Recurrent Ischemia Without Warning

Analysis of Risk Factors for In-Hospital Ischemic Events Following Successful Thrombolysis With Intravenous Tissue Plasminogen Activator

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Ischemic events after successful thrombolysis have been reported to occur in 18–32% of patients treated for acute myocardial infarction with thrombolytic therapy, and previous studies in which patients received streptokinase suggest that risk of early recurrent ischemia is closely related to the presence of a high-grade residual stenosis. If these events are predictable after intravenous recombinant tissue-plasminogen activator (rt-PA) thrombolytic therapy, then further intervention after its use could be targeted at selected patients. One-hundred ninety-two patients from the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) I and TAMI III trials had successful rt-PA–mediated thrombolysis without immediate coronary angioplasty (PTCA). One-hundred seventy-four of these patients (92%) had prehospital discharge angiography. The mean age was 56±11 years; 81% were men; the infarct-related artery was the left anterior descending in 76 (39.8%), the left circumflex in 24 (12.6%), and the right coronary artery in 91 (47.6%). Thrombolysis with rt-PA resulted in a residual 73±13% diameter and 0.95±0.51 mm stenosis by quantitative coronary arteriography, and Thrombolysis in Myocardial Infarction (TIMI) flow grade 2 in 59.2% and 3 in 40.8% of stenoses as assessed on angiograms obtained 90 minutes after the initiation of rt-PA therapy. Recurrent ischemic events (ischemia requiring emergency percutaneous transluminal coronary angioplasty or urgent bypass surgery, reocclusion of the infarct-related artery, or cardiac death) occurred in 41 patients (21.3%). The recurrent ischemic events were not related to any of eight prospectively defined variables: the infarct-related artery, TIMI flow grade, percent diameter stenosis, absolute luminal diameter, angiographically-defined thrombus, diffuse disease or ectasia in the infarct-related artery, or Ambrose morphology of the infarct-related stenosis. Thus, 1) recurrent ischemic events are frequent after rt-PA and 2) such events are *not* predictable by findings available by in-depth quantitative and morphologic assessment at the time of angiography performed 90 minutes after rt-PA administration. It follows with the inability to stratify a patient's risk of recurrent ischemia that the decision for triage to coronary revascularization procedures after successful thrombolysis with rt-PA remains an especially difficult one. (*Circulation* 1989;80:1159–1165)

Early recurrent ischemic events occur in 18–32% of patients treated for acute myocardial infarction with successful thrombolytic therapy.[1–6] The ability to predict which patients are likely to have such events would have a profound impact on triage to definitive coronary revascularization procedures. Reports from series of patients treated with intracoronary or intravenous streptokinase have suggested that the presence of a high-grade residual stenosis predicts the recurrence of recurrent ischemia.[1–5] These studies, however, were performed in a limited number of patients who often underwent serial coronary angiography until arterial patency was demonstrated and in whom there was no detailed morphologic assessment of the infarct-related artery and stenosis.

Recently, the administration of intravenous human recombinant tissue-plasminogen activator (rt-PA) has been shown to achieve higher early patency

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rates than intravenous streptokinase in patients treated for acute myocardial infarction.[8,9] The predictors of recurrent ischemia after the use of rt-PA in this setting have not been reported.

Over the course of the Thrombolysis and Angioplasty in Acute Myocardial Infarction (TAMI) trials, in which intravenous rt-PA was used, we have accrued a large population of patients who had successful thrombolysis and no immediate coronary angioplasty. By protocol design, these patients underwent urgent coronary angiography at the time of recurrent ischemia and systematic repeat angiographic evaluation before hospital discharge. This cumulative experience with over 190 patients who did not undergo early mechanical revascularization, despite a high-grade residual infarct-artery stenosis in most, afforded us the opportunity to study several key variables that might predict recurrent ischemia. We tested the hypothesis that a high-grade residual stenosis, a delayed flow pattern, or several morphologic abnormalities would predispose patients to recurrent ischemia.

Methods

Origin and Initial Treatment of Patients

All patients from the TAMI I and III studies[6,7] who had Thrombolysis in Myocardial Infarction (TIMI) flow grade equal to or more than 2[8] on angiograms performed 90 minutes after the administration of intravenous rt-PA, who did not have immediate coronary angioplasty, and who had follow-up angiography or cardiac death before hospital discharge were eligible for this analysis. The criteria for patient entry into the TAMI I and III studies has been previously described,[6,7] but briefly, patients had to have less than 4–6 hours of chest pain and electrocardiographic ST-segment elevation equal to or more than 1 mm in two or more contiguous leads and were excluded if they were considered to be at high risk of bleeding with intravenous thrombolytic therapy.

Patients in TAMI I received intravenous single-chain tissue-plasminogen activator (Genentech, South San Francisco, California), 60 mg the first hour, 20 mg during the second and third hours, and 10 mg for each of the last 5 hours, or 1 mg/kg body wt in the first hour and the remaining amount (of a total of 150 mg) given in equal amounts per hour in a 5-hour maintenance infusion.[6] Patients in TAMI III received 135–150 mg of intravenous rt-PA over 6 hours, administered in a manner similar to the second dosing schedule for TAMI I. During cardiac catheterization, patients in TAMI I received 5,000 units intravenous heparin. Patients in TAMI III were randomized to receive 10,000 units heparin at the time of initial rt-PA administration or immediately after the 90 minute angiogram. Patients in TAMI II[10] were not included in this study because they received combination rt-PA and urokinase in varying doses.

Postreperfusion Therapy and Follow-up

After cardiac catheterization, patients in both TAMI I and III received 500–1,000 units/hr intravenous heparin, adjusted to maintain the partial thromboplastin time at 1.5–2 times control. Patients also received 325 mg aspirin daily and 30–60 mg diltiazem orally four times a day.

The protocol for both trials required that patients who had recurrence of more than 20 minutes of angina that was not responsive to nitrates and was accompanied by electrocardiographic ST-segment changes be returned to the cardiac catheterization laboratory and considered for emergency angioplasty or bypass surgery. At 7–10 days, cardiac catheterization was performed on all patients who provided informed consent to determine the patency of the infarct-related artery.

Recurrent ischemic events were defined as any of the following that had occurred before hospital discharge: 1) emergency angioplasty for recurrent ischemia judged to be from the infarct artery; 2) urgent bypass surgery for ischemia from the infarct artery; 3) reocclusion, defined as recurrent total occlusion (TIMI flow grade 0 or 1) of the infarct-related artery, without attempted angioplasty or bypass surgery; or 4) cardiac death.

Angiographic Core Laboratory

All cineangiograms were forwarded to the TAMI Angiographic Core Laboratory for analysis. This included measurement of the 90-minute post–rt-PA residual stenosis with use of an automated edge-detection computer algorithm,[11] evaluation of the flow pattern of the infarct-related artery (TIMI flow grades 0–3, with grade 2 further subdivided as follows: 2A, delayed filling of the infarct-related artery with completion of filling by five cardiac cycles after contrast injection; 2B, delayed infarct-artery filling with completion of filling achieved after five cardiac cycles; and 2C, delayed filling of the infarct-related artery with markedly prolonged washout that, if present, took scoring priority over 2A, 2B, or 3), and scoring of the infarct-related stenosis for prospectively defined morphologic characteristics (Table 4).[12,13] All analyses were performed by a single experienced observer, unaware of the clinical outcome for each patient, from angiograms obtained 90 minutes (or if these were not obtained, from the earliest possible angiograms performed thereafter) after rt-PA administration.

Statistical Analysis

Data entry onto the case report forms was performed at the clinical sites and the Angiographic Core Laboratory, and the Biostatistical Core Unit at Duke University provided quality control of the data. Data are expressed as mean±1 SD. Patient and angiographic characteristics at baseline and clinical outcomes were tabulated, and variables were compared with clinical outcome using multiple logistic regression analysis. For the purpose of this analysis, patients without follow-up angiography or findings suggestive of reocclusion were included

TABLE 1. Patient Characteristics

Age (yr)	56.4±10.7
Gender (% male)	80.7
Diabetes (%)	14.6
History of smoking (%)	47.4
History of hypertension (%)	42.2
History of hyperlipidemia (%)	13.0
Heart rate (beats/min)	77±18
Systolic blood pressure (mm Hg)	133±25
Aspirin use at home (%)	24.0
Aspirin administration in the catheterization lab (%)	6.3

with patients with documented infarct-artery patency. All reported p values are two tailed.

Concern regarding the acceptance of a spurious apparent correlation (a type I statistical error) required that formal testing be performed on a limited number of variables.[14] The following variables to be formally tested were determined prospectively: the infarct-related artery, TIMI flow, percent diameter stenosis, absolute stenosis diameter, thrombus associated with infarct-related stenosis, diffuse disease in the infarct-related artery, Ambrose morphology of the infarct artery-related stenosis, and ectasia associated with the infarct artery-related stenosis.

The following other patient variables were also recorded but were not formally tested as correlates of the clinical end point: age, gender, diabetes, history of smoking, hypertension, hypercholesteremia, heart rate, and blood pressure on presentation to the cardiac catheterization laboratory, stenosis calcification, stenosis associated with a branch point, stenosis associated with a bend point,[13] stenosis length (mm), collateral vessels beyond the stenosis, intermittent artery patency in the cardiac catheterization laboratory, use of aspirin at home before hospital admission, and the administration of aspirin in the cardiac catheterization laboratory. Patients with "silent" reocclusion were considered to have had their reocclusion at the time of its angiographic documentation.

Results

Patient and Stenosis Characteristics

Selected patient and infarct-related artery characteristics are described in Tables 1 and 2, respectively. There was no significant difference in any of the characteristics listed between patients with or without angiographic follow-up, although there was a tendency ($p>0.05$) for the group with follow-up to have fewer patients with collateral vessels beyond the infarct-related stenosis (14.9% versus 33.3%) and more patients who were smokers (49.4% versus 26.7%).

Recurrent Ischemic Events

The specific types of recurrent ischemic events are shown in Table 3. The median time to recurrent ischemia was 6.0 days (range, 0.1–26.8 days). If silent reocclusions and deaths are excluded, the median time to recurrent ischemia was 3.6 days (Figure 1). Comparisons of the frequencies or mean values for the formally tested variables in the groups with and without recurrent ischemia are shown in Table 4. None of the selected variables were significantly correlated ($p\leq0.10$) with recurrent ischemia in the logistic regression analysis. Similar results were obtained when those patients who had death or silent reocclusion as their only recurrent ischemic event were excluded. Relations of diameter stenosis and absolute residual diameter stenosis with clinical outcomes are shown graphically in Figures 2 and 3,

TABLE 2. Infarct Artery and Stenosis Characteristics

Infarct related artery	
LAD*	39.8
LCX†	12.6
RCA‡	47.6
TIMI flow grade§	
2C	22.8
2B	13.0
2A	23.4
3	40.8
Percent diameter stenosis (%)	73±13
Absolute diameter stenosis (mm)	0.95±0.51
Thrombus (%)	68.4
Diffuse disease (%)	21.3
Ectasia (%)	48.7
Ambrose morphology‖	
0	30.1
1	37.6
2	31.2
3	1.1
Calcification (%)	32.8
Proximity to bend (%)	53.2
Proximity to branch (%)	59.4
Collateral vessels (%)	16.7
Stenosis length (mm)	3.8±2.5
Intermittent artery patency in the catheterization lab (%)	2.7

*LAD, left anterior descending coronary artery; †LCX, left circumflex coronary artery; ‡RCA, right coronary artery; §see "Methods" for definitions; ‖Ambrose: 0, concentric; 1, eccentric with smooth borders and no narrow neck; 2, eccentric with irregular borders or a narrow neck; 3, serial stenoses.

TABLE 3. Recurrent Ischemic Events

Event	Patients (*n*)
Death only	4
Emergency PTCA only	11
Urgent bypass surgery only	4
Reocclusion only	8
Death and emergency PTCA	1
Reocclusion and emergency PTCA	12
Reocclusion and urgent bypass surgery	1
Total (%)	41/192 (21.3%)

PTCA, percutaneous transluminal coronary angioplasty.

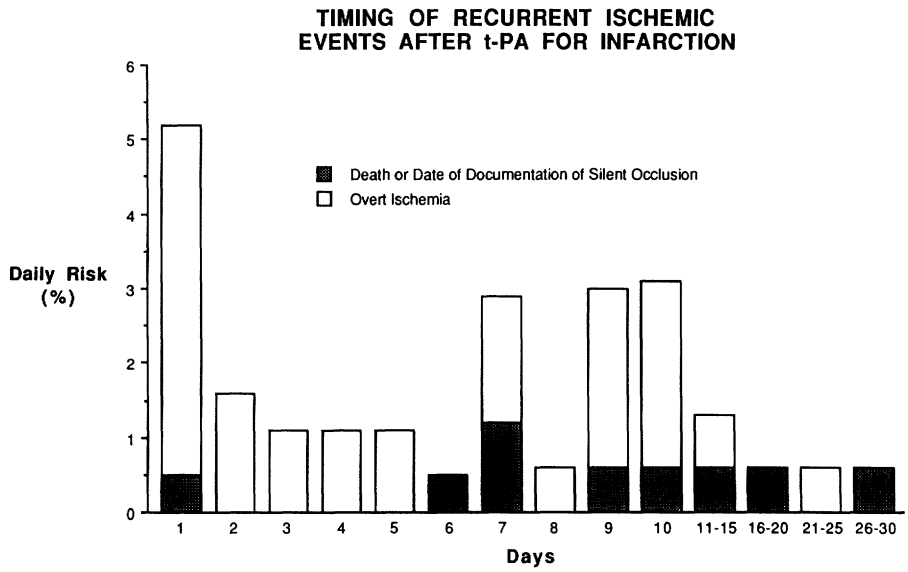

FIGURE 1. *Bar graph of daily risk (%) of recurrent ischemic events. Open bars indicate risk of overt ischemia. Hatched bars indicate risk of death or date of angiographic documentation of silent total occlusion of infarct-related artery.*

respectively. In addition, there were no clear relations between any of the other variables recorded and risk of recurrent ischemic events.

Discussion

The major finding of this study is that no variable or combination of variables tested were predictive for recurrent ischemic events after successful thrombolysis. The present study is the largest sample of patients who received thrombolytic therapy and have undergone detailed serial quantitative and morphologic angiographic evaluation. The results contradict those of prior studies[1–5] and point out a major deficiency in our overall approach to patient management after reperfusion therapy for acute myocardial infarction. Reports from small series of patients treated with streptokinase suggest that early angiography may identify patients at high risk of recurrent ischemia, for whom early coronary angioplasty or bypass surgery might be beneficial (Table 5).[2–5] In contrast, the data from the current study, a much larger series of patients treated with intravenous rt-PA, suggest that recurrent ischemic events in such patients are not predictable at the time of angiography performed 90 minutes after rt-PA administration.

The discrepant findings of the current study compared with previous reports may be related to several factors. First, in each of the previous reports, less than 60 patients were assessed, and in only three were there quantitative angiographic measurements performed. The difference in sample size and newer objective methodology, compared with studies performed more than 5 years ago, may in part account for the discordance. Second, the statistical methodology differs as the current study is the first one to use multivariable regression analysis with predetermined variables, compared with univariate analysis and post hoc variable selection used in the earlier studies. The present study was considerably broader in scope, including various TIMI grades, the presence of intramural thrombus, diffuse disease or ectasia, lesion length, and Ambrose morphology. Third, a different thrombolytic agent, which is relatively fibrin selective, was used.[15] For rt-PA, the fibrinogen depletion in these patients was only 25–35%,[9,16] compared to high-dose streptokinase that typically results in 50–80% decline in fibrinogen.[9,16] Further, rt-PA has a short half-life of less than 5 minutes, whereas the half-life of streptokinase is approximately 18 minutes,[17] and with the differences in coronary thrombolytic efficacy established for rt-PA versus streptokinase by randomized trials,[8,9] it is clear that these agents are dissimilar.

Limitations

This study has several limitations. First, due to the number of adverse outcomes, only eight variables could be formally tested as possible predictors of recurrent ischemia, and nontested variables might have predicted outcome. Second, this study combines the results of two randomized trials, and it is possible that the different dosages of rt-PA or the timing of administration of heparin may have influenced outcome. This appears unlikely due to the similar rates of recurrent ischemia for both rt-PA doses in TAMI I[18] and for both groups in TAMI 3.[7] Third, the inability to determine whether recurrent ischemia contributed to the death of the four patients who died without catheterization immediately before death slightly lessens the power of the study. Nonetheless, the results were unchanged whether these patients were considered to have recurrent ischemia or if they were excluded from the analysis. Fourth, an accurate assessment of the importance of therapeutic heparinization on likelihood of recurrent ischemia could not be made because the duration and extent of anticoagulation were not coded in TAMI I patients. Finally, these results were obtained in patients receiving a somewhat larger dose of rt-PA than is currently recom-

TABLE 4. Potential Correlates of Recurrent Ischemic Events*

	Recurrent ischemia (n=41)	No recurrent ischemia (n=151)
Characteristics formally tested		
Infarct artery (%)		
LAD†	46.3	38.0
LCX‡	4.9	14.7
RCA§	48.8	47.3
Diameter stenosis (%)	74.4±11.1	72.7±14.0
Absolute diameter stenosis (mm)	0.91±0.44	0.97±0.53
TIMI grade (%)		
2C	33.1	20.0
2B	5.1	15.2
2A	3.1	23.5
3	38.5	41.4
Ambrose morphology (%)		
0	33.3	29.3
1	23.1	41.5
2	43.6	27.9
3	0.0	1.4
Thrombus (%)	75.0	66.7
Diffuse disease (%)	22.5	21.0
Ectasia (%)	50.0	48.3
Selected characteristics not formally tested		
Clinical		
Age (yr)	56±11	56±11
Aspirin received in catheterization lab (%)	2.4	7.3
Diabetes (% type 1 or 2)	14.6	14.6
Gender (% male)	78.1	81.5
Heart rate (beats/min)	74±21	78±17
Home aspirin use (%)	25.0	23.8
Hyperlipidemia (%)	26.8	9.3
Hypertension (%)	46.3	41.1
Smoking (%)	51.2	46.4
Systolic arterial pressure (mm Hg)	132±21	133±26
Angiographic		
Collateral vessels present (%)	26.8	13.8
Intermittent infarct-artery patency (%)	5.3	2.1
Stenosis at a bend point (%)	59.0	51.7
Stenosis at a branch point (%)	62.5	58.5
Stenosis calcification (%)	39.0	31.0
Stenosis length (mm)	3.7±2.3	3.8±2.5

*No characteristic was correlated with recurrent ischemic events in formal multiple logistic regression testing ($p \leq 0.10$); †LAD, left anterior descending coronary artery; ‡LCX, left circumflex coronary artery; §RCA, right coronary artery.

mended, and the importance of this difference as it relates to these findings is unknown.

Implications

Improved methods of maintaining arterial patency after successful thrombolysis are clearly required. In addition, the frequent yet unpredictable occurrence of recurrent ischemia after successful thrombolysis, in conjunction with the findings of three randomized trials[6,19,20] that immediate angioplasty carries with it a high risk compared with no immediate intervention, suggests that further revascularization, when needed, can be deferred in all patients with successful thrombolysis. Indeed, the TIMI II data suggest that only a minority of such patients (19%) will have spontaneous or exercise-induced ischemia requiring further revascularization within 42 days of their infarction.[21] However, early catheterization may still be useful in some patients to define high-risk anatomy (e.g., left main disease) and to allow for the potential beneficial

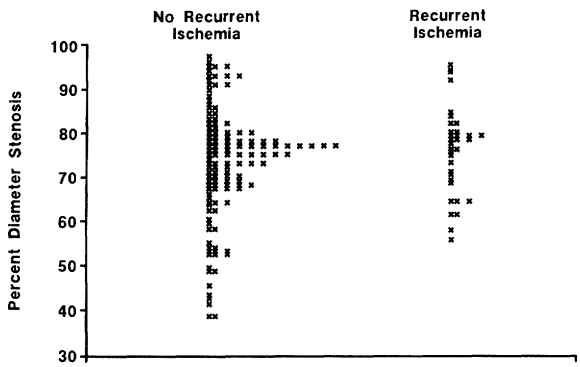

FIGURE 2. *Plot of relation of percent diameter stenosis at infarct-related coronary site to occurrence of recurrent ischemia.*

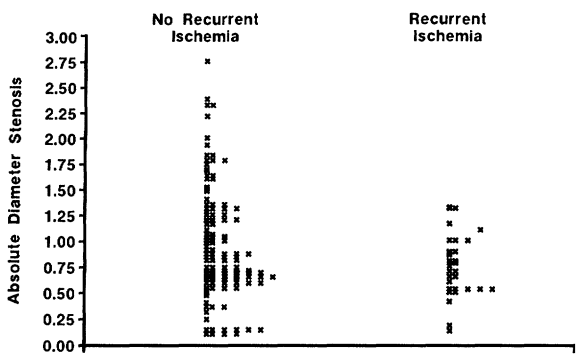

FIGURE 3. *Plot of relation of absolute diameter of infarct-related stenosis to occurrence of recurrent ischemia.*

effects of "rescue" angioplasty.[10,22] Further assessment of the benefit of emergency revascularization and improved methods of risk stratification in this setting will be needed to provide optimal patient care at a minimal cost. Careful surveillance will be necessary to detect the sometimes occult[23] signs and symptoms of recurrent ischemia, particularly if further intervention in this setting can be proven beneficial.

The implication of the variable timing of recurrent ischemia on the decision to transfer patients to hospitals capable of further, more definitive intervention (thrombolysis, angioplasty, or bypass surgery) is dependent on the results of these secondary interventions. These results have not been well characterized. For example, if repeat administration of thrombolytic therapy was often successful, then transfer might rarely be required. If thrombolytic therapy was commonly unsuccessful and if only very early reperfusion (less than 1 hour) were to result in a dramatic improvement in survival or ventricular function, then immediate transfer of all patients to tertiary centers might be justified, despite expected higher overall patient costs. If reperfusion within 1–2 hours were to prove beneficial, then provision for urgent patient transfer would suffice, at an expected cost savings. Finally, if intervention were to have little expected effect on outcome, then transfer could be limited to patients who tolerated recurrent ischemia poorly. Such data are not available from

TABLE 5. Prediction of Recurrent Ischemia After Successful Thrombolysis for Acute Myocardial Infarction

Author	Thrombolytic agent	Patients (*n*)	Predictor	Risk in presence of predictor	Risk in absence of predictor	Quantitative angiography	Prospective variable identification
Serruys[2]	i.c. streptokinase	60	≥58% Diameter stenosis	17/27	2/33	Yes	No
Harrison[3]	i.c. streptokinase	24	Lumen area <0.4 mm^2	7/13	0/11	Yes	No
Gash[4]	i.c. or i.v. streptokinase	24	>75% Diameter stenosis	5/17	1/7	No	No
Badger[5]	i.c. streptokinase	20	Lumen diameter <0.6 mm	5/12	0.8	Yes	No
Present study	i.v. rt-PA	192	None			Yes	Yes

studies assessing ventricular function at 7–10 days after the index infarction because recovery from secondary "stunning"[24] would not be expected to be complete at the time of assessment.

The inability to identify, on the basis of early clinical or angiographic findings, which patients might benefit from immediate or delayed[25] revascularization after successful thrombolysis provides rationale for a conservative approach[21] to most patients who receive rt-PA for acute myocardial infarction, and yet remains a major deficiency in our aggressive approach to myocardial infarction today.

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