),[10,11] which used 90-minute patency and evaluated enzymatic and ECG end points, allows a strong and consistent conclusion to be drawn with regard to the predictive value of grade 3 versus grade 2 perfusion, measured both at 90–240 minutes and at 1 day, on subsequent outcome measures.

Comments on Statistical Approach

Simple comparisons of grade 2 with grade 3 ("complete perfusion") patients could have been made using *t* tests and would also have demonstrated significant differences (e.g., for comparisons of global and infarct zone ejection fraction at discharge and 1 month, peak LDH and times to peaks for three enzymes, and morbidity index). This less-sophisticated approach may have been appropriate had this been the only comparison of interest. However, other comparisons among the perfusion grades also were of interest, such as grade 2 versus grades 0/1 (the "closed-artery" group). Of prime interest was the question of whether grade 3 perfusion could still be differentiated from the other grades by outcome at 1 week and at 1 month despite the frequent use of reperfusion interventions (angioplasty, bypass) after the 1-day angiogram in these patients with initially poor perfusion. When multiple comparisons are made, when testing is performed among more than two groups, and when adjustment for differences in baseline variables is desired (e.g., acute myocardial infarction location), *t* testing is no longer appropriate or feasible, and ANOVA is required. When the ANOVA among groups is significant, specific pairwise testing may be considered, such as Dunnett's test or the orthogonal contrast method used here, to identify the source of the difference.[20,21] The orthogonal contrast method appeared to be best suited to our analysis because it takes advantage of the ordered grades of patency and uses a prospectively defined comparison strategy, thus increasing the power to discriminate differences. Comparisons progressively step up from grades 0/1 to 2, and then to 3, analyzing where important differences in outcome occur along the spectrum of patency grades. With this approach, we showed that outcome differences did not occur in stepping up from grades 0/1 to 2, but only in stepping up further to grade 3.

Study Limitations and Advantages

As for other data base analyses, interpretation of our results should take into account that the outcome-by-patency analysis in the TEAM-3 population explores a secondary hypothesis of the study and is based on nonrandomized groups of differing size. However, the characteristics of the three groups were well balanced for most baseline factors. Furthermore, end points were measured by blinded observers and analyzed centrally. There was an imbalance among groups in site of infarction, but the statistical comparisons were adjusted for this imbalance, and differences persisted after adjustment. Because the size of the patient groups with patency grades 0/1 and 2 were relatively small, the power to distinguish differences in outcome (e.g., ejection fraction) is low in our study for comparisons of grades 0/1 versus 2, and small differences cannot be excluded. The power of comparisons of grade 3 with grade 2 or grades 0–2 was adequate (i.e., 80–85%) for differences in outcome of the magnitude we observed (i.e., about 5–6% points in ejection fraction) but may not have discriminated if differences had been smaller. The study was of insufficient size to make valid mortality comparisons.

Patients in the study received one of two thrombolytic regimens. However, because the patency profiles achieved were similar, the results could be pooled across the two treatment groups. The outcome analysis by patency group is confounded by the use of frequent late (more than 1 day) and a few early (within 12 hours) interventions in patients judged to have inadequate perfusion or who had clinical ischemia. However, these interventions, applied to normalize perfusion, would be expected, if anything, to diminish true differences among the patency groups and were performed equally (overall) or more frequently (early on) in those with the lower perfusion grades. In fact, adjustment for interventions within the ANOVA did not affect the results. The optimal time to measure patency is controversial[7,8,40] and may vary, depending on the outcome variable of interest; the determination of the relation of outcome to patency at 1 day in this study is complementary to that of outcome to 90–240-minute patency in our previous study.[11] This study establishes an association between perfusion of grades 0–2 and a less-optimal functional outcome than that achieved with grade 3 perfusion, but the findings here do not demonstrate causality between perfusion grade and outcome. (In some patients, for example, grade 2 perfusion might *reflect* extensive infarction with microvascular injury and a "no-reflow phenomenon."[31])

As in any multicenter study, ventriculographic, enzymatic, or ECG data points were missing in some patients. This represented a small minority of patency-evaluable patients (i.e., 10% of data were missing for the predischarge radionuclide ventriculogram, the primary end point, and 1% and 6% for CK and LDH enzyme peaks, respectively). We do not believe that these missing data account for the reported differences among patency groups. The clinical morbidity index included all patency evaluable patients.

The results of this study should not be construed to imply that benefit is not achieved in patients with grades 0–2 patency who later achieve complete reperfusion through rescue procedures or delayed spontaneous reperfusion. An increasing number of studies have suggested that achieving infarct artery patency even beyond the time period when myocardial salvage is substantial may lead to benefit, perhaps by improving infarct healing, reducing infarct expansion and aneurysm formation, and reducing the propensity to future heart failure events and life-threatening ventricular arrhythmias.[5,6,46,47] The value and appropriate timing of "rescue" procedures after unsuccessful thrombolysis should be addressed in separate studies.[48]

Conclusions

A significant relation was shown between the different TIMI patency grades of infarct-related arteries, determined at 1 day, and ventriculographic, enzymatic, and ECG indicators of myocardial infarct size. The behavior of TIMI grade 2 (partial) perfusion, traditionally lumped together with grade 3 perfusion to comprise the total patency rate in most thrombolysis studies, was similar to that of grades 0/1 in most comparisons, whereas grade 3 perfusion contrasted significantly with the others, indicating substantial reductions in infarct size for patients achieving and maintaining grade 3 flow. The implication of these and our earlier findings is that grade 2 perfusion is generally not associated with optimal myocardial salvage and clinical outcome, and therefore grade 3 perfusion should be considered the best measure of success of thrombolytic therapy.

Appendix

Investigators of the multicenter TEAM-3 were as follows.

Principal investigator (No. of patients enrolled)	Study site	Co-investigator(s); study coordinator(s)
Jeffrey L. Anderson (30)	Salt Lake City, Utah	Labros A. Karagounis; Steve Ipsen, Ann Allen
Kevin F. Browne (30)	Lakeland, Fla.	Alan S. Brenner; Robert Roy
Predimen K. Shah (26)	Los Angeles, Calif.	Bojan Cercek; Adrian Antonescue
Douglas C. Morris (24)	Atlanta, Ga.	Henry Lieberman; Roberta Reed
Dan J. Fintel (21)	Chicago, Ill.	Richard Davison; Caryn Cochran, Lloyd Klein
Hiltrud S. Mueller (19)	New York, N.Y.	Mark A. Greenberg; Barbara Ventura
Allan M. Ross (14)	Washington, D.C.	Alan G. Wasserman; Gail Cavallo
Suzanne M. Hall (13)	Portland, Ore.	Beth Moore
Jack C. Askins (12)	Ogden, Utah	Steve Byrne
Andrew J. Doorey (12)	Newark, Dela.	Barry Denenberg; Nancy Gale
Cindy L. Grines (12)	Lexington, Ky.	Barbara Cutshaw
Ian Sarembock (10)	Charlottesville, Vir.	Eric R. Powers; Christine Tedesco
Patricia G. Fitzpatrick (9)	Rochester, N.Y.	Kristin Ainsworth
John Gregory (9)	Summit, N.J.	Maureen Chapnick
Rodney A. Johnson (9)	Baltimore, Md.	Sue Hall
Neal S. Kleiman (9)	Houston, Tex.	Phyllis Nelson, Rita Hill
D. Gregory Hopkins (8)	Santa Rosa, Calif.	Catherine Russell
K. Peter Rentrop (8)	New York, N.Y.	Janet Breen
Aryan N. Mooss (7)	Omaha, Neb.	Sayed Mohiuddin; Edwina Butkus
Elliott Rapaport (7)	San Francisco, Calif.	Ilene Lim; Carolyn Somelofski
Patricia Cole (6)	St. Louis, Mo.	Atul Shah; Lisa R. Spinner
Jeffrey Garrett (6)	Pittsburgh, Pa.	Stanley Grossman; Jane LaGrotteria
Ruben Lewin (5)	Milwaukee, Wisc.	Teresa Jaeger
Ray D. Magorien (4)	Columbus, Ohio	Colleen Lang
William N. O'Neill (4)	Royal Oak, Mich.	Gerald Timmis; Cynthia Tollis
Fred Leya (3)	Chicago, Ill.	Sarah Johnson; Rosita Picchi
Richard Conti (2)	Gainesville, Fla.	Jackie Bush
JoAnn Lindenfeld (2)	Denver, Colo.	Kathleen Stringer, Karen Keller

TEAM-3 Central Coordinating Staff consisted of Principal Investigator: Jeffrey L. Anderson, MD, University of Utah; Radionuclide Core Laboratory: Lewis C. Becker, MD, The Johns Hopkins University; Hematology Core Laboratory: Victor Marder, MD, University of Rochester; Angiography Core Laboratory: Sherman G. Sorensen, MD; Fidela LI Moreno, MD, University of Utah/LDS Hospital; ECG Core Laboratory/Enzyme analysis: Labros A. Karagounis, MD, University of Utah/LDS Hospital; Study Coordinator: Marian Roskelley, University of Utah/LDS Hospital; Statistical Consultants: Ronald Menlove, PhD, University of Utah; and Independent reviewer (verification of drug assignment code): Joseph S. Alpert, MD, Worcester, Mass.

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