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CLINICAL STUDIES

Mechanism of Benefit of Combination Thrombolytic Therapy for Acute Myocardial Infarction: A Quantitative Angiographic and Hematologic Study

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Objectives. **The goal of this study was to lend insight into the mechanisms responsible for the beneficial effects of combination thrombolytic therapy.**

Background. **Combination thrombolytic therapy for acute myocardial infarction has been associated with less reocclusion and fewer in-hospital clinical events than has monotherapy.**

Methods. **Infarct-related quantitative coronary dimensions and hemostatic protein levels were evaluated in 287 patients with acute myocardial infarction during the early (90-min) and convalescent (7-day) phases after administration of recombinant tissue-type plasminogen activator (rt-PA), urokinase or combination rt-PA and urokinase.**

Results. **Minimal lumen diameter was similar in the 90-min and 7-day phases after treatment with rt-PA, urokinase and combination rt-PA and urokinase (0.72 ± 0.45 mm, 0.62 ± 0.53 mm and 0.75 ± 0.58 mm, respectively, at 90 min, $p = 0.16$; and 1.05 ± 0.56 mm, 1.12 ± 0.72 mm and 0.94 ± 0.54 mm, respectively, at 7 days, $p = 0.22$). In-hospital clinical event and reocclusion rates were less frequent in patients receiving combination therapy than in those receiving monotherapy (25% vs. 38% and 32% for rt-PA and urokinase, respectively, $p = 0.084$; and 3% vs. 13% and 9% for rt-PA and urokinase, respectively, $p = 0.03$), but these events were unrelated to early or late coronary dimensions. Patients receiving combination therapy or urokinase monotherapy had significantly higher peak fibrin degradation products (1,307 ± 860 and 1,285 ± 898 μg/ml vs. 435 ± 717 μg/ml, respectively, $p < 0.0001$) and lower nadir fibrinogen levels (0.85 ± 1.00 and 0.75 ± 0.53 g/liter vs. 1.90 ± 0.86 g/liter, respectively, $p < 0.0001$) than did those receiving rt-PA monotherapy. Peak fibrinogen degradation products indirectly correlated ($p = 0.004$) and baseline ($p = 0.026$) and nadir ($p = 0.089$) fibrinogen levels directly correlated with reocclusion.**

Conclusions. **Lower in-hospital clinical event and reocclusion rates observed with combination thrombolytic therapy may relate to systemic hematologic factors rather than to the residual lumen obstruction after thrombolysis.**

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To achieve both rapid infarct-related artery recanalization typically associated with fibrin-specific thrombolytic agents (such as recombinant tissue-type plasminogen activator [rt-PA]) and sustained arterial patency frequently attributed to nonspecific thrombolytic agents (such as urokinase), combination thrombolytic therapy has been used as an alternative to monotherapy in patients with acute myocardial infarction (1–3). Compared with monotherapy, combination thrombolytic therapy has been associated with lower in-hospital clinical event and reocclusion rates, although 90-min infarct-related artery patency and recovery of ventricular function appear similar with combination therapy and monotherapy regimens (1).

Two potential factors may be responsible for the reduced rates of in-hospital clinical events and reocclusion associated with combination thrombolytic therapy. First, compared with monotherapy, combination thrombolytic therapy may enhance clot lysis, thereby resulting in a lower residual

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thrombus burden and a less avid substrate for recurrent platelet aggregation and reocclusion. Alternatively, combination thrombolytic therapy may produce more pronounced alterations of hemostatic protein variables, culminating in fibrinogen depletion, elevation of fibrinogen degradation products and reduced platelet aggregability. Sustained alteration of the favorable hemostatic protein milieu may allow stabilization of the fibrin-plaque segment, thereby preventing reocclusion.

To lend insight into the mechanisms responsible for the beneficial effects associated with combination thrombolytic therapy, infarct-related quantitative coronary dimensions were evaluated in 287 patients with acute myocardial infarction during the early (90-min) and convalescent (7-day) phases after administration of rt-PA, urokinase or a combination rt-PA and urokinase. Hemostatic protein levels were also monitored during the 1st 24 h after treatment. The relations among infarct-related residual coronary dimensions, hemostatic variables and in-hospital clinical events and reocclusion were examined.

Methods

Patient selection. In the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI-5 trial) (1), 575 patients with acute myocardial infarction admitted to seven regional cardiology centers were randomized in a 3 × 2 factorial design to one of three thrombolytic regimens (rt-PA, urokinase or combination rt-PA and urokinase) and to immediate cardiac catheterization with "rescue angioplasty," if indicated, or to delayed catheterization. Inclusion criteria included 1) symptoms compatible with acute myocardial infarction of ≤6 h duration, 2) ≥0.1 mV ST segment elevation in two or more contiguous leads, and 3) age <76 years. Patients with contraindications to thrombolytic therapy such as prior stroke, recent trauma or surgery, refractory hypertension, active bleeding, cardiopulmonary resuscitation for >10 min, prior coronary bypass surgery, prior Q wave infarction or cardiogenic shock were excluded. Thrombolytic treatment regimens included 1) rt-PA (Activase, Genentech; 100 mg for 3 h [60 mg 1st h with a 6-mg bolus and 20 mg/h for 2 h]; 2) urokinase (Abbokinase, Abbott Laboratories; 1.5 mU bolus and 1.5 mU infusion for 1 h); or 3) combination rt-PA (1 mg/kg body weight, and urokinase, 1.5 mU for 1 h). Unless contraindicated, all patients received aspirin (325 mg), heparin (5,000 U bolus and an infusion of 1,000 U/h for 48 h adjusted to maintain the activated partial thromboplastin time to 1.5 to 2 times normal) and diltiazem (30 to 60 mg 3 times/day). Nitrates and angiotensin-converting enzyme inhibitors were used only if clinically indicated. The protocol was approved by the Institutional Review Board at each of the clinical sites.

Study group (Fig. 1). This report includes the 287 patients who were randomly assigned to early (90-min) arteriography after treatment with rt-PA, urokinase or combination rt-PA and urokinase. Early catheterization was not performed in 5 patients because of patient or physician refusal in 3 cases; death in 1 case and other complications in 1, and the study was technically insufficient for quantitative analysis in an additional 10 patients. Convalescent arteriography was performed 7 days after thrombolytic treatment in 176 patients; in the absence of intercurrent ischemic events (coronary angioplasty in 48 patients; emergency coronary bypass surgery in 38 and death in 3); other complications in 4, or patient or physician refusal in 3.

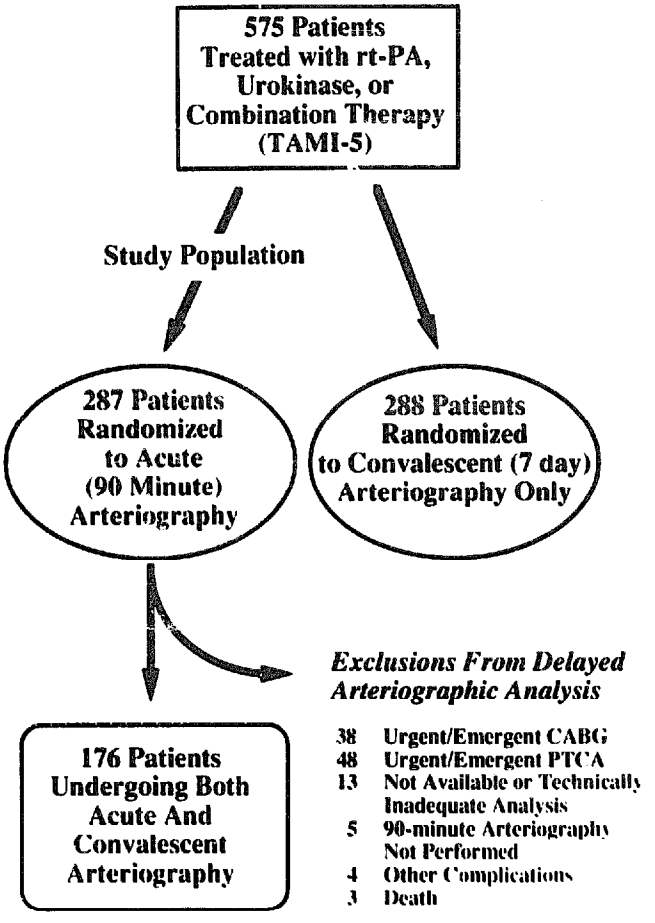

Figure 1. Schematic representation of patients randomized to 90-min and 7-day arteriography after treatment with recombinant tissue-type plasminogen activator (rt-PA), urokinase or combination rt-PA and urokinase. CABG = coronary bypass surgery; PTCA = coronary angioplasty; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction.

Cardiac catheterization. Cardiac catheterization was generally performed from the right or left femoral artery by using 5F or 6F Judkins catheters unless peripheral vessel tortuosity mandated use of larger catheters or "rescue" coronary angioplasty was performed. Cineangiograms of the infarct-related artery were obtained in two or more orthogonal projections and infarct-related artery patency was determined by using the Thrombolysis In Myocardial Infarction (TIMI) criteria (4). Both coronary angiography and contrast ventriculography were technically adequate for quantitative analysis in 197 patients during the 90-min phase and in 150 patients during the 7-day phase.

Quantitative arteriographic analysis. The 90-min and 7-day cineangiograms were forwarded to the University of Michigan Core Angiographic Laboratory, where quantitative coronary analysis was performed by an observer who had no knowledge of the clinical and ventriculographic outcome. By using a previously validated quantitative computer-assisted method (5), end-diastolic cine frames demonstrating the infarct-related artery stenosis in its most severe projection were digitized using a cine-video converter. An automated edge detection algorithm was applied to the digitized image and the arterial contour was determined. With use of the diagnostic coronary catheter as the reference diameter, the absolute minimal lumen diameter of a user-defined normal and a stenotic segment were determined. The residual minimal lumen diameter was used as an approximation of the degree of clot dissolution in the 90-min and 7-day phases (6). A minimal lumen diameter of 0.0 mm was assigned to patients with total occlusion, and a minimal lumen diameter was not imputed for patients who underwent coronary bypass surgery or for whom follow-up angiograms were not available. Multivessel disease was defined as two or more epicardial coronary vessels with ≥50% lumen diameter stenoses.

The effects of minimal lumen diameter on subsequent clinical events, reocclusion and left ventricular function were analyzed by using logistic and linear regression analysis. In addition, on the basis of the retrospective, unpublished analysis of 90-min angiograms from the TAMI-1 and TAMI-3 trials, a trend toward more frequent reocclusion was noted when the infarct-related minimal lumen diameter was ≤1.0 mm. Therefore, to further analyze the predictors of in-hospital clinical events, reocclusion and recovery of left ventricular function, patients were dichotomized into those with a 90-min infarct-related minimal lumen diameter ≤1.0 mm and those with an infarct-related minimal lumen diameter >1.0 mm. In addition, to evaluate the effect of delayed clot lysis on the recovery of left ventricular function during the convalescent period, patients were also categorized into those with a ≤0.5-mm change in the infarct-related minimal lumen diameter or those with a >0.5-mm change in minimal lumen diameter from the 90-min to the 7-day arteriogram.

Quantitative left ventricular function analysis. Single-plane contrast left ventriculography was performed from the 30° right anterior oblique projection. Global and regional wall motion analysis was performed by an observer who had no knowledge of the clinical outcome and the quantitative angiographic analysis. Ventricular contours from selected nonpostpremature end-diastolic and end-systolic cine frames were hand drawn and digitized. By using a computer-assisted ventricular analysis program, global left ventricular ejection fraction was determined with the area-length method (7); regional wall motion, expressed as the SD per chord, was determined with the method of Sheehan et al. (8). The 90-min and 7-day ventriculograms were analyzed, and the changes in global and regional left ventricular function were determined. Ventriculographic analysis was not performed if the only beats available were postpremature ventricular complexes, if inadequate contrast filling of the entire ventricular cavity occurred or if significant motion artifact was present during the ventriculogram.

Clinical events. The following in-hospital clinical events were obtained from the clinical case report form: 1) death; 2) reinfarction, diagnosed by a second elevation of cardiac enzymes; 3) reocclusion, defined angiographically; 4) recurrent ischemia, defined by >20 min of symptoms compatible with myocardial ischemia associated with new ST or T wave changes; 5) the need for coronary angioplasty or coronary bypass surgery before the planned 7-day catheterization; and 6) congestive heart failure, diagnosed by radiographic pulmonary edema, rales more than bibasilar or requirement for inotropic support.

Hemostatic protein analysis. Blood samples, collected on 0.01 *M* citrate and 200 KIU/ml aprotinin at baseline and 1, 4 and 24 h after fibrinolytic therapy, were immediately processed and kept frozen at −20°C until assayed at the core hematology laboratory. Fibrinogen was determined by a coagulation rate assay (9), and fibrinogen degradation products were analyzed by the tanned red cell agglutination inhibition technique (10). D-dimer levels were determined with the method of Elms et al. (11).

Statistical analysis. For descriptive presentation of the data, continuous baseline and treatment variables were summarized as mean values ± SD, whereas discrete variables were expressed as percentages. Binary outcomes among the drug regimens were compared with conventional chi-square analysis. Similarly, continuous outcomes among the drug regimens were compared with use of the Kruskal-Wallis test. Univariable logistic regression was used to examine the relation between minimal lumen diameter at 90 min and the occurrence of reocclusion and in-hospital events. The relation between minimal lumen diameter and left ventricular function was displayed with dichotomous cut points but also characterized with linear regression analysis. A p value <0.05 was considered significant.

Results

Clinical characteristics. The clinical characteristics of patients randomized to early cardiac catheterization and to treatment with one of the three thrombolytic regimens have been reported previously (1). In general, these clinical features were similar in each of the three treatment groups (Table 1), although more patients treated with rt-PA were male and had a history of prior myocardial infarction. The infarct-related artery was most often the right coronary artery, followed in frequency by the left anterior descending and circumflex coronary arteries. Mean symptom duration was 3.2 ± 1.9 h (range 1.1 to 7.4) before administration of thrombolytic therapy and was similar in the treatment groups. In-hospital clinical events and reocclusion were less

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Table 1. Baseline Characteristics of Patients Receiving rt-PA, Urokinase or Combination Thrombolytic Therapy

	rt-PA (n = 95)	Urokinase (n = 95)	Combination (n = 97)
Age (yr)	56 ± 11	57 ± 10	58 ± 10
Male (%)	89	77	71
Prior MI (%)	22	8	12
Multivessel disease (%)	44	63	51
Infarct-related artery (%)			
LAD	36	38	42
LCx	14	15	8
RCA	48	46	49
Left main	1	0	0
Unknown	1	1	1
Symptom duration (h)	3.5 ± 2.8	3.0 ± 1.2	3.2 ± 1.3
Reocclusion (%)*	13	9	3
Any in-hospital event (%)†	38	32	25

Data are presented as mean value ± SD or percent of subgroup. *p = 0.03. †p = 0.084. LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; rt-PA = recombinant tissue-type plasminogen activator; RCA = right coronary artery. Adapted, with permission, from Califf et al. (1).

frequent in patients receiving combination thrombolytic therapy (1).

Acute and convalescent infarct-related minimal lumen diameter. Compared with those receiving rt-PA or urokinase monotherapy, patients receiving combination rt-PA and urokinase had a slightly larger, but not significantly different, minimal lumen diameter immediately after initiation of thrombolysis (p = 0.16) (Table 2). Minimal lumen diameter was independent of the location of the infarct-related artery and symptom duration. Minimal lumen diameter at 7 days also was similar in the three treatment groups. Notably, the change in minimal lumen diameter from the 90-min to the 7-day studies also did not vary by combination versus monotherapy treatment regimen.

Hemostatic protein levels. Patients receiving urokinase and combination rt-PA and urokinase had significantly lower 1-h, 4-h, 24-h and nadir fibrinogen levels compared with those of patients receiving rt-PA (Table 3). Similarly, 1-h, 4-h, 24-h and peak fibrinogen degradation products and D-dimer levels were significantly higher in patients receiving urokinase and combination rt-PA and urokinase than in those receiving rt-PA monotherapy.

Angiographic and hemostatic correlates of in-hospital clinical events and reocclusion. Although patients with in-hospital clinical events had a somewhat smaller 90-min infarct-related minimal lumen diameter, these values were not significantly different from that of patients without such events (0.64 ± 0.52 mm vs. 0.72 ± 0.53 mm; p = 0.26). Furthermore, in the subgroup of patients with angiographically documented coronary reocclusion, infarct-related minimal lumen diameter was similar to that in patients without subsequent reocclusion (0.70 ± 0.52 vs. 0.68 ± 0.59; p = 0.87). Baseline, peak and nadir hemostatic protein concentrations did not correlate with acute minimal lumen diameter

Table 2. Minimal Lumen Diameter After rt-PA, Urokinase or Combination Thrombolytic Therapy

	rt-PA	Urokinase	Combination
% Patency	76 (68/89)	73 (67/92)	77 (70/91)
$MLD_{90\ min}$ (mm)	0.72 ± 0.45 (86)	0.62 ± 0.53 (88)	0.75 ± 0.58 (85)
By IRA			
LAD	0.81 ± 0.46 (30)	0.59 ± 0.55 (35)	0.67 ± 0.48 (37)
LCx	0.51 ± 0.34 (12)	0.47 ± 0.38 (12)	0.93 ± 0.57 (6)
RCA	0.72 ± 0.47 (43)	0.68 ± 0.56 (41)	0.80 ± 0.66 (42)
By symptom-onset			
<2 h	0.66 ± 0.54 (18)	0.66 ± 0.62 (17)	0.63 ± 0.44 (15)
2 to 4 h	0.74 ± 0.40 (46)	0.62 ± 0.53 (55)	0.80 ± 0.61 (51)
>4 h	0.73 ± 0.50 (22)	0.54 ± 0.46 (16)	0.71 ± 0.59 (19)
$MLD_{Day\ 7}$ (mm)	1.05 ± 0.56 (57)	1.12 ± 0.72 (54)	0.94 ± 0.54 (65)
$\Delta MLD_{90\ min-7\ day}$ (mm)	0.22 ± 0.55 (55)	0.30 ± 0.69 (52)	0.08 ± 0.42 (61)
By IRA			
LAD	0.14 ± 0.34 (18)	0.39 ± 0.80 (18)	0.07 ± 0.37 (29)
LCx	0.43 ± 0.98 (6)	0.13 ± 0.21 (6)	−0.12 ± 0.45 (6)
RCA	0.22 ± 0.57 (30)	0.28 ± 0.68 (28)	0.15 ± 0.46 (26)

Data are expressed as percent of subgroup or mean value ± SD with the number of patients in parentheses. ΔMLD = change in minimal lumen diameter; IRA = infarct-related artery; MLD = minimal lumen diameter; other abbreviations as in Table 1.

(Table 4). However, baseline and nadir fibrinogen levels directly correlated and peak fibrinogen degradation products indirectly correlated with angiographically documented reocclusion.

Correlates of recovery of left ventricular function. By linear regression analysis, a direct correlation between the infarct-related minimal lumen diameter and regional wall motion at 90 min (p = 0.021) was noted, although no other relations were found between 90-min or 7-day minimal lumen diameter and 90-min or 7-day global or regional left ventricular function. Values for 90-min and 7-day global left ventricular function and infarct-zone regional wall motion were also comparable in patients with a 90-min infarct-related minimal lumen diameter ≤1 mm and in those with minimal lumen diameter >1 mm (Table 5). The 90-min infarct-related minimal lumen diameter was identical (0.8 mm) in patients with a final left ventricular ejection fraction ≤0.40 or >0.40.

Discussion

Alterations in hemostatic protein concentrations. In patients with acute myocardial infarction, combination therapy

Table 3. Hemostatic Protein Levels in Patients Receiving rt-PA, Urokinase and Combination Thrombolytic Therapy

	rt-PA (n = 95)	Urokinase (n = 95)	Combination (n = 97)
Fibrinogen (g/liter)			
Baseline	3.36 ± 2.48	2.88 ± 0.96	3.13 ± 1.02
1	2.91 ± 1.15	0.98 ± 0.58	0.78 ± 0.61
4	1.90 ± 0.96	0.77 ± 0.61	0.69 ± 0.54
24	2.90 ± 3.55	1.46 ± 0.50	1.51 ± 0.61
Nadir*	1.90 ± 0.86	0.75 ± 0.53	0.85 ± 1.00
FDP (μg/ml)			
Baseline	20 ± 33	102 ± 451	19 ± 53
1	414 ± 880	1,166 ± 1,024	1,365 ± 1,025
4	375 ± 656	1,265 ± 887	1,325 ± 840
24	156 ± 306	398 ± 441	486 ± 559
Peak*	435 ± 717	1,285 ± 898	1,307 ± 860
D-dimer (ng/ml)			
Baseline	152 ± 186	244 ± 439	186 ± 279
1	565 ± 392	908 ± 623	745 ± 682
4	1,073 ± 1,344	992 ± 644	1,261 ± 816
24	796 ± 1,132	713 ± 632	841 ± 585
Peak*	1,091 ± 1,333	1,031 ± 756	1,271 ± 842

Values are expressed as mean value ± SD. *$p < 0.001$ compared with baseline levels. FDP = fibrin degradation products; rt-PA = recombinant tissue-type plasminogen activator.

with rt-PA and urokinase has been shown to reduce in-hospital clinical ischemic events more effectively than has either agent administered alone (1). However, the mechanism responsible for the favorable clinical outcome in patients receiving combination thrombolytic therapy has remained somewhat elusive. Infarct-related artery patency rates and recovery of left ventricular function have been shown to be equivalent using single-agent and combination thrombolytic strategies (1–3). Similarly, in the present study, quantitative angiographic analysis of infarct-related coronary artery dimensions in 287 patients failed to demonstrate that the lower in-hospital clinical event rate observed in patients receiving combination thrombolytic therapy resulted from more extensive early or late coronary thrombolysis. Notably, patients receiving combination rt-PA and urokinase and urokinase monotherapy had more profound depletion of fibrinogen and larger production of fibrinogen degradation products and D-dimer than did patients receiving rt-PA monotherapy. These alterations in hemostatic protein concentrations were correlated with angiographically documented reocclusion, suggesting that lower clinical event rates may relate to systemic hematologic factors rather than to the residual lumen obstruction after thrombolysis.

Extent of clot lysis after combination thrombolytic therapy versus monotherapy. Within 90 min after intravenous thrombolytic administration, infarct-related artery patency was obtained in the majority of patients with acute myocardial infarction (12–18). Despite successful reperfusion, a "critical" residual stenosis generally persists (6,12–19). Pathologic study suggests that the residual stenosis is composed of ruptured atherosclerotic plaque with superimposed platelet- and fibrin-rich thrombi (20,21) that may serve as a nidus for subsequent reocclusion. In the absence of reocclusion, the residual coronary stenosis may improve progressively during the convalescent period (6,16,18,20), as a result of both thrombus dissolution and remodeling of the atherosclerotic plaque.

Recombinant tissue-type plasminogen activator (4) and related fibrin-selective thrombolytic agents (22) may be more effective than nonselective agents in establishing early infarct-related artery recanalization. However, a major drawback of the fibrin-selective agents appears to be early reocclusion, which may occur in 12% of patients despite concomitant therapy with aspirin and heparin (23). Fibrin-nonselective agents, such as streptokinase and urokinase, may be less effective in establishing early infarct-related recanalization, but they are associated with less frequent late reocclusion, owing, in part, to more profound effects on hemostatic protein levels resulting from systemic fibrinolysis. As a result of this "catch-up" phenomenon, similar patency rates with fibrin-selective and nonselective agents have been shown 24 h after administration of thrombolytic agents (22).

The differential effects on early infarct-related artery recanalization and reocclusion of fibrin selective and nonselective agents have led some to suggest that combination thrombolytic administration may be more effective than monotherapy in establishing early and sustained infarct-related artery recanalization (1–3). Combined use of a fibrin-selective agent such as rt-PA and a fibrin-nonselective agent such as urokinase may result in more timely and sustained thrombolysis than could be achieved by either agent alone. No prior studies have used quantitative angiography as the reference standard to examine the effects of combination and monotherapy regimens on the magnitude of clot lysis.

In this report, infarct-related artery patency rates and

Table 4. Effect of Hemostatic Protein Levels on Reocclusion and Minimal Lumen Diameter at 90 Minutes

	Reocclusion*			Minimal Lumen Diameter at 90 Minutes†		
	Relation	Chi-Square	p Value	Relation	Chi-Square	p Value
$Fibrinogen_{Baseline}$	Direct	4.96	0.026	Direct	0.036	0.85
$Fibrinogen_{Nadir}$	Direct	2.90	0.089	Indirect	0.146	0.70
$FDP_{Baseline}$	Indirect	0.92	0.340	Indirect	0.490	0.48
FDP_{Peak}	Indirect	8.10	0.004	Direct	0.751	0.39

*Logistic regression analysis. †Linear regression analysis. FDP = fibrin degradation products.

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Table 5. Effect of the Extent of Thrombolysis on Left Ventricular Function

	Minimal Lumen Diameter at 90 Minutes		Δ in Minimal Lumen Diameter	
	≤1.0 mm	>1.0 mm	≤0.5 mm	>0.5 mm
90 min				
LVEF	53.3 ± 12.9 (156)	51.9 ± 14.1 (41)	—	—
Infarct zone RWM	−2.61 ± 1.01 (156)	−2.53 ± 1.12 (41)	—	—
Noninfarct zone RWM	0.24 ± 1.77 (156)	0.39 ± 1.91 (41)	—	—
7 days				
LVEF	55.0 ± 11.8 (107)	53.5 ± 14.5 (43)	55.0 ± 12.4 (122)	51.7 ± 13.4 (25)
Infarct zone RWM	−2.06 ± 1.24 (107)	−2.03 ± 1.29 (43)	−1.99 ± 1.28 (122)	−2.42 ± 1.03 (25)
Noninfarct zone RWM	0.12 ± 1.32 (107)	0.18 ± 1.43 (43)	0.58 ± 0.94 (93)	0.19 ± 0.84 (22)
Δ				
Δ LVEF	0.6 ± 7.3 (87)	2.2 ± 8.1 (31)	1.8 ± 7.4 (93)	−2.9 ± 7.0 (22)
Δ Infarct zone RWM	0.44 ± 0.97 (87)	0.74 ± 0.80 (31)	0.58 ± 0.94 (93)	0.19 ± 0.84 (22)
Δ Noninfarct zone RWM	−0.12 ± 0.97 (87)	−0.16 ± 1.06 (31)	−0.03 ± 0.97 (93)	−0.66 ± 0.98 (22)

Data are expressed as mean value ± SD with the number of patients in parentheses. Δ = change from 90 min to 7 days; LVEF = left ventricular ejection fraction (%); RWM = regional wall motion (SD/chord).

values for residual minimal lumen diameter did not differ significantly early after the administration of rt-PA, urokinase or combination rt-PA and urokinase. Minimal lumen diameter in this study was similar to that obtained in previous reports with use of intracoronary streptokinase (6) and after a 40-mg intravenous infusion of rt-PA (16). Improvements in minimal lumen diameter (0.3 to 0.5 mm during the 7-day convalescent period) were also similar to those seen after rt-PA monotherapy (16) and were not significantly different among the patients treated with combination versus monotherapy. These data suggest that the degrees of initial and delayed clot lysis, as determined by quantitative angiographic methods, are similar whether patients are treated with single-agent rt-PA or urokinase or with combination rt-PA and urokinase.

Angiographic and hemostatic protein correlates of in-hospital clinical events and reocclusion. Recurrent ischemic events including coronary reocclusion occur in up to 21% of patients after successful thrombolysis with rt-PA (12) and are often associated with significant in-hospital morbidity and mortality (23). Smaller series have suggested that the residual lumen diameter after thrombolytic therapy may be an important determinant of risk for recurrent ischemic events (17,24,25). However, in a report by Ellis et al. (12) of 190 patients with angiographically documented successful thrombolysis qualitative morphometric and quantitative angiographic variables were not useful in predicting in-hospital ischemic events. In the present study of nearly 300 patients, quantitatively determined infarct-related minimal lumen diameters were also of no help in predicting either in-hospital clinical events or angiographically documented reocclusion.

Experimental studies suggest that recurrent thrombosis after thrombolysis may occur principally as a consequence of recurrent platelet aggregation and thrombosis at the site of the residual coronary stenosis (26–28). In these models reocclusion was prevented or at least ameliorated by specific platelet inhibition (27,28). Alterations of hemostatic protein levels may also influence reocclusion after thrombolysis. In a series of 386 patients receiving 150 mg of rt-PA, peak fibrinogen degradation products ($p = 0.038$) and changes in fibrinogen levels from baseline to nadir ($p = 0.0003$) were indirectly correlated with reocclusion (29). Notably, quantitative blood loss was also correlated with nadir fibrinogen levels and peak fibrinogen degradation products. Systemic fibrinogen degradation appears to be less extensive with lower doses of rt-PA; <15% of patients develop fibrinogen levels <1 g/l when the currently approved dose of 100 mg of rt-PA is administered (3).

In the present study, patients treated with combination thrombolytic therapy or urokinase monotherapy had significantly lower nadir fibrinogen levels and higher fibrinogen degradation products than did patients treated with rt-PA monotherapy. Peak fibrinogen degradation products were indirectly related to angiographic reocclusion, suggesting that extensive systemic fibrinogen degradation may have been responsible for the lowered clinical event rates and lower rates of reocclusion observed with combination therapy. Similar to a prior report (29), no relation was noted between alterations in hemostatic protein levels and reperfusion, assessed in the present report by quantitative angiographic methods.

Correlates of early and 7-day left ventricular function. Several factors, including baseline left ventricular function (30), time to reperfusion (31) and infarct-related artery patency (32), have been related to the recovery of left ventricular function after myocardial infarction. At least two prior studies (14,33) have suggested that severity of the residual stenosis may be an important determinant of subsequent recovery of left ventricular function. In a series of 38 patients receiving intracoronary streptokinase, residual minimal lumen diameter after successful reperfusion was <0.4 mm in 7 patients and ≥0.4 mm in 31 (14). Recovery of regional wall motion was significantly less in patients with a

critical residual stenosis after thrombolysis (0.0 ± 0.9 SD/chord vs. 1.0 ± 1.3 SD/chord for residual stenosis ≥0.4 mm, $p < 0.05$). Another smaller study of 20 patients undergoing intravenous or intracoronary thrombolysis followed by coronary angioplasty suggested that recovery of ventricular function in the convalescent period was related to successful treatment of the residual stenosis by balloon angioplasty (33). Notably, in larger series of patients randomized to immediate versus delayed angioplasty after administration of thrombolytic therapy, early treatment of the residual stenosis using balloon angioplasty failed to demonstrate any beneficial effect on ventricular function (34,35).

Detailed analysis of global left ventricular function and regional wall motion was available in 150 patients in the convalescent phase of myocardial infarction in the present study. As assessed by both continuous and dichotomized outcome measures, only early minimal lumen diameter was correlated with early infarct-zone regional wall motion ($p = 0.021$). Notably, neither early acute nor convalescent minimal lumen diameter was correlated with the recovery of global or regional ventricular function. Minimal lumen diameter was also similar in patients with a convalescent left ventricular ejection fraction of ≤ or >0.40. These findings support previous data (14,30,32) suggesting that the critical determinant of recovery of ventricular function is coronary *reperfusion*, with the extent of clot lysis and severity of residual stenosis of less importance.

Limitations of the study. The present analysis has several limitations. First, the angiographic criterion used to assess the degree of clot lysis, the minimal lumen diameter, may incompletely represent the geometric resolution of coronary thrombus in patients with acute myocardial infarction. For example, changes in stenosis area (16) may provide a more accurate representation of the degree of clot lysis, but this method is difficult to apply to a single 90-min arteriogram, particularly when the lesion length is not precisely known. Second, the use of automated edge detection analysis of digitized arteriograms may be of limited discriminating value in lesions with a minimal lumen diameter <1.0 mm (36). Nevertheless, the use of the quantitatively determined end point in the present study should have demonstrated some beneficial effect if combination thrombolytic therapy is truly more effective in lysing thrombus. Technically adequate ventriculographic analysis was available in approximately 60% of patients receiving thrombolytic therapy; exclusions were most commonly due to difficulties in obtaining a ventriculogram suitable for quantitative analysis. Moreover, because of the effects of noninfarct zone hyperkinesia and late potential prognostic importance of left ventricular remodeling, left ventricular ejection fraction may not be the optimal end point for the clinical evaluation of left ventricular function (37). Finally, front-loading rt-PA regimens (infusion over 90 min) have been associated with higher patency rates than have the standard 3-h infusions of rt-PA (38). Whether added clinical benefit over that of front-loaded rt-PA monotherapy is achieved by using combination thrombolytic therapy with a more rapid infusion of rt-PA is currently under evaluation.

Conclusions. The present results suggest that the extent of clot lysis, assessed by the minimal lumen diameter of the infarct-related artery at 90 min and 7 days, is similar in patients receiving rt-PA, urokinase or combination rt-PA and urokinase. In-hospital clinical events, reocclusion and the recovery of global and regional left ventricular function appear to be independent of the degree of initial and late clot lysis. More profound alterations in hemostatic protein concentrations, that is, fibrinogen, fibrinogen degradation products and D-dimer levels, were noted in patients receiving urokinase and a combination of rt-PA and urokinase than in patients receiving rt-PA monotherapy; these hemostatic protein concentrations correlated with reocclusion. Thus, the lowered clinical event rates and lowered rates of reocclusion noted in patients receiving combination thrombolytic therapy may be due to hemostatic factors unrelated to the degree of initial or late clot lysis.

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