

A COMPARISON OF RECOMBINANT UROKINASE WITH VASCULAR SURGERY AS INITIAL TREATMENT FOR ACUTE ARTERIAL OCCLUSION OF THE LEGS

KENNETH OURIEL, M.D., FRANK J. VEITH, M.D., AND ARTHUR A. SASAHARA, M.D.,
FOR THE THROMBOLYSIS OR PERIPHERAL ARTERIAL SURGERY (TOPAS) INVESTIGATORS

ABSTRACT

Background Recent controlled trials suggest that thrombolytic therapy may be an effective initial treatment for acute arterial occlusion of the legs. A major potential benefit of initial thrombolytic therapy is that limb ischemia can be managed with less invasive interventions.

Methods In this randomized, multicenter trial conducted at 113 North American and European sites, we compared vascular surgery (e.g., thrombectomy or bypass surgery) with thrombolysis by catheter-directed intraarterial recombinant urokinase; all patients (272 per group) had had acute arterial obstruction of the legs for 14 days or less. Infusions were limited to a period of 48 hours (mean [\pm SE], 24.4 ± 0.86), after which lesions were corrected by surgery or angioplasty if needed. The primary end point was the amputation-free survival rate at six months.

Results Final angiograms, which were available for 246 patients treated with urokinase, revealed recanalization in 196 (79.7 percent) and complete dissolution of thrombus in 167 (67.9 percent). Both treatment groups had similar significant improvements in mean ankle-brachial blood-pressure index. Amputation-free survival rates in the urokinase group were 71.8 percent at six months and 65.0 percent at one year, as compared with respective rates of 74.8 percent and 69.9 percent in the surgery group; the 95 percent confidence intervals for the differences were -10.5 to 4.5 percentage points at six months ($P=0.43$) and -12.9 to 3.1 percentage points at one year ($P=0.23$). At six months the surgery group had undergone 551 open operative procedures (excluding amputations), as compared with 315 in the thrombolysis group. Major hemorrhage occurred in 32 patients in the urokinase group (12.5 percent) as compared with 14 patients in the surgery group (5.5 percent) ($P=0.005$). There were four episodes of intracranial hemorrhage in the urokinase group (1.6 percent), one of which was fatal. By contrast, there were no episodes of intracranial hemorrhage in the surgery group.

Conclusions Despite its association with a higher frequency of hemorrhagic complications, intraarterial infusion of urokinase reduced the need for open surgical procedures, with no significantly increased risk of amputation or death. (N Engl J Med 1998;338:1105-11.)

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ACU TE arterial occlusion of the legs is associated with a substantial risk of limb loss and death despite surgical intervention primarily consisting of thrombectomy or bypass grafting.¹⁻³ Percutaneous, catheter-directed infusion of thrombolytic agents has been used as an alternative to open surgery in such cases.⁴⁻⁶ Thrombolysis can restore arterial flow by dissolving an occluding thrombus and can be followed by endovascular or relatively simple open procedures to correct any lesions unmasked by thrombolysis. Instead of a complex open procedure, a smaller elective procedure is performed under optimal conditions.⁷

Despite the theoretical advantages of thrombolysis, the safety and efficacy of the procedure remain controversial. Since it may restore flow more slowly than immediate surgical revascularization, tissue ischemia may progress to infarction before the artery has recanalized.⁸ Hemorrhage is a potential complication.⁹ The balance between the potential benefits of catheter-directed thrombolysis and the risk of associated complications can be assessed only through large, controlled trials. In a preliminary randomized, dose-ranging trial of thrombolysis using recombinant urokinase and involving 213 patients with acute lower-limb ischemia, we found that a regimen of 4000 IU of urokinase per minute for 4 hours, followed by an infusion of 2000 IU per minute for up to 44 additional hours, produced complete clot lysis in 71 percent of patients.¹⁰ Mortality rates and amputation-free survival rates in this group were similar to those in the surgical control group, but patients treated with thrombolysis required significantly fewer major surgical procedures. Three of 144 patients (2.1 percent) treated with urokinase had intracranial bleeding, although the one fatal complication occurred 10 days after the completion of urokinase therapy and after the initiation of warfarin therapy.

The Thrombolysis or Peripheral Arterial Surgery trial was a randomized, multicenter study designed to compare the efficacy (as assessed by amputation-free survival) and safety of catheter-administered uro-

From the Department of Surgery, University of Rochester School of Medicine and Dentistry, Rochester, N.Y. (K.O.); the Department of Surgery, Albert Einstein School of Medicine, Bronx, N.Y. (F.J.V.); and the Department of Medicine, Harvard Medical School, Boston (A.A.S.). Address reprint requests to Dr. Ouriel at the Department of Surgery, University of Rochester, 601 Elmwood Ave., Rochester, NY 14642.

kinase and conventional open surgery as initial treatment in patients with acute peripheral arterial occlusion threatening the viability of the leg. The urokinase used in the trial was a plasminogen activator of 48,000 daltons, produced from a genetically engineered mouse hybridoma cell line. It is similar to the urokinase that occurs naturally in humans, which is derived from urine. The urokinase currently available in the United States is derived by tissue culture and is smaller (32,000 daltons).

METHODS

Eligibility Criteria

To be eligible for the study, patients had to have had an acute thrombotic or embolic occlusion of a leg (native artery or bypass graft) within 14 days before randomization that met the guidelines for reversible limb-threatening ischemia.¹¹ Patients had to be over 17 years of age and medically eligible for either thrombolytic or surgical intervention; women who were pregnant or in whom pregnancy was a possibility were excluded. The trial was conducted in 113 centers in North America and Europe (see the Appendix) and approved by their respective institutional review boards or ethics committees. The investigators were surgeons or interventional radiologists experienced in thrombolytic techniques.

Randomization

Eligible patients were randomly assigned to treatment groups at enrollment by an independent randomization center accessed by telephone after informed consent was obtained and a diagnostic arteriogram confirmed the presence of an occlusion. At the time of randomization, the investigator recorded the patient's planned surgical treatment, in the event the patient was assigned to surgery. The randomization process was stratified according to whether a native arterial segment or a bypass graft was involved.

Treatment

Urokinase was infused through an intraarterial catheter at a rate of 4000 IU per minute during an initial four-hour infusion period and at a rate of 2000 IU per minute thereafter; the infusion ports were placed within the thrombus whenever possible. Concurrent unfractionated heparin was also administered intravenously to reach a target activated partial-thromboplastin time that was 1.5 to 2 times the control value. Infusions were stopped when lysis was complete, when no further progress was evident on arteriography, or after 48 hours of therapy. Successful urokinase therapy was generally followed by surgical or endovascular interventions if a suitable lesion was identified. After 62 patients had been treated with urokinase, the safety monitoring committee identified an unacceptably high rate of intracranial hemorrhage (4.8 percent), and the initial requirement for therapeutic doses of heparin was abolished; thereafter, the protocol prohibited its use. Small, subtherapeutic amounts of heparin, administered through the arterial sheath, were permitted in order to prevent pericatheter thrombosis; aspirin, initially mandatory, was also discontinued during thrombolysis. Warfarin therapy was to be initiated in any patient who had an occlusion of embolic origin, who required a prosthetic graft to infrapopliteal arteries, in whom the lesion responsible could not be identified, or who was thought to have a hypercoagulable syndrome.

Outcome Measures

The primary end point of the study was amputation-free survival six months after randomized treatment. Secondary end points were survival free of open surgical procedures at six months among patients in the urokinase group, amputation-free survival at one year, the degree of clot lysis and increase in ankle-

brachial blood-pressure index, and the rates of adverse effects of treatment, including hemorrhagic complications. The extent of clot lysis was based on arteriographic measurements; lysis of more than 95 percent was defined as complete lysis. The arteriogram selected for evaluation was that obtained closest to the end of the infusion of study drug but no more than four hours after the end of infusion. The measurement of post-treatment ankle-brachial blood pressure used was the last measurement obtained within 96 hours after the initiation of therapy. Indexes above 1.3 were considered spurious on the basis of vessel incompressibility and were excluded from the analysis. An episode of major bleeding was defined as the occurrence of any of the following within 14 days after therapy: severe blood loss (>500 ml), blood loss requiring transfusion, blood loss causing hypotension, or intracranial hemorrhage.

Statistical Analysis

In determining the number of patients needed for the study, we assumed amputation-free survival rates at six months of 77 percent with urokinase and 55 percent with surgery.¹² Given this assumption, a total of 500 patients was required to provide more than 95 percent power to detect significant differences at the two-sided 0.05 level. Fisher's exact test was used to analyze categorical data unless the number of categories was too large, in which case Pearson's chi-square test was used. Analysis of variance was based on the type III sum of squares. Censored data were analyzed with Kaplan-Meier adjusted rates, and their standard errors with construction of a z statistic. All P values were based on two-sided tests. Statistical analyses were done with SAS software (version 6.09, SAS Institute, Cary, N.C.). The primary analysis was based on the intention-to-treat principle and included all randomized patients; safety analyses included all patients who actually received the treatment assigned.

RESULTS

Between August 1993 and December 1994, 548 patients underwent randomization; 4 patients subsequently withdrew their consent for randomized therapy and use of their data, leaving 272 in each treatment group (Table 1). Thirty-three of the 544 patients received no randomized treatment: 17 assigned to thrombolysis and 16 assigned to surgery. The most common reasons were failure to place the catheter or guide wire (10 patients in the thrombolysis group) and withdrawal of consent (5 patients in the surgical group); the remaining 18 patients were excluded for a variety of reasons. These 33 patients were included in the intention-to-treat analysis but were excluded from the analysis of adverse effects. The group assigned to thrombolysis had a significantly higher proportion of men ($P=0.046$), patients with hepatic and renal insufficiency ($P=0.027$), and patients with pain at rest at presentation ($P=0.003$). No significant differences were found between the groups with regard to the duration of symptoms or the nature, location, or length of the arterial occlusion (Table 2). Thrombotic events were much more frequent than embolic events, and patients with occluded bypass grafts slightly outnumbered those with native arterial occlusions. The occluded bypass grafts were made of polytetrafluoroethylene in 57 percent, polyester in 11 percent, autogenous vein in 19 percent, a composite of polytetrafluoroethylene and

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS IN THE UROKINASE AND SURGICAL-TREATMENT GROUPS.*

CHARACTERISTIC	UROKINASE GROUP (N=272)	SURGERY GROUP (N=272)
Age — yr	64.9±0.78	64.5±0.78
Sex — no. (%)		
Male	192 (71)	170 (62)
Female	80 (29)	102 (38)
Race — no. (%)		
White	215 (79)	216 (79)
Nonwhite	57 (21)	56 (21)
History of smoking — no. (%)	208 (76)	213 (78)
Concurrent medical illnesses — no. (%)		
Coronary artery disease	114 (42)	118 (43)
Hepatic or renal insufficiency	58 (21)	37 (14)
Transient cerebral ischemia or stroke	45 (17)	39 (14)
Cancer	33 (12)	31 (11)
Hypertension	169 (62)	156 (57)
Hypercholesterolemia	61 (22)	68 (25)
Diabetes	85 (31)	72 (26)
Congestive heart failure	39 (14)	31 (11)
Prestudy medications		
Aspirin	85 (31)	89 (33)
Oral anticoagulants	67 (25)	58 (21)
Pentoxifylline	37 (14)	30 (11)
Dipyridamole	11 (4)	8 (3)
Ischemic signs and symptoms — no./total no. of patients (%)		
Skin		
Pallor	108/265 (41)	100/268 (37)
Mottled appearance, cyanosis	104/265 (39)	98/268 (37)
Poikilothermy	251/268 (94)	245/268 (91)
Pain at rest	209/267 (78)	178/268 (66)
Motor deficit	76/267 (28)	62/268 (23)
Sensory deficit	141/268 (53)	125/268 (47)
Muscle changes	21/267 (8)	13/268 (5)
Ischemic ulceration	26/268 (10)	21/268 (8)
Gangrene	13/268 (5)	16/268 (6)
Ankle-brachial blood-pressure index†	0.15±0.015	0.18±0.015

*Plus-minus values are means ±SE.

†The ankle-brachial blood-pressure index was determined in 237 patients in the urokinase group and 240 patients in the surgery group.

vein in 4 percent, and other or unknown materials in 9 percent. There were no significant differences between the groups in the frequencies of planned surgical procedures, as recorded by the patients' physicians before randomization. Thromboembolectomy was the most common planned surgical procedure, chosen in 66 percent of patients, with bypass grafting chosen in 32 percent. Amputation was not selected as the planned procedure for any patient.

Access to the thrombus or embolus was successful in 244 of 256 patients assigned to urokinase in whom positioning of the guide wire into the thrombus was attempted. In 218 of these 244 patients, the guide wire was confirmed to have penetrated the clot. The mean (±SE) duration of urokinase infusion was 24.4±0.86 hours; the mean dose was 3.5±0.11 million IU. Final angiograms were available for 246 patients treated with urokinase; recanalization was evident in 196 patients (79.7 percent),

TABLE 2. OCCLUSION CHARACTERISTICS IN THE UROKINASE AND SURGICAL-TREATMENT GROUPS.*

CHARACTERISTIC	UROKINASE GROUP	SURGERY GROUP	P VALUE
Type of occlusion — no./total no. of patients (%)			0.93†
Native artery	122/272 (45)	120/272 (44)	
Bypass graft	150/272 (55)	152/272 (56)	
Cause of occlusion — no./total no. of patients (%)			0.71†
Thrombosis	233/270 (86)	231/272 (85)	
Embolism	37/270 (14)	41/272 (15)	
Duration of symptoms before randomization — days (no. of patients)	4.2±0.23 (272)	4.0±0.23 (272)	0.69‡
Location of occlusion — no./total no. of patients (%)			0.94†
Axillofemoral	5/270 (2)	5/271 (2)	
Infrainguinal	202/270 (75)	199/271 (73)	
Suprainguinal	63/270 (23)	67/271 (25)	
Length of occlusion — cm (no. of patients)	32.4±1.42 (266)	31.7±1.44 (259)	0.73‡

*Plus-minus values are means ±SE. Data were missing for some patients.

†The P value was based on Fisher's exact test.

‡The P value was based on one-way analysis of variance.

with complete dissolution of the thrombus occurring in 167 patients (67.9 percent).

Clinical Outcomes

Amputation-free survival rates six months after randomization were 71.8 percent in the urokinase group and 74.8 percent in the surgery group (P=0.43; 95 percent confidence interval for the difference between treatments, -10.5 to 4.5 percentage points); the respective rates at one year were 65.0 percent and 69.9 percent (P=0.23; 95 percent confidence interval, -12.9 to 3.1 percentage points). There was also no significant difference in the rates of amputation-free survival at discharge from the hospital (83.5 percent in the urokinase group and 88.6 percent in the surgery group, P=0.08). The mortality rates for the urokinase and surgery groups were 8.8 and 5.9 percent, respectively, at hospital discharge (P=0.19), 16.0 and 12.3 percent at six months (P=0.22 by Kaplan-Meier analysis), and 20.0 and 17.0 percent one year after randomization (P=0.39 by Kaplan-Meier analysis). The ankle-brachial blood-pressure index rose significantly after treatment in both groups (P<0.001 by one-way analysis of variance), with no significant difference between groups (P=0.23). At the end of six months, Kaplan-Meier analyses showed that 31.5 percent of the patients in the urokinase group had had only percutaneous procedures, as compared

TABLE 3. OPERATIVE INTERVENTIONS AND WORST OUTCOMES AT SIX MONTHS AND ONE YEAR.*

INTERVENTION OR OUTCOME	UROKINASE GROUP (N=272)		SURGERY GROUP (N=272)	
	6 MO	1 YR	6 MO	1 YR
	no. of interventions			
Operative intervention				
Amputation	48	58	41	51
Above the knee	22	25	19	26
Below the knee	26	33	22	25
Open surgical procedures	315	351	551	590
Major	102	116	177	193
Moderate	89	98	136	145
Minor	124	137	238	252
Percutaneous procedures	128	135	55	70
	% of patients			
Worst outcome†				
Death	16.0	20.0	12.3	17.0
Amputation	12.2	15.0	12.9	13.1
Above the knee	5.6	6.5	6.1	7.5
Below the knee	6.6	8.5	6.8	5.6
Open surgical procedures	40.3	39.3	69.0	65.4
Major	23.6	24.3	39.3	39.3
Moderate	10.3	8.7	16.3	13.4
Minor	6.4	6.3	13.4	12.7
Endovascular procedures	16.9	15.4	2.1	1.7
Medical treatment alone	14.6	10.3	3.7	2.8

*Major surgical procedures included the insertion of a new bypass graft, replacement of an existing graft, and excision or repair of aneurysm. Moderate procedures included graft revision, endarterectomy, profundaplasty, exploratory vascular surgery, and transmetatarsal amputation. Minor procedures included thromboembolectomy or embolectomy, amputation of digits, and fasciotomy. Endovascular procedures included percutaneous transluminal angioplasty, atherectomy, stent placement, suction thrombectomy, and thrombolytic therapy.

†The most severe clinical outcome for each patient is reported on the basis of Kaplan-Meier analysis.

with 5.8 percent of the surgical patients ($P \leq 0.001$) (Table 3). The length of hospitalization was similar, a median of 10 days in both treatment groups among patients who survived to discharge. Among the patients who were randomly assigned to initial thrombolysis, those with occlusions in bypass grafts had better clinical outcomes and rates of clot dissolution (Table 4) and lower rates of major hemorrhagic complications than patients with occlusions in native arteries.

Thirty days after the intervention, about 30 percent of the patients in both groups were taking aspirin and 57 percent were taking warfarin. The percentages of patients taking aspirin rose slightly at six months and one year, whereas the percentages taking warfarin declined slightly at each point. At no time during follow-up was there a difference of more than 4 percentage points between the groups in the reported use of either medication. Only 7.5

percent of patients took both warfarin and aspirin; about 20 percent took neither drug.

Thrombolytic and Operative Interventions

During the initial hospitalization, 54 percent of the patients in the urokinase group and 91 percent of those in the surgery group required an open surgical procedure, underwent amputation, or died ($P \leq 0.001$). Twenty-three percent of patients assigned to initial thrombolysis needed no further interventions before discharge from the hospital. Table 3 shows the frequency of surgical procedures performed up to six months and one year after treatment in the two groups, as well as the estimated frequency of the most severe outcome for each patient. During the first six months after treatment, patients who were randomly assigned to surgery underwent 551 open surgical procedures, whereas the patients assigned to initial thrombolysis had 315.

Treatment Complications

Major hemorrhagic complications occurred in 32 patients (12.5 percent) in the urokinase group, as compared with 14 patients (5.5 percent) in the surgery group ($P = 0.005$). Twenty-one of the patients in the urokinase group had major bleeding at vascular-access sites (e.g., sites of catheter insertion and venipuncture); in four patients, bleeding was associated with an open surgical procedure after thrombolysis. In addition, 14 patients in the urokinase group had bleeding in areas other than vascular-access sites, as compared with 5 patients assigned to surgery ($P = 0.04$ by Fisher's exact test). The patients' ages, durations of infusion, and activated partial-thromboplastin times at base line were unrelated to the risk of bleeding. The relative risk of major bleeding in patients in the urokinase group, on the basis of selected characteristics, is presented in Table 5. There was a significant association between the coadministration of heparin and the risk of major bleeding ($P = 0.02$ by Fisher's exact test). Transfusions of more than one unit of packed red cells were required in 92 patients in the urokinase group and 69 patients in the surgery group ($P = 0.03$ by Fisher's exact test). Intracranial hemorrhage occurred in four patients in the urokinase group (1.6 percent), one of whom died on the second day of hospitalization. This 67-year-old man, with a history of hypertension, presented with a 10-day history of worsening ischemia in the left leg. Death occurred after an intraarterial infusion of 1.3 million IU of urokinase over a period of 4.7 hours, with concomitant aspirin and heparin therapy. By contrast, there were no instances of intracranial bleeding in the surgery group.

Distal embolization of partially thrombolized material occurred 41 times in 36 patients treated with urokinase. The emboli were dissolved in 19 of the 26 cases treated only with continued urokinase

TABLE 4. RESULTS OF THROMBOLYSIS AND SURGERY IN PATIENTS WITH OCCLUSIONS IN NATIVE ARTERIES AND BYPASS GRAFTS.*

INTERVENTION	NATIVE-ARTERY OCCLUSIONS (N=242)			BYPASS-GRAFT OCCLUSIONS (N=302)		
	UROKINASE (N=122)	SURGERY (N=120)	P VALUE	UROKINASE (N=150)	SURGERY (N=152)	P VALUE
Complete dissolution of clot on final angiogram — no./total no. of patients (%)	67/112 (60)	NA	—	100/134 (75)	NA	—
Increase in ankle-brachial index	0.44±0.04	0.52±0.04	0.15†	0.48±0.03	0.50±0.03	0.76‡
Mortality — %						
6 mo	20.8	15.9	0.33‡	12.1	9.4	0.45‡
1 yr	24.6	19.6	0.36‡	16.2	15.0	0.77‡
Amputation-free survival — %						
6 mo	67.6	76.1	0.15‡	75.2	73.9	0.79‡
1 yr	61.2	71.4	0.10‡	68.2	68.8	0.91‡

*Plus-minus values are means ±SE. NA denotes not applicable.

†The P value was based on one-way analysis of variance.

‡The P value was based on Kaplan-Meier analysis.

therapy. Amputation or death during the initial hospitalization occurred in 19 percent of patients with emboli and 16 percent without emboli. Additional complications included pericatheter thrombosis in 13 patients, the development of a false aneurysm at the catheter-insertion site in 7 patients, perforation or intimal damage in 3 patients, and rigors possibly related to urokinase infusions in 2 patients.

DISCUSSION

For several decades, thrombolysis with agents such as streptokinase, urokinase, and recombinant tissue plasminogen activator has been investigated in uncontrolled trials as a therapeutic alternative to operation for arterial occlusion in the legs.^{5,6,13,14} In the past two years, three randomized trials have been published comparing thrombolysis with surgery for arterial occlusion. The first trial, the Rochester study, randomly assigned 57 patients with acute limb-threatening ischemia (duration, ≤7 days) to thrombolysis with urokinase and 57 to immediate operation.¹² At one year, the amputation-free survival rates were 75 percent and 52 percent, respectively, a statistically significant difference. In the multicenter Surgery versus Thrombolysis for Ischemia of the Lower Extremity (STILE) study, 393 patients were randomly assigned to surgery or to thrombolysis with either recombinant tissue plasminogen activator or urokinase.¹⁵ Clinical outcomes for both thrombolysis groups were similar, so their data were combined for the overall comparison of thrombolysis with surgery. Post hoc stratification of patients into two subgroups on the basis of the duration of symptoms before enrollment (>14 days vs. ≤14 days) showed that among patients with symptoms of longer duration, the surgical group had lower amputation rates than the thrombolysis groups at

TABLE 5. RELATIVE RISK OF MAJOR BLEEDING IN THE PATIENTS TREATED WITH UROKINASE, ACCORDING TO SELECTED CHARACTERISTICS.

CHARACTERISTIC	NO. OF PATIENTS	BLEEDING no. (%)	RELATIVE RISK (95% CI)*	P VALUE†
Female	74	10 (14)	1.11 (0.55–2.23)	0.84
Male	181	22 (12)		
Type of occlusion				
Native	115	17 (15)	1.38 (0.72–2.64)	0.35
Graft	140	15 (11)		
Cause of occlusion				
Embolus	34	5 (15)	1.20 (0.50–2.91)	0.78
Thrombus	221	27 (12)		
Therapeutic heparin‡				
Yes	102	19 (19)	2.19 (1.13–4.24)	0.02
No	153	13 (9)		
Treatment with aspirin				
Yes	65	12 (18)	1.75 (0.91–3.39)	0.13
No	190	20 (11)		

*CI denotes confidence interval.

†The P values were calculated by two-tailed Fisher's exact test.

‡Patients were considered to have received therapeutic heparin if the activated partial-thromboplastin time was at least 1.5 times the upper limit of normal at least once during urokinase infusion. Heparin was required by protocol for the first 62 treated patients, after which it was prohibited. Additional patients were shown to have elevated activated partial-thromboplastin times after the protocol was modified.

6 months (3 percent vs. 12 percent, P=0.01). In contrast, among patients with symptoms of shorter duration, patients assigned to thrombolysis had lower rates than surgical patients (11 percent vs. 30 percent, P=0.02). In our preliminary urokinase dose-ranging study, the one-year amputation-free survival rate in the group assigned to receive 4000 IU of

urokinase per minute (52 patients) was 74.6 percent, as compared with 66.9 percent in the surgical group (58 patients) ($P=0.38$).¹⁰

Our current results differ from those of the Rochester study. In our study, initial thrombolytic therapy was not superior to operative intervention with respect to the major end points of survival and limb salvage. Indeed, there was a trend toward a higher amputation-free survival rate in the surgical group. Treatment philosophies and patient selection appear to be critical factors requiring further study in identifying candidates suitable for thrombolytic therapy. Our patients were less acutely ill than those in the Rochester series, as manifested by the duration and magnitude of limb ischemia, age differences, and the incidence of coronary artery disease. The high amputation rate in the patients with acute ischemia who were assigned to surgery in the STILE study may relate to investigator concern that attempts to salvage a limb may ultimately increase mortality. Referral to a randomized study may also be conditioned by the clinical judgments of surgeons: no study reported outcomes in patients treated outside the study.

The identification of risk factors for hemorrhage will improve our ability to select candidates for thrombolysis. The Rochester study reported an 11 percent rate of serious bleeding complications in patients receiving urokinase, with one death due to cerebral hemorrhage. The STILE study reported a 5.6 percent rate of serious hemorrhage in patients receiving thrombolytic agents, with low fibrinogen levels identified as a risk factor. In the preliminary dose-ranging study of urokinase,¹⁰ the rate of severe hemorrhage at all anatomical sites was 7 percent and at non-insertion sites 5 percent, but the study population was too small to allow the identification of a difference among the three dosages. In the current trial, we found a 12.5 percent incidence of major bleeding with urokinase, with an increase in the risk of hemorrhage when patients received concurrent heparin. Although the potential for clinically significant hemorrhage in patients undergoing thrombolysis remains a concern, our study data suggest that the risk of hemorrhage at sites distant from the catheter can be reduced by restricting the concomitant use of heparin.

Our data demonstrate that an initial strategy of thrombolysis, as compared with immediate surgery, reduces the number of open procedures required for acute ischemia of the lower leg and allows some patients to avoid surgical intervention altogether without a significant increase in mortality, the amputation rate, or the duration of hospitalization. The substitution of thrombolysis and closed procedures for open surgery should be attractive to both patients and health care providers. In many instances, thrombolysis can offer patients definitive treatment with less accompanying trauma than major surgery.

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APPENDIX

The following institutions participated in the study: Albany Memorial Hospital (Albany, N.Y.), Balboa Naval Hospital (San Diego, Calif.), Baylor University (Dallas), Berkshire Medical Center (Pittsfield, Mass.), Bowman Gray School of Medicine (Winston-Salem, N.C.), Brigham and Women's Hospital (Boston), Budai Railway Hospital (Budapest, Hungary), Carl T. Hayden Medical Center (Phoenix, Ariz.), Catholic Medical Center (Manchester, N.H.), Central County Hospital (Miskolc, Hungary), Christ Hospital (Cincinnati), Cleveland Clinic (Cleveland and Fort Lauderdale, Fla.), Creighton University (Omaha, Nebr.), Dakota Medical Center (Fargo, N.D.), Doctors Hospital North (Columbus, Ohio), Elmhurst Memorial Hospital (Elmhurst, Ill.), Emory University (Atlanta), Englewood Hospital (Englewood, N.J.), Erlanger Medical Center (Chattanooga, Tenn.), Florida Hospital (Orlando), Flushing Hospital (Flushing, N.Y.), Fresno Community Hospital (Fresno, Calif.), Hahnemann University (Philadelphia), Harbor-UCLA (Torrance, Calif.), Hoag Memorial Hospital (Newport Beach, Calif.), Holy Cross Hospital (Calgary, Alta.), Holy Redeemer Hospital (Meadowbrook, Pa.), Hôtel Dieu (Montreal), Illinois Masonic Medical Center (Chicago), Iowa Methodist Medical Center (Des Moines), Jackson Hospital (Montgomery, Ala.), Jackson Memorial Medical Center (Miami), Jeanes Physician Office Building (Philadelphia), Kaposi Mor Megyei Korhaz (Tallian, Hungary), Keesler Air Force Medical Center (Keesler Air Force Base, Miss.), Los Angeles County and University of Southern California Medical Center (Los Angeles), Lancaster General Hospital (Lancaster, Pa.), Loma Linda University (Loma Linda, Calif.), Long Beach Memorial Medical Center (Long Beach, Calif.), Los Alamitos Medical Center (Los Alamitos, Calif.), Massachusetts General Hospital (Boston), Mayo Clinic (Rochester, Minn.), Medical Center Hospital of Vermont (Burlington), Medical University of South Carolina (Charleston), Memorial Hospital (Hollywood, Fla.), Mercy General Hospital (Sacramento, Calif.), Mercy Hospital (Muskegon, Mich.), Mercy Hospital (Port Huron, Mich.), Montefiore Hospital (Bronx, N.Y.), Mount Diablo Medical Center (Concord, Calif.), New Britain General Hospital (New Britain, Conn.), New York Medical College (Valhalla), Newark Beth Israel Medical Center (Newark, N.J.), Northridge Hospital (Northridge, Calif.), Northwestern Memorial Hospital (Chicago), Ohio State University (Columbus), Oklahoma University (Oklahoma City), Osteopathic Medical Center of Texas (Fort Worth), Presbyterian Hospital (Dallas), Presbyterian Medical Center (Philadelphia), Princeton Baptist Medical Hospital (Birmingham, Ala.), Rhode Island Hospital (Providence), Rochester General Hospital (Rochester, N.Y.), Saint Anthony's Hospital (St. Petersburg, Fla.), Saint David's Hospital (Austin, Tex.), Saint Francis Hospital (Beech Grove, Ind.), Saint Francis Medical Center (Peoria, Ill.), Saint Joseph Hospital (Denver), Saint Joseph's Hospital (Atlanta), Saint Luc Hospital (Montreal), San Pedro Peninsula Hospital (San Pedro, Calif.), Sarasota Memorial Hospital (Sarasota, Fla.), Sentara Hampton General Hospital (Hampton, Va.), Sentara Norfolk General Hospital (Norfolk, Va.), Seton Medical Center (Daly City, Calif.), Shore Memorial Hospital (Somers Point, N.J.), Sir Mortimer B. Davis Jewish General Hospital (Montreal), Southern Illinois University (Springfield), Sparrow Hospital (Lansing, Mich.), State University of New York at Buffalo (Buffalo), State University of New York at Stony Brook (Stony Brook), Staten Island University (New York), Straub Pacific Health Foundation (Honolulu), Tampa General Hospital (Tampa, Fla.), Temple University (Philadelphia), Texas A&M University (Temple), Texas Technical University (Lubbock), Toledo Vascular Institute (Toledo, Ohio), Tulane University (New Orleans), U.S. Air Force Medical Center (Travis Air Force Base, Calif.), University Hospital (Cincinnati), University Hospital (London, Ont.), University of Arizona (Tucson), University of Calgary (Calgary, Alta.), University of California Irvine (Orange), University of California San Francisco (San Francisco), University of Illinois (Chicago), University of Maryland (Baltimore), University of Minnesota (Minneapolis), University of Mississippi (Jackson), University of Rochester (Rochester, N.Y.), University of Texas (Galveston), University of Utah (Salt Lake City), University of Virginia (Charlottesville), University of Wisconsin (Madison), Vanderbilt University (Nashville), Washington Hospital Center (Washington, D.C.), Wentworth-Douglass Hospital (Dover, N.H.), West Virginia University (Morgantown), Wilford Hall Medical Center (Lackland Air Force Base, Tex.), William S. Middleton Memorial Hospital (Madison, Wis.), and Veterans Affairs Medical Centers in the following cities: Tucson, Ariz.; San Francisco; Palo Alto, Calif; Long Beach,

Calif.; Miami; Tampa, Fla.; Bay Pines, Fla.; Decatur, Ga.; Allen Park, Mich.; Kansas City, Mo.; Bronx, N.Y.; Oklahoma City; Pittsburgh; Charleston, S.C.; and Salt Lake City.

REFERENCES

1. Yeager RA, Moneta GL, Taylor LM Jr, Hamre DW, McConnell DB, Porter JM. Surgical management of severe acute lower extremity ischemia. *J Vasc Surg* 1992;15:385-93.
2. Jivegard L, Holm J, Schersten T. Acute limb ischemia due to arterial embolism or thrombosis: influence of limb ischemia versus pre-existing cardiac disease on postoperative mortality rate. *J Cardiovasc Surg (Torino)* 1988;29:32-6.
3. Hill SL, Donato AT. The simple Fogarty embolectomy: an operation of the past? *Am Surg* 1994;60:907-11.
4. Dotter CT, Rosch J, Seaman AJ. Selective clot lysis with low-dose streptokinase. *Radiology* 1974;111:31-7.
5. Hess H, Ingrisch H, Mietaschk A, Rath H. Local low-dose thrombolytic therapy of peripheral arterial occlusions. *N Engl J Med* 1982;307:1627-30.
6. McNamara TO, Fischer JR. Thrombolysis of peripheral arterial and graft occlusions: improved results using high-dose urokinase. *AJR Am J Roentgenol* 1985;144:769-75.
7. Earnshaw JJ. Thrombolytic therapy in the management of acute limb ischaemia. *Br J Surg* 1991;78:261-9.
8. Ricotta J. Intra-arterial thrombolysis: a surgical view. *Circulation* 1991;83:Suppl I:I-120-I-121.
9. Marder VJ. Bleeding complications of thrombolytic treatment. *Am J Hosp Pharm* 1990;47:Suppl 2:S15-S19.
10. Ouriel K, Veith FJ, Sasahara AA. Thrombolysis or peripheral arterial surgery: phase I results. *J Vasc Surg* 1996;23:64-73.
11. Suggested standards for reports dealing with lower extremity ischemia: prepared by the Ad Hoc Committee on Reporting Standards, Society for Vascular Surgery/North American Chapter, International Society for Cardiovascular Surgery. *J Vasc Surg* 1986;4:80-94.
12. Ouriel K, Shortell CK, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg* 1994;19:1021-30.
13. Sicard GA, Schier JJ, Totty WG, et al. Thrombolytic therapy for acute arterial occlusion. *J Vasc Surg* 1985;2:65-78.
14. Graor RA, Risius B, Denny KM, et al. Local thrombolysis in the treatment of thrombosed arteries, bypass grafts, and arteriovenous fistulas. *J Vasc Surg* 1985;2:406-14.
15. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity: the STILE trial. *Ann Surg* 1994;220:251-68.

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