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Increased Serum Levels of Fibrinogen Degradation Products Due to Treatment With Recombinant Tissue-Type Plasminogen Activator for Acute Myocardial Infarction Are Related to Bleeding Complications, But Not to Coronary Patency

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The association of increasing serum levels of fibrinogen degradation products after recombinant tissue-type plasminogen activator (rt-PA) therapy with bleeding and early coronary patency was assessed in 242 patients with acute myocardial infarction. After administration of 5,000 IU heparin, a median of 40 mg (range 35 to 60) of double chain rt-PA was given intravenously in 90 min. Bleeding occurred in 62 patients; in 73% of patients it was observed within the 1st 24 h and 84% of events consisted of hematoma or prolonged bleeding, or both, at puncture sites. Bleeding events occurred 2.12 times as often in patients with serum levels of fibrinogen degradation products >85 mg/liter as in patients with serum levels <22 mg/liter (95% confidence interval 1.01 to 4.43).

The infarct-related coronary vessel was patent in 65% of patients at 90 min after the start of rt-PA infusion. In patients with high serum levels of fibrin(ogen) degradation products, coronary patency at 90 min after the start of rt-PA infusion was not better (13% less, 95% confidence interval −33%, 13%) than in patients with low serum levels. This uncoupling of thrombolytic effect in terms of coronary patency and systemic fibrinogenolysis confirms the experimentally demonstrated fibrin specificity of double chain rt-PA in human subjects. Because fibrin specificity of single chain rt-PA is at least similar to that of double chain rt-PA, the observations in this analysis most likely hold also for single chain rt-PA.

These findings suggest that a dose of rt-PA just below the threshold that causes systemic fibrinogenolysis might be optimal in terms of bleeding and coronary patency. Measurements of fibrinogen degradation products during rt-PA infusion might help to titrate rt-PA dosing in individual patients.

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Recombinant human tissue-type plasminogen activator (rt-PA) has been shown in the Thrombolysis in Myocardial Infarction (TIMI I) trial (1) to be twice as effective as intravenous administration of streptokinase to recanalize occluded infarct-related coronary arteries in patients with acute myocardial infarction and to yield more frequently patent coronary arteries 90 min after the start of treatment (2). Furthermore, rt-PA preserves left ventricular function (3,4) and reduces both enzymatic infarct size and mortality after myocardial infarction (3,5).

It is a fibrin-specific thrombolytic agent: plasminogen is converted to plasmin primarily at the site of the thrombus. However, at high dosages used for treatment of acute myocardial infarction, this fibrin specificity is partly lost and fibrinogen breakdown in the circulation occurs in part of the patients (2,6). In patients treated with intracoronary streptokinase or urokinase, increasing systemic fibrinogenolysis is associated with more frequent recanalization (7,8). It is unknown whether this sequence is similar for patients treated with rt-PA. Furthermore, it is unknown to which degree fibrinogen degradation products developing after

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administration of rt-PA contribute to the occurrence of bleeding complications.

In this analysis, the association of increasing serum levels of fibrinogen degradation products with bleeding and early coronary patency after rt-PA therapy in 242 patients with acute myocardial infarction is assessed. The influence of other known determinants of bleeding or coronary patency on this association (confounding) is eliminated by multivariate logistic regression analysis.

Methods

Patients and management. The present investigation is based on data from patients treated with rt-PA in the first three trials of the European Co-operative Study Group for rt-PA (2,9,10) in which the protocols and methods for data collection were similar. All protocols were approved by institutional committees on human research and for all three trials only patients who gave informed consent were eligible for participation. The first trial (9) was a double-blind and randomized comparison of coronary patency after rt-PA (0.75 mg rt-PA/kg body weight intravenously over 90 min) with coronary patency after placebo in 129 patients from six centers. In the second trial (2), coronary patency after 0.75 mg rt-PA/kg body weight given intravenously over 90 min was compared with coronary patency after 1.5 million IU streptokinase given intravenously over 60 min in 129 patients from seven centers. In the third trial (10), coronary patency and the influence of a second infusion of 30 mg rt-PA over 6 h on subsequent reocclusion at 6 to 24 h was assessed in 123 patients from 11 centers treated with 40 mg rt-PA over 90 min.

Patients between 21 and 70 years of age with ≥30 min of chest pain and ST segment elevation of ≥0.3 mV in two or more electrocardiographic (ECG) precordial leads or ≥0.2 mV in two or more limb leads were eligible for inclusion, provided that rt-PA infusion could be started within 6 h from onset of symptoms in the first two trials and within 4 h in the third trial. In the first two trials, patients with a previous infarction were excluded, whereas a previous myocardial infarction in another territory did not disqualify the patient for the third study. Otherwise, exclusion criteria were identical.

All consenting patients were immediately registered at an independent telephone service and received treatment allocation from that service. After blood sampling for coagulation assays, an intravenous bolus of 5,000 IU heparin was given. Thereafter, an intravenous infusion of rt-PA was given over 90 min. The same batch of primarily double chain rt-PA was used in all three studies (G-11021, manufactured by Genentech Inc. and supplied by Boehringer Ingelheim International GmbH).

Coronary angiography. The first coronary angiogram of the infarct-related vessel was performed between 75 and 90 min after the start of rt-PA infusion. In the patients of the third study, coronary angiography was repeated at 6 to 24 h. All coronary angiograms were centrally assessed by teams of three assessors, of whom two were always present to maintain consistency. The infarct-related segment was identified on the basis of ECG and angiographic evidence. Patency was defined as complete distal filling of the infarct-related coronary artery, not through collateral vessels, within three cardiac cycles at the first adequate contrast injection.

Bleeding events. The protocol required a detailed description of all bleeding complications at the end of the rt-PA infusion, after the first coronary angiogram and at discharge, including hematoma >5 cm in diameter and prolonged bleeding of >30 min duration.

Hemostasis variables. Blood samples were collected before and at 60 and 90 min after the start of rt-PA infusion. Tubes for blood collection were provided containing 0.5 ml sodium citrate (final concentration 0.01 mol/liter) and aprotinin to counteract proteolysis by in vitro plasmin formation (final concentration 150 KIU/ml) for the determination of levels of fibrinogen, fibrinogen degradation products and activated partial thromboplastin time. Blood samples were centrifuged within 1 h and stored at −20°C. All hemostasis tests were performed centrally in the Central Coagulation Laboratory (Leuven). Methods of assessment have been described previously (11). The normal value for the plasma level of fibrinogen is 2 to 4 g/liter and for serum level of fibrin(ogen) degradation products is <8 mg/liter.

Data analysis. Of the 251 patients allocated to rt-PA in the three European trials, 9 were excluded from this analysis: 2 did not receive the full dose of rt-PA, 6 had unassessable 90 min angiograms, and 1 had bleeding that was noticed during rt-PA infusion and therefore could not be related to the serum level of fibrinogen degradation products after rt-PA administration. The remaining 242 patients received the full dose of rt-PA and had assessable 90 min angiograms.

Because the exact start of bleeding complications is often difficult to assess, all bleeding events throughout the hospital phase were included in this analysis. Bleeding rate was defined as the percent of patients with at least one bleeding event. When more than one bleeding event was reported for a patient, the time of the first noticed event was used. Patency rate was defined as the percent of patients with a patent infarct-related artery on the angiogram at the end of the 90 min rt-PA infusion.

Patients were grouped in three equally sized subgroups according to the serum level of fibrinogen degradation products after rt-PA infusion. The chosen levels of fibrin(ogen) degradation products of 22 and 85 mg/liter are therefore arbitrary. Three groups were selected to enable assessment of trends in bleeding and coronary patency and because more groups would weaken strength of associations. Subse-

Table 1. Effect of rt-PA Infusion on Hemostasis Variables in 242 Patients

	1st Trial (n = 61)	2nd Trial (n = 62)	3rd Trial (n = 119)	Total (n = 242)*
rt-PA dosage (mg)	60 (40,60)	55 (35,60)	40 (40,40)	40 (35,60)
Fibrinogen (g/liter)				
Before infusion	2.7 (2.3 to 3.5)	2.4 (2.0 to 2.8)	2.6 (2.3 to 2.9)	2.6 (2.2 to 2.9)
At 60 min	2.0 (1.7 to 2.5)	1.8 (1.3 to 2.2)	2.3 (1.9 to 2.7)	2.1 (1.7 to 2.6)
At 90 min	1.4 (0.9 to 2.3)	1.3 (0.9 to 1.7)	1.8 (1.2 to 2.2)	1.5 (1.0 to 2.2)
Fibrin(ogen) degradation products (mg/liter)				
Before infusion	5 (5 to 7)	6 (5 to 12)	3 (2 to 3)	5 (3 to 5)
At 60 min	15 (8 to 34)	20 (12 to 35)	14 (9 to 27)	17 (9 to 31)
At 90 min	38 (14 to 155)	40 (20 to 120)	36 (15 to 90)	38 (17 to 110)
Activated partial thromboplastin time (s)				
Before infusion	60 (51 to 75)	61 (50 to 73)	58 (51 to 86)	60 (51 to 75)
At 60 min	102 (81 to 141)	99 (73 to 152)	158 (105 to 180)	125 (85 to 180)
At 90 min	112 (72 to 165)	126 (96 to 180)	180 (145 to 180)	163 (98 to 180)

*For fibrinogen and fibrin(ogen) degradation products, the number of patients with assessable blood samples before infusion, at 60 min and at 90 min, respectively, was 198, 212 and 210; for activated partial thromboplastin time, 199, 212, 208. Continuous variables are given as median with the 1st and 3rd quartile in parentheses. rt-PA = recombinant tissue-type plasminogen activator.

quently, bleeding and patency rates were determined in each subgroup. The subgroup with low serum levels of fibrin(ogen) degradation products was chosen as the reference group. The second and third subgroups were compared with the reference group with use of rate ratios (that is, the rate in the second or third group divided by the rate in reference group); 95% confidence intervals for rate ratios were determined according to the method of Katz et al. (12).

Distortion in the relation between serum levels of fibrin or fibrinogen degradation products and bleeding or patency (confounding) caused by unequal distributions of other known determinants of bleeding or patency among these subgroups was simultaneously eliminated by multivariate logistic regression analysis. The following determinants of bleeding were considered: 1) trial in which the patient participated, 2) age, 3) gender, 4) pulmonary rales before allocation, 5) thrombocyte count before rt-PA infusion, 6) fibrinogen after rt-PA, 7) activated partial thromboplastin time after rt-PA, reflecting mainly the degree of heparinization, 8) streptokinase given after rt-PA, and 9) second infusion of rt-PA in the third trial (10). Similarly, for coronary patency, the determinants considered were: 1) trial in which the patient participated, 2) age, 3) gender, 4) use of intravenous nitrates, which has been reported to be beneficial for coronary patency in the setting of thrombolytic therapy (13,14), and 5) activated partial thromboplastin time, prolonged mainly by heparinization, which possibly improves thrombolytic efficacy (15,16). A detailed description of the design of the multivariate logistic regression models and methodology to obtain adjusted rate ratios and 95% confidence intervals is given in the Appendix.

Results

Clinical features. The median age of the 242 patients was 56 years (range 31 to 70); 223 were male (84%). The median delay from the onset of symptoms to the start of rt-PA infusion was 2.8 h (range 0.9 to 5.8). A median dose of 40 mg (range 35 to 60) of rt-PA was administered over 90 min. Ten patients (4.1%) died during the hospital stay, 2 on the 1st day and 8 after the 4th day. No death was related to a bleeding complication. Cardiogenic shock was the cause of death in five patients, thromboembolism in 2, cardiac tamponade in 2 and electromechanical dissociation during late angiography in 1.

Hemostasis variables before, during and after rt-PA (Table 1). A moderate decrease in fibrinogen and a moderate increase in serum level of fibrin or fibrinogen degradation products were observed during rt-PA infusion. Before treatment, 1% of the patients (2 of 198 with analyzable blood samples) had a fibrinogen level <1 g/liter and at 90 min 22% (46 of 210 with analyzable blood samples). At 90 min, a serum level of fibrin(ogen) degradation products ≥22 mg/liter was found in 67% of the patients (141 of 210 with assessable blood samples). The activated partial thromboplastin time was increasingly prolonged during rt-PA infusion, a finding that reflects the heparin administration and to a minute extent the formation of fibrin(ogen) degradation products.

In the first two trials, the rt-PA dosage was higher than that in the third trial (Table 1). This is reflected in a trend toward a lesser decrease in fibrinogen and lower serum levels of fibrin(ogen) degradation products at 90 min after start of rt-PA infusion in the third trial (10). Nevertheless,

Table 2. Survey of the 62 Bleeding Events in All 242 Patients and the Time That the Bleeding Was First Noticed

No. of Patients With	Within 24 h	24 to 48 h	After 48 h	Total
Retroperitoneal bleeding	—	1	—	1
Hematemesis	2	—	—	2
Hematuria	1	—	1	2
Hematuria + gum bleeding	1	—	—	1
Gum bleeding	2	—	—	2
Hematuria + prolonged bleeding	—	—	1	1
Hematoma and/or prolonged bleeding				
Blood transfusion given	6	2	1	9
No blood transfusion given	33	7	3	43
Unexplained anemia	—	—	1	1
Total	45	10	7	62
No. of patients with blood transfusion	—	6	4	10

the activated partial thromboplastin time was more prolonged than that in the other trials, probably by more rigid heparinization in the third trial.

Bleeding events (Table 2). In seven patients, two bleeding events were reported; the bleeding rate was 26% (62 of 242 patients). Most bleeding complications occurred within the 1st 24 h (73%) and consisted of hematoma or prolonged bleeding, or both, at a puncture site (84%). Two patients had hematemesis; one was treated with cimetidine, the other did not receive special therapy. Retroperitoneal bleeding was suspected in another patient with epigastric pain and decrease in hemoglobin from 14.7 to 10.2 g/dl; no special treatment was given and the patient was discharged on the 11th day. No intracranial bleeding occurred. Blood transfusion was given to 10 (16%) of 62 patients with a bleeding event: for hematoma in 7 patients, a combination of hematoma and prolonged bleeding in 2 and unexplained anemia in 1 patient. No patient classified as a nonbleeder received blood transfusion.

Table 3. Increasing Serum Levels of Fibrin(ogen) Degradation Products (mg/liter at 90 min) in Relation to Bleeding and Coronary Patency Rate

Fibrin(ogen) Degradation Products at 90 min (mg/liter)		Crude Rate Ratio	Adjusted Rate Ratio
	Bleeding Rate		
<22	16% (11/69)	Reference	Reference
22 to 85	29% (20/69)	1.82 (0.94 to 3.50)	1.40 (0.73 to 2.65)
≥85	38% (27/72)	2.35 (1.27 to 4.37)	2.12 (1.01 to 4.43)
Missing	13% (4/32)	0.78 (0.27 to 2.28)	0.83 (0.27 to 2.55)
	Patency Rate		
<22	70% (48/69)	Reference	Reference
22 to 85	58% (40/69)	0.83 (0.65 to 1.08)	0.75 (0.57 to 0.99)
≥85	64% (46/72)	0.92 (0.73 to 1.16)	0.87 (0.67 to 1.13)
Missing	75% (24/32)	1.08 (0.84 to 1.39)	1.13 (0.82 to 1.56)

Crude and adjusted rate ratio, respectively, before and after elimination of distortion of the relation between serum levels of fibrin(ogen) degradation products and bleeding or coronary patency caused by unequal distribution of other determinants of bleeding or coronary patency over the various categories of serum levels of fibrin(ogen) degradation product (see Methods); 95% confidence intervals are presented in parentheses.

Fibrinogen degradation products and bleeding (Table 3). The bleeding rate was higher among patients with higher serum levels of fibrin(ogen) degradation products. Patients with a serum level of >85 mg/liter had a bleeding complication approximately twice as often as did those with a serum level <22 mg/liter. This relation was maintained after adjustment by multivariate logistic regression analysis. The variables that were used for this adjustment are listed in the Appendix. The other variables mentioned in the Methods section did not influence the relation between serum levels of fibrin(ogen) degradation products and bleeding. Figure 1 depicts the relation between serum levels of fibrinogen degradation products and bleeding, adjusted for the variables listed in the Appendix, together with its 95% confidence range.

Coronary patency. At 90 min after the start of rt-PA infusion, the infarct-related vessel was found patent in 159 of the 242 patients (patency rate 65%, 95% confidence interval 59 to 71). The patency rate was similar in the three trials: 61% (95% confidence interval 48 to 73) in the first trial, 69% (95% confidence interval 56 to 80) in the second trial and 66% (95% confidence interval 56 to 74) in the third trial.

Fibrin or fibrinogen degradation products and patency (Table 3). A trend of decreasing coronary patency was observed with increasing serum levels of fibrinogen degradation products before and after correction by logistic analysis. The variables used in the logistic regression model are given in the Appendix. The other determinants of coronary patency mentioned in the Methods section did not distort the relation between fibrin(ogen) degradation products and coronary patency. Figure 2 illustrates the absence of higher patency rates with increasing serum levels of fibrinogen degradation products.

Discussion

Recombinant tissue-type plasminogen activator (rt-PA) is an effective thrombolytic agent with limited systemic fibrinogenolysis in the vast majority of patients, when compared with intravenous streptokinase. However, bleeding has remained a frequent side effect in the clinical trials so far (1,2,3,6). This analysis reveals that increasing serum levels of fibrinogen degradation products are related to more frequent bleeding complications, but not to greater coronary patency at 90 min after the start of rt-PA infusion.

Fibrinogen degradation products and bleeding. The relation between fibrin(ogen) degradation products and bleeding might be explained by the fact that fibrinogen degradation

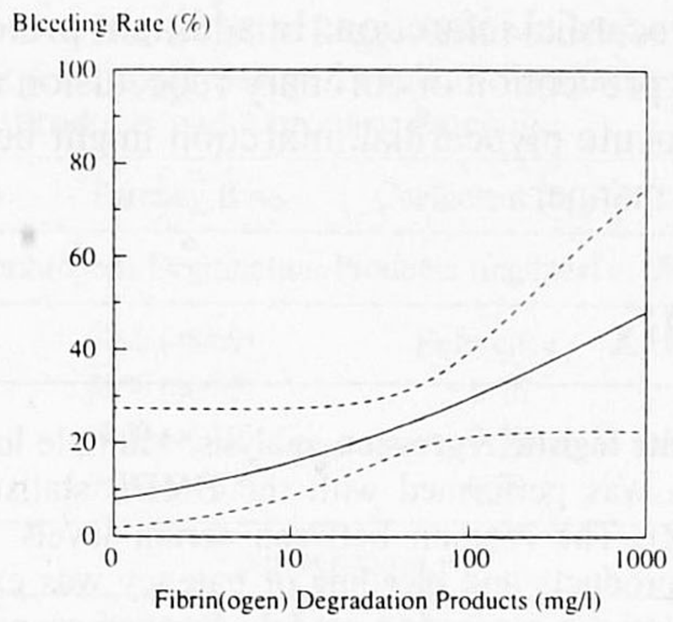
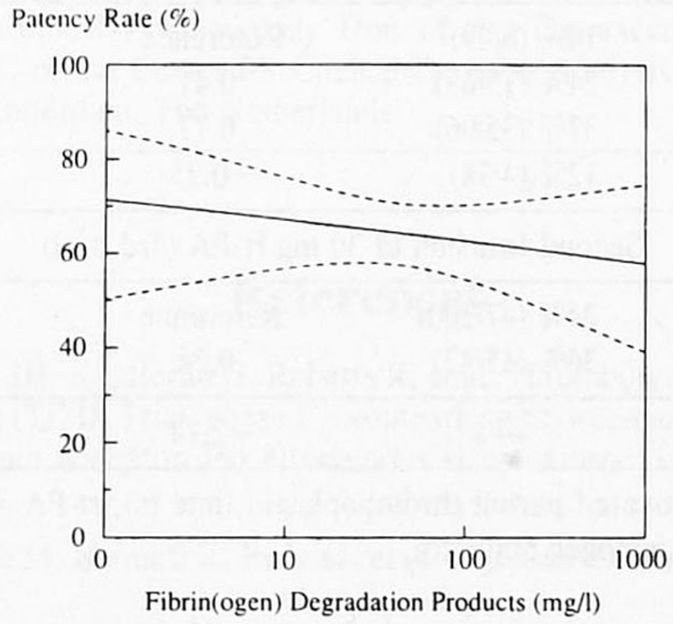


Figure 1. Bleeding rate as a function of increasing serum levels of fibrin(ogen) degradation products (as continuous variable, logarithmic scale) at 90 min after start of rt-PA infusion. Confounding by other determinants of bleeding was eliminated by multiple logistic regression analysis. The dotted lines represent 95% confidence limits. rt-PA = recombinant tissue-type plasminogen activator.

products act as antithrombins, fragment Y being the most active (18). There is evidence that fibrinogen degradation after rt-PA results in relatively large amounts of early degradation products belonging to the fragment X and Y groups (11). In addition, fibrinogen degradation products inhibit fibrin polymerization, resulting in a defective fibrin structure, and impair platelet function (18). Also, the TIMI study group reported a relation between serum levels of fibrinogen degradation products and bleeding after administration of double and single chain rt-PA (6). However, in that report no adjustment for confounding variables was made by multivariate regression analysis.

The adjusted rate ratios of 1.40 and 2.12 for bleeding at increasing levels of fibrinogen degradation products are probably an underestimation of the strength of the relation

Figure 2. Coronary patency rate as a function of increasing serum levels of fibrinogen degradation products (as continuous variable, logarithmic scale) at 90 min after infusion of rt-PA. Confounding by other determinants of coronary patency was eliminated by multiple logistic regression analysis. The **dotted lines** represent 95% confidence limits. rt-PA = recombinant tissue-type plasminogen activator.



because they are conditional on the prolongation of activated partial thromboplastin time, which is partly caused by fibrinogen degradation products.

Fibrinogen degradation products and patency. Increasing serum levels of fibrin(ogen) degradation products were not related to better coronary patency at 90 min, but tended to be inversely related to coronary patency. The TIMI study group (19) also reported an inverse relation between systemic fibrinogenolysis and recanalization at 90 min for double chain rt-PA; patients with recanalization had 31% decline in fibrinogen versus 41% in those patients without recanalization (95% confidence interval for this 10% difference: 8% to 12%). The possibility of an inverse relation is worth further investigation, both in vitro and in animal and clinical studies. An explanation could be that systemic fibrinogenolysis counteracts the fibrinolytic efficacy of rt-PA through negative feedback (inactivation of t-PA by fibrinogen degradation products?).

In patients treated with streptokinase or urokinase, recanalization occurs more frequently with increasing serum levels of fibrinogen degradation products (7,8). This finding is in agreement with the fact that streptokinase and urokinase are not fibrin specific and result in conversion of plasminogen to plasmin in the free circulation, producing breakdown of fibrinogen and clotting factors V and VIII (18).

It could be argued that prolongation of activated partial thromplastin time might not be a determinant of coronary patency, because the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) study group (20) recently reported that patients given heparin concomitant with rt-PA did not have a higher coronary patency rate than did patients given rt-PA alone. Also, it has been suggested (21) that heparin might reduce plasmin formation by t-PA at the site of the thrombus. Therefore, the multivariate logistic regression analysis in this analysis was repeated without activated partial thromboplastin time. The same trend was found for the relation between serum levels of fibrinogen degradation products and coronary patency, although less pronounced (rate ratio and 95% confidence interval for serum level of fibrinogen degradation products from 22 to 85 mg/liter, 0.82; 0.63 to 1.06; for serum level of fibrinogen degradation products ≥85 mg/liter, 0.92, 0.72 to 1.18).

Limitations of the analysis. The test developed by Merskey that we used in these studies does not differentiate between fibrin degradation and fibrinogen degradation products. However, this lack does not invalidate our analysis because the degradation products after thrombolysis with rt-PA for acute myocardial infarction consist primarily of fibrinogen degradation products (22). Similarly, in pulmonary embolism where fibrin mass is much larger than that in coronary thrombosis, predominantly fibrinogen degradation products were found (23). Therefore, in the present analysis the degradation products observed most likely reflect fibrinogen degradation and not fibrin degradation.

Another concern could be that in vitro degradation of fibrinogen might have occurred between blood collection and deep-freezing, which is not completely eliminated by aprotinin. If indeed fibrinogen degradation products in the present analysis originated mainly from in vitro degradation, the serum level of such products reflects lytic activity in serum rather than in vivo fibrinogen breakdown. Greater lytic activity in serum would then be associated with increased bleeding rate, but not with higher coronary patency.

One should be cautious in extrapolating the relation between fibrinogen degradation products and bleeding events that was observed in the present analysis to other forms of bleeding (e.g., intracranial bleeding). In this investigation, the incidence of serious bleeding events was too low to allow separate analyses of various types of bleeding. Finally, it should be appreciated that in all patients in these trials acute angiography was performed to assess coronary patency. One would expect less frequent bleeding if acute catheterization is not performed. However, in patients treated with rt-PA without acute angiography, similar incidence rates ranging from 23% to 29% and similar types of bleeding have been reported (3,24).

Implications of the present analysis. Increasing serum levels or fibrinogen degradation products were related to more frequent bleeding, but not to better coronary patency. The observation that thrombolytic effect and systemic fibrinogenolysis were completely uncoupled confirms the fibrin specificity of double chain rt-PA in patients. These findings probably hold also for single chain rt-PA because fibrin specificity of single chain rt-PA is at least similar to fibrin specificity of double chain rt-PA. Although single chain rt-PA needs to be administered at higher doses than does double chain rt-PA, because of its shorter plasma half-life, it resulted in less fibrinogen breakdown at equipotent doses in terms of coronary recanalization (6).

These considerations suggest that there may be an optimal dose of rt-PA for every individual with maximal thrombolytic effect and without fibrinogen breakdown, whereas at higher doses, systemic fibrinogenolysis is induced with an increased risk for bleeding but without better thrombolytic effect. Determination of fibrinogen degradation product levels during rt-PA infusion might help to identify this optimal dose for an individual patient. Rapid tests for quantitative or semiquantitative determination of levels of fibrinogen degradation products, preferrably in whole blood and specifically measuring fibrinogen degradation products, should be developed. These tests might enable the clinician to titrate the rt-PA dosage, in a manner similarly to the titration of insulin dosage on the basis of blood sugar levels. This approach, which is restricted to fibrin-specific thrombolytic agents, might be even more relevant for possible indications as pulmonary lung embolism, artificial heart valve thrombosis and venous thrombosis, where time is less crucial than that in acute myocardial infarction. In addition, prolonged rt-PA infusion for prevention of coronary reocclusion after thrombolysis for acute myocardial infarction might be individualized in this manner.

Appendix

Multivariate logistic regression analysis. Multiple logistic regression analysis was performed with the BMDP statistical package (program LR). The relation between serum levels of fibrinogen degradation products and bleeding or patency was expressed in a multivariate logistic regression model. A set of reported variables that were known to be predictors of bleeding or patency was selected. These variables were forced in a model, one at a time, together with the various categories of serum levels of fibrin(ogen) degradation products. Only those variables affecting the relation

Table 4. Multivariate Logistic Regression Model for the Assessment of the Relation Between Serum Levels of Fibrin(ogen) Degradation Products and Bleeding

Variable ($X_{i,j}$)	Bleeding Rate	Coefficient ($b_{i,j}$)	Standard Error
Fibrin(ogen) Degradation Products (mg/liter) at 90 min			
<22	16% (11/69)	Reference	—
22 to 85	29% (20/69)	0.47	0.46
≥85	38% (27/72)	1.10	0.55
Missing	13% (4/32)	−0.25	0.77
Pulmonary Rales Before Allocation			
No	22% (43/194)	Reference	—
Yes	40% (19/48)	0.90	0.39
Thrombocytes Before Infusion (10^9/liter)			
<220	39% (26/74)	1.13	0.45
220 to 280	23% (15/71)	0.31	0.47
≥280	19% (11/71)	Reference	—
Missing	39% (10/26)	1.35	0.57
Fibrinogen at 90 min (g/liter)			
<1.21	31% (22/70)	−0.40	0.56
1.21 to 1.91	24% (18/74)	−0.35	0.44
≥1.91	27% (18/66)	Reference	—
Missing	13% (4/32)	−0.25	0.77
aPTT at 90 min (s)			
<95	16% (8/49)	Reference	—
95 to 180	24% (15/63)	0.41	0.52
≥180	37% (35/96)	0.77	0.49
Missing	12% (4/34)	−0.25	0.77
Second Infusion of 30 mg rt-PA (3rd trial)			
No	24% (47/200)	Reference	—
Yes	36% (15/42)	0.54	0.42
Intercept	—	−2.74	0.61

aPTT = activated partial thromboplastin time (s); rt-PA = recombinant tissue-type plasminogen activator.

Table 5. Multivariate Logistic Regression Model for Assessment of the Relation Between Serum Levels of Fibrin(ogen) Degradation Products and Coronary Patency

Variable ($X_{i,j}$)	Patency Rate	Coefficient ($b_{i,j}$)	Standard Error
Fibrin(ogen) Degradation Products (mg/liter) at 90 min			
<22	70% (48/69)	Reference	—
22 to 85	58% (40/69)	−0.76	0.38
≥85	64% (46/72)	−0.39	0.37
Missing	75% (24/32)	0.39	0.54
Nitroglycerin iv			
No	62% (106/170)	Reference	—
Yes	72% (52/72)	0.58	0.32
aPTT at 90 min (s)			
<95	59% (29/49)	Reference	—
95 to 180	56% (35/63)	−0.24	0.39
≥180	71% (68/96)	0.62	0.38
Missing	77% (26/34)	0.39	0.54
Intercept	—	0.59	0.35

iv = intravenous; other abbreviations as in Table 4.

between the various categories of these serum levels and bleeding or patency were combined in a final model. Adjusted rate ratios and 95% confidence intervals for the various categories of serum levels of fibrinogen degradation products were obtained according to the method of Miettinen (17) by the following formula, in which the mean was entered for all variables (X_i) other than the category of serum levels of fibrinogen degradation products for which the adjusted rate ratio was determined; one for the category of serum level of fibrinogen degradation products under study (variable X_j) in the numerator and 0 in the denominator:

$$\text{Rate ratio} = \frac{[1+\exp(-(\text{intercept}+\Sigma_i b_i X_i + b_j*1))]^{-1}}{[1+\exp(-(\text{intercept}+\Sigma_i b_i X_i + b_j*0))]^{-1}}$$

95% confidence interval: rate ratio$^{(1-1.96/\text{chi-0})}$, rate ratio$^{(1+1.96/\text{chi-0})}$;

where chi-0 is the ratio of the fitted coefficient for the category of serum level of fibrinogen degradation products of which the confidence interval has to be determined, to the standard error (SE) of this coefficient. Coefficients (b_i, b_j) and standard errors for all variables in the final model are listed in Tables 4 and 5.

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