

Adjunctive Thrombolytic Therapy During Angioplasty for Ischemic Rest Angina

Results of the TAUSA Trial

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Background Acute closure is increased after angioplasty in unstable angina, and adjunctive intracoronary thrombolytic therapy has been used successfully to increase angiographic success. The role of prophylactic thrombolytic therapy during angioplasty in unstable angina is unknown.

Methods and Results Four hundred sixty-nine patients with ischemic rest pain with or without a recent (<1 month) infarction were randomized in double-blind fashion to intracoronary urokinase or placebo. Randomization was carried out in two sequential phases. In phase I, 257 patients were randomized to 250 000 U of urokinase or placebo given in divided doses at the time of angioplasty. In phase II, 212 patients were randomized to 500 000 U of urokinase or placebo in divided doses. All patients were pretreated with aspirin, and activated clotting times were followed to maintain them at >300 seconds during angioplasty. Angiographic end points of thrombus after angioplasty were insignificantly decreased by urokinase (30 [13.8%] versus 41 [18.0%] with placebo; $P=NS$). Acute closure, on the other hand, was

increased with urokinase (23 [10.2%] versus 10 [4.3%] with placebo; $P<.02$). The difference in acute closure between urokinase and placebo was more striking at the higher dose of urokinase ($P<.04$) than in phase I at the lower urokinase dose ($P=NS$). Adverse in-hospital clinical end points (ischemia, infarction, or emergency coronary artery bypass surgery) were also increased with urokinase versus placebo (30 [12.9%] versus 15 [6.3%], respectively; $P<.02$). Angiographic and clinical end points were worse with urokinase in unstable angina without recent infarction than with angioplasty after a recent infarction.

Conclusions Adjunctive urokinase given prophylactically during angioplasty for ischemic rest angina as administered in this trial is associated with adverse angiographic and clinical events. These detrimental effects may be related to hemorrhagic dissection, lack of intimal sealing, or procoagulant or platelet-activating effects of urokinase. (*Circulation*. 1994;90:69-77.)

Key Words • thrombolysis • angioplasty • angina

Acute closure is increased after percutaneous transluminal coronary angioplasty (PTCA) for unstable angina, and thrombosis has been suggested as a possible mechanism.¹⁻⁴ Most uncontrolled reports have shown that in acute closure presumably secondary to thrombosis, repeat balloon dilatation alone may be ineffective in restoring patency. In this situation, the administration of intracoronary thrombolytic agents along with redilatation has been reported to improve angiographic and clinical success.⁵⁻⁸ We previ-

ously published the results of a small randomized, double-blind pilot study assessing the role of small doses of intracoronary urokinase as prophylaxis immediately before angioplasty for ischemic rest angina.⁹ This study suggested that the formation of intracoronary thrombus after angioplasty could be decreased by intracoronary urokinase, although acute closure and in-hospital clinical events were similar to those in patients treated with placebo. To further assess the role of thrombolytic therapy in this circumstance, a larger trial was undertaken with higher doses of urokinase and monitoring of heparin therapy with activated coagulation times.

Methods

The Thrombolysis and Angioplasty in Unstable Angina (TAUSA) trial was a randomized, multicenter, double-blind study to assess the role of intracoronary urokinase during angioplasty for unstable angina or postinfarct rest angina. The primary end points were both angiographic and clinical and consisted of acute closure, the presence of definitive filling defects after angioplasty, recurrent in-hospital ischemia, myocardial infarction, urgent coronary artery bypass graft (CABG), or death. The participating centers, responsible physicians, and study nurses are listed in "Acknowledgments." Patients were randomized into the study between July 1990

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and September 1992. Criteria for inclusion were either unstable angina with ischemic rest pain <7 days before angioplasty, non-Q-wave infarction <7 days before angioplasty, or a recent (<30 days) non-Q-wave or Q-wave infarction with recurrent rest pain <7 days before angioplasty. In all patients a "culprit" lesion with $\geq 70\%$ visual diameter stenosis in a native coronary artery or saphenous vein graft was identifiable and considered suitable for angioplasty. Lesions in degenerated vein grafts were excluded as well as native coronary lesions with abundant (one or more filling defects occupying the entire lumen and ≥ 5 mm in length) intracoronary thrombi before angioplasty. An additional criterion for enrollment was that the ECGs during an episode of rest pain show transient ST or T changes or, if not available during pain, the baseline ECGs show diagnostic Q waves or resting ST or T changes. Patients with normal baseline ECGs (if none were available during an episode of ischemic rest pain) and those with completely normal ECGs during rest pain were excluded. Additionally, patients >75 years old were initially excluded. However, the age limit was increased to 80 years after the first 200 patients were randomized. Other exclusions included uncontrolled hypertension (>180/110 mm Hg), prior cerebrovascular accident, recent (<10 days) major surgery, bleeding diatheses, active gastrointestinal or genitourinary bleeding, hematocrit <30%, or prior enrollment in the TAUSA pilot study or trial.

Randomization was carried out in two phases. Because the pilot study dose of intracoronary urokinase (Abbokinase, Abbott Laboratories) was low (150 000 U), higher doses were selected for the trial. In phase I, 250 000 U of intracoronary urokinase or placebo was infused. An interim analysis was prospectively planned after the first 200 patients to assess the potential risk/benefit of using a higher dose than in phase I. Because there were no significant differences in efficacy or bleeding between urokinase and placebo, the remaining patients in phase II were randomized to 500 000 U of urokinase or placebo. This dose was preplanned by the investigators before initiation of the study. The preliminary results of this interim analysis were known only to the principal investigator and the data monitoring group at Abbott Laboratories.

Study Protocol

Patients signed informed consent for angioplasty and for participation in the study protocol. This protocol was approved by the Institutional Review Board of each institution. Patients already receiving aspirin were pretreated with 80 mg of oral aspirin on the day of the procedure or 325 mg if they were not receiving aspirin therapy. After vascular access was obtained, 10 000 U of heparin was administered intravenously. Additional heparin was given to maintain the activated coagulation time at >300 seconds. Randomization schedules were generated by Abbott Laboratories and were specific for each center. Each center was given a series of patient numbers that corresponded to the individual boxed vials of urokinase or placebo. The study drug was dispensed sequentially by number as patients were enrolled.

Phase I

After 75 μ g of intracoronary nitroglycerin the culprit lesion was visualized in orthogonal views. We blindly infused 150 000 U of intracoronary urokinase or placebo over 3 minutes into the ostium of the right or left main coronary artery just before wire placement, and the angiogram was repeated in the same views. When the angiographer felt that the lesion was adequately dilated after the final inflation, a 1-minute post-PTCA angiogram was performed again in the same orthogonal views after nitroglycerin. If the angiographer was satisfied with these results, another 100 000 U of urokinase or placebo was infused over 3 minutes. If the angiographer was not satisfied with the 1-minute post-PTCA angiogram, he/she could redilate the lesion. Each angiographer was also asked to comment whether more than the usual number of dilatations was necessary

before reaching the 1-minute post-PTCA angiogram because of an inadequate result.

Phase II

The same protocol was followed for phase II except that the dose and duration of infusion were increased. Immediately before wire placement, 250 000 U of intracoronary urokinase or placebo was blindly infused over 10 to 15 minutes into the ostium of the right coronary artery or left main artery. After the 1-minute post-PTCA angiogram, another infusion of 250 000 U or placebo was infused over 10 to 15 minutes. This duration of infusion was arbitrarily decided on to ensure that the lesion would be bathed in a continuous infusion of drug without drastically changing the protocol.

In both phases the last angiogram was performed 15 minutes after angioplasty. Again the culprit lesion was visualized in the same orthogonal views after nitroglycerin. The angiographers were instructed to remove the guide wire after the 1-minute post-PTCA angiogram. If necessary, each angiographer could redilate after the 15-minute post-PTCA angiogram because of acute closure, dissection, or inadequate results. Additional injections were not allowed between 1 and 15 minutes after angiography unless the patient experienced chest pain, hemodynamic compromise, or both. Multilesion angioplasty was allowed at the same time as long as the other lesions were dilated after the culprit lesion protocol had been completed. Patients were treated overnight with intravenous heparin, and the sheath was removed on the next day. The heparin was infused to maintain the partial thromboplastin time at a level of approximately twice normal.

Core Angiographic Analysis

Each film was analyzed in blinded fashion by two investigators at the core laboratory. All cine films were reviewed on a Vanguard XR-35 and magnified fourfold for the analysis of coronary morphology before and after angioplasty. Quantitative analysis was performed in a single view that best showed the lesion without overlap or foreshortening, using videodensitometric measurements of the lesion and the "normal" vessel (Vanguard Analyzer XR-70).^{10,11} Successful angioplasty was defined as a lesion with a <50% diameter stenosis after the procedure. Each film was also qualitatively analyzed for coronary morphology¹² and Thrombolysis in Myocardial Infarction flow (TIMI flow) as well as qualitative changes after urokinase or placebo. Culprit lesions <100% occluded before angioplasty were categorized as either simple or complex. Complex morphology included lesions with irregular borders, ulcerations, overhanging edges, or discrete filling defects proximal or distal to a significant lesion. Totally occluded lesions were defined by a TIMI flow grade of 0 or 1 before angioplasty.

Definitions of Thrombus, Acute Closure, and Dissection

At 1 and 15 minutes after angioplasty, lesions were classified by the core laboratory as with or without definite thrombus formation. Definite thrombus after angioplasty was defined as one or more filling defects at the site of dilatation in the absence of a major dissection.⁹ Acute vessel closure was defined by the core laboratory as a decrease in TIMI flow to flow grade 0 or 1 with recurrent stenosis similar to or worse than that present before angioplasty. After angioplasty, acute closure was presumed when chest pain occurred with ST-segment changes similar to balloon inflation, necessitating repeat angiography or emergency CABG. When possible, the mechanism of acute closure was characterized as either thrombotic or dissection. If a dissection was present it was assumed that dissection was the mechanism for acute closure. Acute closure associated with filling defects without dissection or with a dissection that was only a linear extraluminal cap in orthogonal views without lumen compromise (minor dissection) was presumed to be thrombotic. If a spiral dissection was

present or a dissection with significant (>50% diameter reduction visually) lumen compromise (both classified as major dissection), any haziness or defect in the lesion was assumed to be part of the dissection and not considered as thrombus.⁹ Lesions were not prospectively classified before angioplasty according to the American Heart Association/American College of Cardiology (AHA/ACC) classification into types A, B, or C.¹³ Retrospectively, all lesions with acute closure were reexamined to determine this classification.

In-Hospital Follow-up Studies

In-hospital follow-up was performed for evidence of recurrent ischemia, myocardial infarction, the need for urgent (<24 hours after PTCA) CABG, or death. Recurrent ischemic pain was defined as chest pain similar to that occurring during balloon inflation with or without ischemic ST-T wave changes. Serial samples of creatine kinase were drawn in patients who experienced ischemic pain with ST changes after angioplasty. Myocardial infarction was defined as recurrent pain associated with creatine kinase elevations greater than twice the upper limits of normal or with diagnostic ECG changes. When feasible, a second angiography was encouraged to identify the angiographic cause of in-hospital events. Bleeding complications were defined as at least moderate (>250 mL) blood loss, the presence of a large hematoma, or the need for transfusion during or after the procedure.

Statistical Analysis

The original study sample size was 948 patients in two treatment groups of 474 patients each, based on expected incidence rates of 10% and 5% for the primary angiographic and clinical end points for placebo and urokinase, respectively. An interim analysis was to be performed after 200 patients were enrolled. The results from this analysis, which examined data from 182 patients, revealed a higher than expected incidence of end points and did not demonstrate differences in efficacy and safety between the two treatment groups. Because of these findings, the sample size in phase II of this study (higher dose of 500 000 IU versus placebo) was determined to be 250 patients (125 per group) and would provide 80% power at the two-sided .05 level, assuming an expected 32% incidence rate for placebo and an expected 16% incidence rate for urokinase.

Tests resulting in two-tailed values of $P \leq .050$, when rounded to three digits, are reported as significant. Occasionally, values of $P > .050$ but $\leq .100$ are reported as marginally significant.

Fisher's exact tests were used to compare the percentages of patients for the following parameters between the two treatment groups: diagnosis (unstable angina versus recent myocardial infarction), cardiovascular medical history, pre-PTCA drug therapy, time of last rest pain before PTCA (≤ 48 hours versus > 48 hours), extent of disease, culprit lesion artery, lesion morphology (complex versus simple), total occlusion before PTCA, PTCA success, definite filling defect at 15 minutes after PTCA, acute closure, any dissection and major dissection at 15 minutes after PTCA, CABG, ischemia after PTCA, and incidence of any clinical end point (recurrent ischemia, (re)infarction, CABG, or death). One-way ANOVA was used to compare the two treatment groups for percent area stenosis and mean heparin infusion duration. The percentages reported for a given characteristic are based on evaluable data in patients who underwent angioplasty.

The clinical end points were ranked in order of increasing severity as follows: no clinical end point, recurrent ischemia, (re)infarction, CABG, and death. Each patient's most severe outcome was counted, and the distributions of the outcomes for both treatment groups were compared using ordinal logistic regression. Wilcoxon rank sum tests were used to test for differences between the two treatment groups in activated clotting time values at given time points.

TAUSA Trial

Protocol

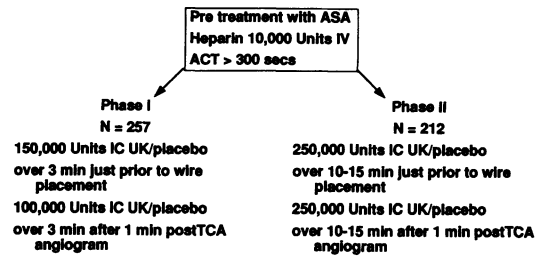


Diagram outlines protocol for the Thrombolysis and Angioplasty in Unstable Angina (TAUSA) trial. ASA indicates aspirin; ACT, activated clotting time; IC UK, intracoronary urokinase; and TCA, angioplasty.

Stepwise logistic regression was used to construct a multiple regression model using acute closure as the response variable. The set of potential predictor variables to be included in the model consisted of the following: patient sex (female or male); patient age (<65 years or ≥ 65 years); study phase (phase I or phase II); treatment group (urokinase or placebo); diagnosis (unstable angina, recent Q-wave myocardial infarction, or recent non-Q wave myocardial infarction); vessel location (left main artery, left anterior descending coronary artery, right coronary artery, left circumflex artery, or saphenous vein graft); duration of pain from onset to PTCA (≤ 1 week or > 1 week); time of last rest pain (≤ 48 hours before PTCA or > 48 hours before PTCA); lesion morphology (simple or complex); filling defect before PTCA (yes or no); pre-PTCA TIMI flow grade (0 or 1, 2, or 3); type of PTCA (primary or restenotic); any dissection at 1 minute after PTCA (yes or no); definite filling defect at 1 minute after PTCA (yes or no); success of PTCA (successful or unsuccessful); and repeat dilation required during PTCA (yes or no). The significance level used to enter a variable into the model was .10, and the significance level used to keep a variable in the model was .05. For a patient to be included in this analysis, he/she must have had a value for each of the possible predictor variables. All statistical analyses were performed using SAS procedures (version 6.07).

Results

Patient Study Group

Four hundred sixty-nine patients were randomized in the TAUSA trial (Figure). Of these, 10 had no PTCA performed or the PTCA was unsuccessful as a result of inability to cross the lesion with a wire (7 in the urokinase group and 3 in the placebo group). In addition, 21 patients underwent PTCA (11 urokinase patients and 10 placebo patients) but did not complete the protocol, usually because of failure to receive the second infusion. There were 257 patients in phase I and 212 in phase II. In phase I, 128 patients were assigned to urokinase and 129 to placebo. In phase II, 104 patients received urokinase and 108 received placebo. All patients except the 10 who did not undergo PTCA were included in the outcome analyses on an "intention to treat" basis.

A detailed log of patient enrollment and exclusions was kept in the hospital of the principal investigator (Mount Sinai Hospital), where 35% of patients were entered in the trial. Forty-nine percent of patients undergoing angioplasty for unstable angina in this hospital were enrolled during this time period. Of the patients not enrolled ($n=173$ [5%]), the most common

TABLE 1. TAUSA Trial: Baseline Characteristics

	Urokinase	Placebo
	No. (%)	No. (%)
Unstable angina	122 (53)	125 (53)
Recent infarction	110 (47)	112 (47)
Rest pain ≤ 48 h	130 (56)	109 (46)*
Male	147 (63)	159 (67)
Diabetes	52 (22)	40 (17)
Hypercholesterolemia	114 (49)	123 (52)
Hypertension	117 (50)	127 (54)
Smoking history	171 (74)	159 (67)*
Previous infarction	145 (63)	146 (62)
Previous angina	97 (42)	90 (38)

* $P < .06$; $P = \text{NS}$ for other comparisons.

reasons for exclusion were age > 75 years ($n=40$), absence of appropriate inclusion criteria ($n=61$), and prior enrollment in the TAUSA trial ($n=20$). Of the patients excluded, no patient received intracoronary urokinase before PTCA. In addition, only 1 patient underwent emergency CABG, and none of the excluded patients died.

Baseline Clinical Characteristics

Two hundred forty-seven patients (52.7%) had a diagnosis of unstable angina (ischemic rest angina without a recent infarction), and 222 patients (47.3%) underwent angioplasty < 1 month after recent infarction (ischemic rest angina after recent myocardial infarction or recent non-Q wave infarction) (Table 1). Risk factors for coronary disease were evenly distributed between urokinase and placebo groups except for a marginally significant higher incidence of smoking in the urokinase group. Antianginal therapy was similar between urokinase and placebo patients (Table 2). Seventy-six percent were on intravenous heparin before angioplasty; these were equally distributed between the urokinase and placebo groups. Fifty-two percent had rest pain ≤ 48 hours before angioplasty; this occurred more frequently in patients randomized to urokinase (56% versus 46% for patients randomized to placebo [$P < .05$]). There were no differences in the percentage of patients with recent rest pain before angioplasty between patients with unstable angina or recent infarction. Angioplasty in the postinfarct group was performed within 1 week of myocardial infarction in 57%

TABLE 2. TAUSA Trial: Preangioplasty Drug Therapy

	Urokinase	Placebo
	No. (%)	No. (%)
β -Blocker	116 (50)	121 (51)
IV nitroglycerin	103 (44)	99 (42)
Aspirin	228 (98)	236 (100)
Aspirin before admission	187 (81)	185 (78)
Heparin	178 (77)	180 (76)

$P = \text{NS}$ for all comparisons.

TABLE 3. TAUSA Trial: Baseline Angiographic Characteristics

	Urokinase	Placebo
	No. (%)	No. (%)
% Area stenosis before PTCA (mean)	91	94*
TIMI flow before PTCA (mean)	2.5	2.6
LAD	108 (47)	110 (46)
RCA	72 (31)	77 (32)
LCX	45 (19)	47 (20)
Complex lesion	127 (54)	121 (51)
Total occlusion	23 (10)	15 (6)
Filling defect before PTCA	32 (14)	24 (10)

PTCA indicates percutaneous transluminal coronary angioplasty; TIMI, Thrombolysis in Myocardial Infarction trial; LAD, left anterior descending coronary artery; RCA, right coronary artery; and LCx, left circumflex artery.

* $P < .02$.

and within 2 weeks of infarction in an additional 31%. In the unstable angina group, 49% of patients had angioplasty performed within 1 week of onset of symptoms.

Baseline Angiographic Characteristics

Fifty-five percent of patients in the trial had one-vessel coronary artery disease, 31% had two-vessel disease, and 14% had three-vessel disease. There was no difference in the extent of coronary disease between the urokinase and placebo groups. The placebo and urokinase groups were evenly matched with regard to certain baseline characteristics (Table 3). The percentages of patients undergoing angioplasty of the culprit lesion in the left anterior descending coronary artery, right coronary artery, and left circumflex artery were similar for the urokinase and placebo groups. Four vein graft lesions were dilated. Seven percent of culprit lesions were restenotic. A majority of lesions (54.1%) had complex morphology indicative of plaque disruption and thrombus formation¹² and were evenly distributed between urokinase and placebo groups. Of the lesions with complex morphology, 56 lesions had discrete filling defects proximal or distal to a significant lesion (32 in the urokinase group and 24 in the placebo group). Total occlusion was found in 8.3% before angioplasty. Percent area stenosis before angioplasty averaged 91.0% with urokinase and 93.7% with placebo; this difference was significantly different ($P < .02$).

Postangioplasty Results

Angioplasty was successful in 95% of culprit lesions. Success was higher in the placebo group (97%) versus the urokinase group (94%), although this difference was not significant.

Filling Defects and Acute Closure

Definite filling defects were present in 4.5% of patients at 1 minute after angioplasty and were equally distributed between the urokinase and placebo groups. Definite filling defects were present in 71 patients (15.9%) at 15 minutes after angioplasty (Table 4). These defects were seen after urokinase in 30 patients

TABLE 4. TAUSA Trial: Angiographic End Points

	Urokinase	Placebo
	No. (%)	No. (%)
Definite filling defect (15 min)	30 (13.8)	41 (18.0)
Phase I	17 (14.0)	23 (18.4)
Phase II	13 (13.4)	18 (17.5)
Acute closure	23 (10.2)	10 (4.3)*
Phase I	14 (11.5)	8 (6.3)
Phase II	9 (8.7)	2 (1.9)†
Major dissection (15 min)	22 (10.1)	19 (8.3)
Phase I	11 (9.1)	14 (11.2)
Phase II	11 (11.3)	5 (4.9)

* $P < .02$, † $P < .04$.

(13.8%) and after placebo in 41 (18.0%). In both phases, definite filling defects were less common with urokinase than placebo, although the differences were not significant. On the other hand, acute closure occurred more frequently with urokinase than placebo (23 [10.2%] versus 10 [4.3%], respectively [$P < .02$]). These differences between urokinase and placebo were more striking in phase II (9 [8.7%] versus 2 [1.9%], respectively [$P = .031$]) than in phase I (14 [11.5%] versus 8 [6.3%], respectively [$P = \text{NS}$]). Of the 33 lesions with acute closure, 11 were located in the right coronary artery, 14 in the left anterior descending coronary artery, and 8 in the left circumflex artery. Twenty-six lesions (79%) were complex before angioplasty, and according to the AHA/ACC classification 26 lesions were type B and the remaining 7 were type A. Of the lesions with discrete filling defects, there were 6 (18.8%) acute closures with urokinase versus 2 (8.3%) with placebo ($P = \text{NS}$). No acute closure was recorded in the 38 lesions that were totally occluded before PTCA.

Coronary Dissection

Any angiographic dissection was noted in 26% at 1 minute after angioplasty and in 31% at 15 minutes. These were equally distributed between urokinase and placebo groups. Major dissection at 15 minutes was found in 41 patients (9.2%) and was equally distributed between those on urokinase (22 [10.1%]) and those on placebo (19 [8.3%]) (Table 4). There were more major dissections with urokinase in phase II compared with placebo (11 [11.3%] versus 5 [4.9%], respectively), but there were more major dissections with placebo in phase I than with urokinase (14 [11.2%] versus 11 [9.1%], respectively). These differences, however, were not significant.

Of the 33 lesions with acute closure, the mechanism of acute closure was dissection in 11 and thrombus in 18. In 4 patients the mechanism was unknown. The activated coagulation times were >300 seconds at the end of the procedure in 71% of patients with acute closure compared with 72% of patients without acute closure ($P = \text{NS}$). During the procedure for the entire population of urokinase and placebo patients, there were no significant differences in the median activated clotting

time value (1 hour after the start of PTCA: urokinase, 322 seconds versus placebo, 336 seconds; $P = \text{NS}$). The median bolus dose of heparin was also similar between urokinase and placebo (10 000 U in both groups).

Using the multiple regression model for acute closure, PTCA failure, major dissection at 1 minute after PTCA, complex lesion morphology, and the need for repeated dilatation were significant predictors of acute closure.

Comparison of Unstable Angina Versus Recent Myocardial Infarction

Patients who underwent angioplasty after a recent non-Q-wave or Q-wave infarction had fewer definite filling defects at 15 minutes with urokinase (10.6%) than with placebo (20.2%) ($P < .06$) (Table 5). On the other hand, in patients who underwent angioplasty for unstable angina without recent infarction, there was a significantly higher incidence of acute closure with urokinase than with placebo (13 [11.0%] versus 3 [2.4%], respectively; $P < .01$). In phase II at the higher dose of urokinase, there were 6 acute closures with urokinase but none with placebo ($P < .01$). Filling defects at 15 minutes were similar (urokinase, 16.7%; placebo, 16.0%). After angioplasty with recent infarct, the incidence of acute closure was similar between urokinase (10 [9.3%]) and placebo (7 [6.3%]). In the placebo group there were no significant differences in angiographic outcome between the unstable angina or recent infarction groups.

Redilatation

During the procedure before completion of the protocol, additional dilatations were required in 34 (15%) of urokinase and in 42 (18%) of placebo patients ($P = \text{NS}$). In some of these patients, the indication for redilatation was for abrupt reclosure of the culprit artery after one or more dilatations. Because some of these reclosures were not noted by the core laboratory since they occurred before the 1-minute post-PTCA angiogram and were easily reversed by repeat balloon inflations, the incidence of acute closure could have been underestimated by excluding these. When these reclosures were included (urokinase, 3 patients; placebo, 3 patients), the combined incidence of acute closure (core laboratory and early reclosures) was still significant with urokinase compared with placebo (26 [11.2%] versus 13 [5.5%], respectively; $P = .025$).

In-Hospital Clinical Events

Table 6 summarizes the clinical end points of the TAUSA trial by ordinal logistic regression. No patient died in the hospital. Seventeen patients (3.6%) underwent emergency CABG (12 [5.2%] in the urokinase group versus 5 [2.1%] in the placebo group [$P = .09$]). Of these 17 patients, 15 went to surgery from the cardiac catheterization laboratory and 2 patients were sent to surgery within the first 24 hours after the procedure. Eleven patients had (re)infarction after angioplasty, with no difference between urokinase and placebo groups. Ischemia after angioplasty occurred in overall 31 patients (6.6%) (23 [9.9%] on urokinase and 8 [3.4%] on placebo, $P = .005$). The percentage of urokinase patients who had a clinical end point of either recurrent ischemia, (re)infarction, or CABG (12.9% [30/232]) was significantly greater ($P = .018$) than the percentage of

TABLE 5. TAUSA Trial: Angiographic End Points

	Unstable Angina		Recent MI	
	Urokinase	Placebo	Urokinase	Placebo
	No. (%)	No. (%)	No. (%)	No. (%)
Definite filling defect (15 min)	19 (16.7)	19 (16.0)	11 (10.6)	22 (20.2)†
Phase I	12 (18.2)	9 (14.5)	5 (9.1)	14 (22.2)
Phase II	7 (14.6)	10 (17.5)	6 (12.2)	8 (17.4)
Acute closure	13 (11.0)	3 (2.4)*	10 (9.3)	7 (6.3)
Phase I	7 (10.6)	3 (4.8)	7 (12.5)	5 (7.8)
Phase II	6 (11.5)	0 (0.0)*	3 (5.9)	2 (4.3)
Any dissection	30 (26)	33 (28)	39 (38)	35 (32)
Major dissection (15 min)	12 (10.5)	7 (5.9)	10 (9.6)	12 (11.0)
Phase I	7 (10.6)	5 (8.1)	4 (7.3)	9 (14.3)
Phase II	5 (10.4)	2 (3.5)	6 (12.2)	3 (6.5)

MI indicates myocardial infarction.

* $P < .01$, † $P < .06$.

placebo patients who experienced at least one of these clinical end points (6.3% [15/237]). The distribution of patients' worst outcomes differed significantly between treatment groups ($P = .014$). In each outcome group, the percentage of urokinase patients was greater than the percentage of placebo patients. In-hospital complication rates were similar between patients with unstable angina and patients with recent myocardial infarction except for a higher incidence of CABG in those with unstable angina who were given urokinase (urokinase, 7; placebo, 0 [$P < .05$]). There were no significant differences in the placebo group. There were no significant differences in the incidence of emergency CABG or

acute closure in the patients randomized in the hospital of the principal investigator compared with the other randomizing hospitals. Bleeding complications were reported for 30 (12.9%) of the patients treated with urokinase and for 21 (8.9%) of the patients given placebo ($P = \text{NS}$). Nonaccess bleeds occurred in 3.8% of the urokinase group versus 2.1% of the placebo group ($P = \text{NS}$).

There was a trend toward fewer complications of angioplasty in the placebo group of phase II compared with phase I. The incidence of acute closure was 2 (1.6%) versus 8 (9.3%), respectively ($P < .07$), and any clinical end point occurred in 4 (3.7%) versus 11 (10.9%), respectively ($P < .07$).

TABLE 6. TAUSA Trial: Clinical End Points

	Urokinase	Placebo
	No. (%)	No. (%)
None	202 (87.1)	222 (93.7)*
Phase I	111 (86.7)	118 (91.5)
Phase II	91 (87.5)	104 (96.3)
Recurrent ischemia	12 (5.2)	5 (2.1)
Phase I	6 (4.7)	4 (3.1)
Phase II	6 (5.8)	1 (0.9)
(Re)infarction	6 (2.6)	5 (2.1)
CABG	12 (5.2)	5 (2.1)
Phase I	8 (6.3)	4 (3.1)
Phase II	4 (3.8)	1 (0.9)
Ischemia, MI, or CABG	30 (12.9)	15 (6.3)†
Phase I	17 (13.3)	11 (8.5)
Phase II	13 (12.5)	4 (3.7)

CABG indicates coronary artery bypass graft; MI, myocardial infarction.

* $P = .014$, ordinal logistic regression.† $P = .018$, Fisher's exact test.

Discussion

Thrombosis is important both in the pathogenesis of unstable angina^{14,15} and as a mechanism of acute closure after angioplasty.¹⁻⁴ Adequate antithrombotic and anticoagulant therapy prevents acute closure,¹⁶⁻¹⁸ whereas the presence of angiographic thrombus before angioplasty increases its incidence.^{2,4} Once acute closure occurs, intracoronary thrombolytic therapy along with redilatation is successful in reopening the artery in 65% to 90% of cases.^{5-8,19} Prolonged infusions of thrombolytic therapy have also been effective in dissolving large amounts of thrombus in saphenous vein grafts and native coronary arteries, permitting angioplasty to proceed without complication.^{20,21}

While these studies suggest a supportive role for thrombolytic therapy during angioplasty, the prophylactic use of thrombolytic therapy before angioplasty in unstable angina has not been well studied. In the TAUSA pilot study 92 patients with ischemic rest angina with or without a recent myocardial infarction received 150 000 U of urokinase or placebo just before wire placement.⁵ The results suggested that urokinase could decrease filling defects after angioplasty for unstable angina, but acute closure and in-hospital adverse clinical events were not decreased with urokinase. Fur-

thermore, urokinase did not decrease filling defects or acute closure in patients with recent myocardial infarction. Because the optimal dose of a thrombolytic agent in this situation is unknown, two higher doses of urokinase were chosen for the present trial. In addition to the larger sample size, heparin therapy was monitored with activated coagulation times.

The present trial does not indicate a role for prophylactic intracoronary urokinase before angioplasty for ischemic rest angina. Not only was urokinase unable to significantly decrease filling defects, but it also significantly increased both the incidence of acute closure and in-hospital adverse clinical events. These negative results with intracoronary thrombolytic therapy in the present trial are similar to recent studies of intravenous thrombolytic therapy in the acute management of unstable angina, in which the incidence of myocardial infarction was increased after use of these agents.^{22,23}

Why urokinase was so detrimental in this trial and yet of some benefit in the pilot study is unknown. It may be related to the higher dose used in the treatment group and/or the use of heparin and aspirin before angioplasty and the monitoring of the heparin dose during angioplasty, which decreased adverse events in the placebo group. Furthermore, differences in the way thrombus was identified after angioplasty may explain these apparent discrepancies between the pilot study and the trial. Only the combined end point of possible and definite filling defects after angioplasty was significantly decreased with urokinase in the pilot study. Because an analysis of adverse in-hospital events did not suggest that possible filling defects had any predictive value, these were not coded for in the present trial. Thus, if possible filling defects were excluded from the pilot study analysis, the differences would no longer be significant and similar to the data from the present trial.

In contrast to the results of angioplasty with urokinase, the results of angioplasty in the placebo group were quite good. Although these patients were in a high-risk group of patients with unstable angina, with a large percentage undergoing angioplasty after a recent infarction and/or with recent rest pain, the incidence of acute closure was relatively low, and the rate of emergency CABG was only 2% in this group of patients treated before the availability of intracoronary stenting. As previously mentioned, it is likely that the usual practice of heparin and aspirin administration before angioplasty and the monitoring of anticoagulation during the procedure contributed to this low incidence of complications.^{17,18,24} A surprising finding of the TAUSA trial was the better results of angioplasty in the placebo group in phase II compared with phase I. Although patient selection did not seem to play a role as determined from the patient log at Mount Sinai Hospital (excluded patients had a low incidence of complications), we cannot totally exclude this as a potential mechanism from other participating institutions. Otherwise, we have no explanation for this finding.

At least two earlier randomized studies have addressed the subject of coronary angioplasty after thrombolytic therapy for unstable angina.^{25,26} Both were small (36 and 83 patients randomized), thrombolytic agents were administered intravenously, and PTCA was performed within 24 hours of thrombolytic therapy. As in the TAUSA trial, no beneficial effects of thrombolytic

therapy were seen; in fact, there was a trend in one preliminary report toward increased complications with urokinase.²⁶

It is interesting to speculate on the possible mechanism or mechanisms for this detrimental effect of intracoronary thrombolytic therapy during angioplasty. Because of the higher incidence of major angiographic dissection during angioplasty, we suspect that increased intimal disruption possibly related to wall hemorrhage or to incomplete intimal sealing may be occurring when urokinase is infused into the coronary artery during angioplasty. This would be analogous to the pathological studies of Waller et al,²⁷ who noted hemorrhagic dissection of the infarct-related coronary artery in patients dying after acute myocardial infarction in whom angioplasty was performed immediately after thrombolysis.

Another possible mechanism may have been related to whether or not thrombus formation was decreased with urokinase. In patients with unstable angina there was no decrease in thrombus after angioplasty, whereas after recent infarction thrombus was decreased ($P=.06$) with urokinase. The combination of increased intimal disruption and no decrease in thrombus formation was probably responsible for the more detrimental effects (more acute closure and adverse in-hospital events) of urokinase noted in this trial in unstable angina than after recent infarction. After recent infarction the increased intimal disruption of urokinase was offset by its ability to decrease thrombus formation, resulting in neither detrimental nor beneficial effects after angioplasty.

Differences between unstable angina and myocardial infarction in the thrombotic or plaque substrate may be responsible for these apparently divergent responses to urokinase in the TAUSA trial. If the thrombus in unstable angina was platelet rich with little fibrin,²⁸ then fibrinolytic agents like urokinase would have little effect. Moreover, the procoagulant effects and the effects of thrombolytic agents on activation of platelets would be detrimental.²⁹ On the other hand, the thrombus in acute myocardial infarction is platelet and fibrin rich, and thrombolytic therapy was able to dissolve or prevent further fibrin formation after angioplasty. It is also possible that differences in the thrombogenicity of the plaque in terms of its ability to activate the coagulation cascade could explain some of these differences between unstable angina and recent infarction. The thrombotic response to spontaneous or angioplasty-induced plaque disruption is perhaps modulated in part by the concentration of tissue factor or other procoagulant substances contained within the atherosclerotic plaques.³⁰ These substances would determine the fibrin rather than the platelet component of the thrombus. Higher concentration of these substances in plaques, causing myocardial infarction, would result both in occlusive thrombi after spontaneous plaque disruption and fibrin formation after angioplasty-induced plaque disruption. The mural, platelet-rich thrombus of unstable angina may contain lower concentrations of these substances. Therefore, only angioplasty after a recent myocardial infarction was associated with a lower incidence of thrombus after an infusion of urokinase.

Study Limitations

The optimal dose, site, and duration of infusion of a thrombolytic agent as administered in this trial are

unknown. Previous studies have used low-dose intracoronary thrombolytics after acute closure, but the dose of these agents for prophylaxis has not been studied. Prolonged infusions of these agents will dissolve preexistent thrombi, and they have been used effectively in selected patients with saphenous vein grafts and native vessels containing large amounts of intracoronary thrombus.^{31,32} These vessels were excluded in this trial, although their incidence in the population studied according to our patient log was low (2 patients). Therefore, between the pilot study and the trial we used three different doses of intracoronary urokinase in an effort to test different doses and different modes of infusion (<5-minute infusions up to 10- to 15-minute infusions).

It is unknown whether more prolonged infusions at a higher dose would have changed the results, but we think it unlikely. Furthermore, the active drug or placebo was administered into the ostium of the coronary artery rather than at the lesion site with an infusion catheter. Since 22 lesions with acute closure were located in the left system, an infusion in the ostium of the left main artery would have been diluted by the time it reached the site of angioplasty. Thus, the causal relation of an infusion of urokinase to these angiographic or clinical events might be questioned. However, ethically we considered it inappropriate to deliver placebo at the site of the lesion with an infusion catheter. In addition, in the right coronary artery, where there would be less washout than in the left main artery, seven of 11 acute closures occurred with an infusion of urokinase, suggesting a causal relation to the active drug.

In conclusion, the study indicates that in the manner in which urokinase was administered, prophylactic thrombolytic therapy should not be used routinely before angioplasty in ischemic rest angina. Furthermore, in light of the low incidence of acute closure and in-hospital adverse events in the placebo group, aspirin and adequate heparinization before and during angioplasty should remain the standard for therapy during balloon angioplasty for unstable angina. With such a low incidence of adverse events when using adequate heparinization alone, we must address the issue of whether selected antithrombin agents such as hirudin or other anti-platelet-activating drugs can further improve on these acute results without adding to the risk of bleeding.

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Thrombolysis and Angioplasty in Unstable Angina (TAUSA) Study Group

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