

PROACT: A Phase II Randomized Trial of Recombinant Pro-Urokinase by Direct Arterial Delivery in Acute Middle Cerebral Artery Stroke

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Background and Purpose—To test the safety and recanalization efficacy of intra-arterial local delivery of plasminogen activators in acute ischemic stroke, a randomized trial of recombinant pro-urokinase (rpro-UK) versus placebo was undertaken in patients with angiographically documented proximal middle cerebral artery occlusion.

Methods—After exclusion of intracranial hemorrhage by CT scan, patients with abrupt onset of symptoms of focal ischemia likely to receive treatment within 6 hours who satisfied all clinical eligibility criteria underwent carotid angiography. Patients displaying Thrombolysis in Acute Myocardial Infarction grade 0 or 1 occlusion of the M1 or M2 middle cerebral artery were randomized 2:1 to receive rpro-UK (6 mg) or placebo over 120 minutes into the proximal thrombus face. All patients received intravenous heparin. Recanalization efficacy was assessed at the end of the 2-hour infusion, and intracerebral hemorrhage causing neurological deterioration was assessed at 24 hours.

Results—Of 105 patients who underwent angiography, 59 were excluded from randomization. Among the 46 patients randomized, 40 were treated with rpro-UK (n=26) or placebo (n=14) a median of 5.5 hours from symptom onset. Recanalization was significantly associated with rpro-UK ($2P=.017$). Hemorrhagic transformation causing neurological deterioration within 24 hours of treatment occurred in 15.4% of the rpro-UK-treated patients and 7.1% of the placebo-treated patients ($2P=.64$). Both recanalization and hemorrhage frequencies were influenced by heparin dose.

Conclusions—Intra-arterial local rpro-UK infusion was associated with superior recanalization in acute thrombotic/thromboembolic stroke compared with placebo. In this regimen, heparin dose influenced hemorrhage frequency and recanalization. Although symptomatic hemorrhage remains a concern, this study suggests that recanalization is enhanced with rpro-UK and heparin. (*Stroke*. 1998;29:4-11.)

Key Words: stroke, acute ■ angiography ■ hemorrhage ■ pro-urokinase ■ recanalization

There has been a resurgence of interest in the notion that recanalization of recently occluded main stem cerebral arteries by plasminogen activators in the early moments of acute stroke may lead to efficient neurological recovery. The feasibility and safety of cerebral arterial recanalization have been demonstrated in a series of prospective angiography-based trials of intravenous infusion of rt-PA (alteplase).¹⁻³ Recently, intravenous rt-PA (alteplase) has been shown to improve four measures of clinical outcome at 90 days when treatment was initiated within 3 hours of stroke onset.⁴ Reported experience using intra-arterial infusion of fibrinolytic agents in a limited number of patients with complete carotid territory^{5,6} or vertebrobasilar⁶⁻⁸ arterial occlusion sug-

gests that direct intra-thrombus delivery of plasminogen activators within 6 hours of stroke onset can recanalize a greater proportion of major symptomatic cerebral arterial occlusions than intravenous delivery.⁹ The possibility that intra-arterial delivery of a plasminogen activator with early cerebral arterial recanalization may lead to improvement in clinical outcome has not been tested prospectively.

The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial is the first randomized, double-blind, multicenter trial comparing the safety, recanalization frequency, and clinical efficacy of direct intra-arterial infusion of recombinant pro-urokinase (rpro-UK) with placebo in patients with symptomatic MCA occlusion of less than 6

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Selected Abbreviations and Acronyms

| | |
|---------|---|
| ECASS | = European Cooperative Acute Stroke Study |
| MCA | = middle cerebral artery |
| NIHSS | = National Institutes of Health Stroke Scale |
| PROACT | = Prolyse in Acute Cerebral Thromboembolism |
| NINDS | = National Institute of Neurological Disorders and Stroke |
| rpro-UK | = recombinant pro-urokinase |
| rt-PA | = recombinant tissue plasminogen activator |
| TIMI | = Thrombolysis in Acute Myocardial Infarction |
| u-PA | = urokinase plasminogen activator |

hours' duration. rpro-UK is a relatively thrombus-specific, single-chain proenzyme that is converted to two-chain urokinase (u-PA) by fibrin-associated plasmin at the thrombus.¹⁰⁻¹³

The objective of this study was to examine the dose-rate response of directed rpro-UK infusion on recanalization in an angiographically defined subgroup of acute ischemic stroke patients with M1 or M2 MCA occlusions. This subgroup of severely affected patients was expected to have similar clinical presentations and anticipated outcomes. A placebo group was included to evaluate safety aspects of the angiographic and interventional procedures and to provide a basis for assessment of the contribution of rpro-UK to recanalization (without mechanical disruption).

The general hypothesis to be tested in this phase II study was that infusion of rpro-UK within the proximal thrombus face could safely produce superior recanalization compared with placebo. Conceived of as a two-part phase II introduction to a larger phase III comparison of clinical outcome after intra-arterial delivery of rpro-UK with placebo, we report here the results of the 6-mg dose tier of the phase II trial.

Subjects and Methods

Between February 1994 and February 1995, 37 North American clinical centers screened patients with symptoms of acute carotid artery territory stroke for entry into this study ("Appendix"). Patients who fulfilled all inclusion criteria and failed no exclusion criteria were randomized in a ratio of 2:1 to receive either rpro-UK or placebo by intra-arterial infusion. Two rpro-UK doses were to be evaluated. A 6-mg tier (I) was to be completed before the 12-mg tier (II) would be initiated.

The clinical inclusion criteria required that patients (1) have a new onset of focal neurological signs in the MCA distribution allowing randomization and initiation of treatment within 6 hours of the onset of symptoms; (2) have a minimum NIHSS¹⁴ score of 4, except for isolated aphasia or isolated hemianopsia; and (3) be 18 to 85 years old. Clinical exclusion criteria included an NIHSS score >30, coma, minor stroke symptoms, or a history of stroke within the previous 6 weeks; suspected lacunar stroke; seizure at stroke onset; clinical presentation suggestive of subarachnoid hemorrhage (even if the initial CT scan was normal); evidence or history of intracranial hemorrhage at any time or an intracranial neoplasm; uncompensated hypertension (blood pressure >180/100 mm Hg); presumed septic embolus or endocarditis; surgery or trauma (within 30 days); head trauma (within 90 days); active or recent hemorrhage within 14 days; known hereditary or acquired hemorrhagic diathesis; or oral anticoagulation with an international normalized ratio >1.5.

CT scan exclusion criteria were evidence of hemorrhage of any degree, significant mass effect with midline shift, or the presence of an intracranial tumor (except a small meningioma). Patients with early changes of ischemia on CT were included.

Patients who were not excluded by clinical or CT criteria and for whom informed consent was obtained underwent diagnostic cerebral angiography of the symptomatic carotid artery territory. Angiographic inclusion criteria were complete occlusion (TIMI grade 0)¹⁵ or contrast penetration with minimal perfusion (TIMI grade 1) of either the horizontal M1 segment or the M2 division of the MCA. Patients not meeting the angiographic inclusion criteria were followed for neurological deterioration and/or serious adverse events for 24 hours or until alternative treatment was initiated, whichever came first.

If an M1 or M2 occlusion was documented, the patient was allocated by the Central Randomization Center to receive either 6 mg rpro-UK or saline placebo at a 30-mL/h controlled infusion rate (tier I). An infusion microcatheter with a single end hole was placed into the thrombus extending as far as the proximal third of the thrombus. Penetration through the clot was proscribed to avoid mechanical disruption. Local infusion into the M1 segment was permitted when the microcatheter could not be embedded into the clot. More proximal regional infusions were prohibited. A second angiogram was performed at 60 minutes. If partial clot lysis had occurred, the catheter was advanced into the proximal third of the remaining thrombus. The total amount of rpro-UK or placebo was infused over 2 hours in all patients, whether or not complete lysis had occurred previously. A final postinfusion angiogram was then performed through the diagnostic catheter in the cervical internal carotid artery.

The primary efficacy outcome was recanalization of the M1 or M2 MCA at 120 minutes after initiation of infusion. All angiograms were assessed by the Core Neuroradiology Facility, which was blinded to treatment assignment and clinical status. Patients with partial (TIMI 2) or complete (TIMI 3) recanalization were considered "responders." Complete responders were defined as patients with TIMI 3 grade patency in all M1 and M2 arteries. The proportions of patients demonstrating complete, partial, or no recanalization of all target M1 and M2 occlusions on the 120-minute diagnostic angiogram were compared between treatment groups. Clinical outcome was assessed according to the NIHSS,¹⁴ modified Rankin Scale,¹⁶ and Barthel Index¹⁷ at 7 days, 30 days, and 90 days after treatment. All investigators and examining physicians were blinded to treatment assignment.

The primary safety outcome was hemorrhagic transformation causing neurological deterioration within 24 hours of treatment. Established definitions of hemorrhagic transformation were applied to all CT scans.¹⁸ Hemorrhagic infarction was defined as areas of petechial or confluent petechial hemorrhage within regions of more homogeneous ischemic injury. Parenchymatous hematoma formation referred to regions of more homogeneous high attenuation that contributed to mass effect or midline shift of cerebral structures or that were associated with intraventricular extension. Attempts were also made to distinguish hemorrhage from contrast stain of the parenchyma by analysis of Hounsfield units on serial scans. Continuation or termination of the study was dependent on application of prospectively established limits of hemorrhagic transformation with deterioration by the External Safety Committee. Those rules stated that the study would be placed on moratorium if more than nine patients in a dose tier experienced neurological deterioration caused by any form of intracranial hemorrhage. Safety was also assessed by comparison of serious adverse events, other bleeding complications, and changes from baseline laboratory parameters between treatment groups.

All patients received intravenous heparin for 4 hours, on verification of an occluding thrombus. Heparin flush solutions for angiography contained 1 IU/ml heparin in 0.9% sodium chloride and were infused at 60 mL/h. The first 16 patients received a 100-IU/kg bolus followed by a 1000 IU/h constant infusion ("high heparin") for 4 hours. Thereafter, on the recommendation of the External Safety Committee, the heparin regimen was altered to a 2000 IU bolus and 500 IU/h infusion ("low heparin") for the remaining patients. Oral anticoagulants were prohibited for 24 hours after completion of treatment.

For sample size calculations, a spontaneous recanalization frequency at 2 hours of 20% and an expected recanalization frequency of 65% in the rpro-UK group with a 2:1 distribution of rpro-UK to placebo was assumed. It was estimated that 45 patients (30 in the rpro-UK group and 15 in the placebo group) in each of the two dose tiers (6 mg and

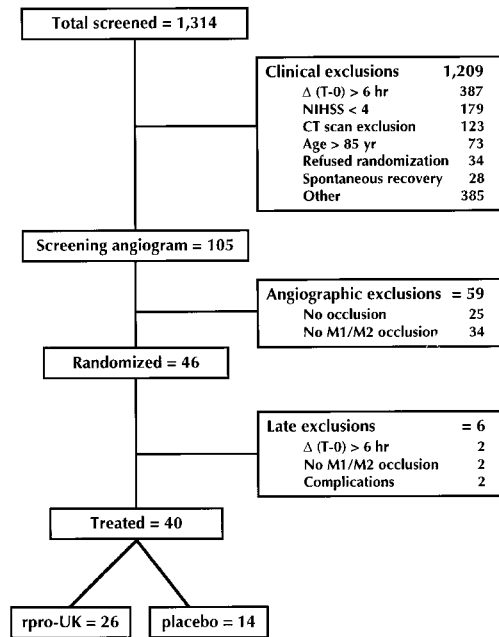


Figure 1. Distribution of patients screened for entry and randomization. Δ (T-0) indicates time from symptom onset to treatment.

12 mg) would provide a power of >80% to detect this difference at the two-sided .05 level.

The trial was halted in February 1995, 1 year after it began, by Abbott Laboratories near the end of the 60-mg dose tier study to determine whether there was sufficient evidence of efficacy and safety to support continuation of a longer-term program. No safety concerns were involved in that decision. The sponsor agreed to provide a copy of the complete database to a statistical unit independent of the original conduct of the study. An independent analysis of the data set from the 105 patients who underwent angiography was performed by the Clinical Trials Methodology Group at the Hamilton Civic Hospitals Research Center and is summarized here.

All attributes and outcomes between treatment groups were compared with the use of Fisher's exact test. All probability values are two sided.

Results

During the study 1314 patients were screened for entry, of whom 105 (8.0%) satisfied all clinical and CT scan entry

criteria and underwent baseline diagnostic angiography (Fig 1). Of the 1209 patients excluded, 387 patients (32.0%) arrived at the hospital too late to start treatment within 6 hours from stroke onset, an additional 179 (14.8%) had an NIHSS score <4, 73 (6.0%) had advanced age, and 447 (37.0%) were excluded for other reasons. An additional 123 (10.2%) patients were excluded by CT scan criteria.

Of the 105 patients who underwent angiography, 46 patients (43.8%) who had complete occlusions of the M1 or M2 MCA were randomized. The remaining 59 patients either had no occlusion within the carotid territory (n=25) or no M1 or M2 lesions (n=34). Of the 46 randomized patients, 6 (5 rpro-UK, 1 placebo) did not receive study medication: 2 patients were randomized prematurely and were subsequently found not to satisfy the angiographic criteria, 2 had post-randomization delays that placed them beyond the 6-hour time limit, and 2 experienced complications of the diagnostic angiography (eg, vasospasm and seizure in separate patients). Those 6 patients were followed together with the 59 nonrandomized and 40 randomized patients for safety outcomes. Analysis of the primary recanalization efficacy outcome was based, therefore, on the 40 patients who completed treatment and follow-up (26 patients in the rpro-UK group and 14 patients in the placebo group).

Of the 105 patients, 77 (73.3%) had occlusions in the carotid territory. The technical feasibility of completing the CT scan studies (Fig 2), the catheter manipulations, and the directed infusion (Fig 3) was demonstrated in each of those patients.

Baseline diagnostic angiography was performed at a median time of 4.5 hours from symptom onset in 105 patients, and treatment was initiated in the 40 patients who received study medication at a median time of 5.5 hours from symptom onset. The rpro-UK and placebo groups were well matched with regard to median entry NIHSS scores, the presumed source of occlusion, sex, and age (Table 1).

Partial or complete recanalization at 120 minutes from treatment onset was observed in 15 of 26 patients (57.7%) treated with rpro-UK compared with 2 of 14 placebo patients (14.3%) ($2P=.017$) (Table 2). Five of the rpro-UK-treated patients displayed complete recanalization (TIMI grade 3 in all

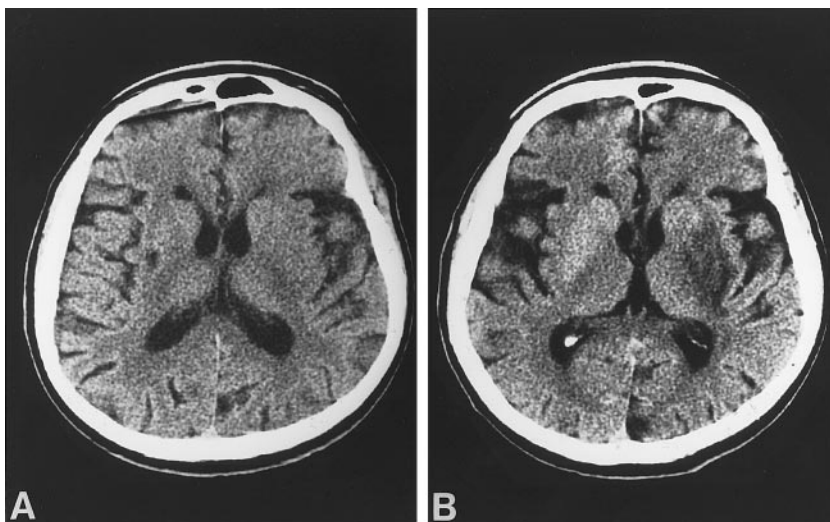


Figure 2. Noncontrast CT scans at baseline (A) and 8 days after presentation (B) in a 70-year-old man with acute right hemiparesis and aphasia who underwent angiography 3.4 hours after symptom onset. A, An old right putamen lacune is evident, but the left hemisphere appears normal. Subtle evidence of edema can be appreciated in the left lentiform nucleus. B, There is a new left lentiform nucleus infarction, but the remainder of the MCA territory appears normal.

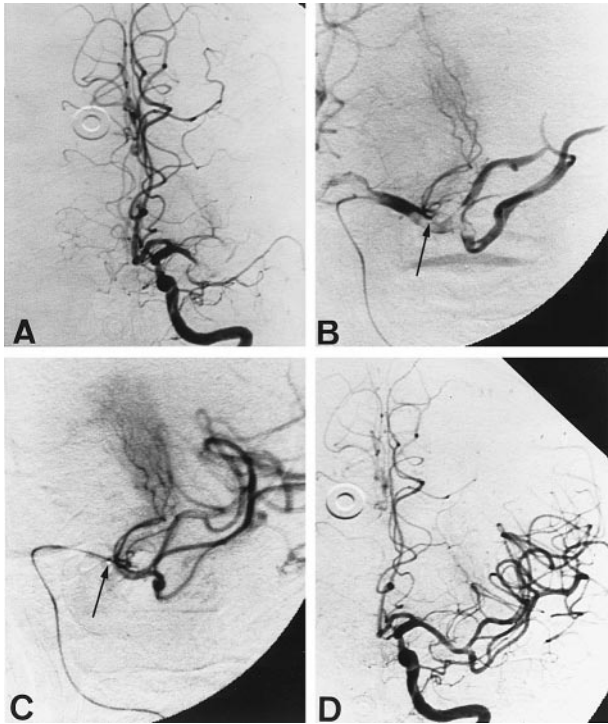


Figure 3. Serial angiograms (frontal views) at baseline (A), baseline with initial catheter placement (B), 60 minutes after infusion (C), and 120 minutes after infusion (D) of rpro-UK in the patient described in Fig 2. A, Left ICA angiogram at baseline. There is an occlusion of the midportion of the left MCA, just beyond the anterior temporal branch. B, Microcatheter placement at baseline. The tip of the catheter (arrow) has been directed into the face of the clot. During hand injection, contrast outlines a large thrombus filling the distal M1 segment and origins of the M2 (hemispheric) branches. C, Microcatheter injection 60 minutes after rpro-UK infusion. The tip of the catheter (arrow) remains in a similar location. Partial lysis is demonstrated compared with baseline. D, Left ICA angiogram at 2 hours after rpro-UK infusion. Note complete lysis and normal-appearing vascular segments distal to the M1 and M2 MCA.

vessels), while none of the placebo patients achieved a complete response (Fig 3).

Early ischemic changes, usually marked by subtle sulcal effacement or loss of gray-white matter distinction, were observed on the initial CT scan in 23 of the 40 treated patients (57.5%). Among those patients, 5 displayed baseline evidence of injury exceeding 33% of the affected hemisphere on the initial CT scan (ECASS criteria¹⁹). All 5 patients with those findings received rpro-UK and developed hemorrhagic transformation within 24 hours.

Intracerebral hemorrhagic complications are summarized in Table 3. Hemorrhagic transformation within 24 hours of treatment occurred in 11 patients (42.3%) in the rpro-UK group compared with 1 patient (7.1%) in the placebo group ($2P=.030$) (Table 3). Among the rpro-UK patients, 9 displayed hemorrhagic infarctions (among whom 1 patient displayed ventricular extension), 1 patient had a parenchymatous hematoma, and 1 patient had both a hemorrhagic infarction and a parenchymatous hematoma, as did the single placebo patient. Three patients had evidence of contrast extravasation and hemorrhagic infarction. Hemorrhagic transformation causing neurological deterioration within 24 hours of treat-

TABLE 1. Characteristics of Treated Patients

| | rpro-UK | Placebo |
|-------------------------------|-----------|-----------|
| n | 26 | 14 |
| Male sex | 14 (54%) | 5 (36%) |
| Race (white) | 20 (77%) | 10 (71%) |
| Age, y | 66.5±11.0 | 69.6±11.1 |
| NIHSS* | 17.0 | 19.0 |
| Source/etiology of occlusion | | |
| Cardiac | 14 (54%) | 9 (64%) |
| Angiography | 2 (8%) | 0 (0%) |
| Atherosclerosis of ICA | 2 (8%) | 1 (7%) |
| Unknown | 8 (31%) | 4 (29%) |
| Δ(T-0), h* | 5.4 | 5.7 |
| Occlusion location within MCA | | |
| ICA/MCA | 1 (4%) | 0 (0%) |
| M1 | 14 (54%) | 7 (50%) |
| M2 | 11 (42%) | 7 (50%) |

ICA indicates internal carotid artery; Δ(T-0), time from symptom onset to treatment.¹⁷

*Median values. All other values are mean±SD (age) or literal values.

ment occurred in 4 (15.4%) of the rpro-UK-treated patients and 1 placebo-treated patient (7.1%) ($2P=.64$). Hemorrhage causing clinical deterioration at any time within the study period occurred in 4 patients (15.4%) who received rpro-UK and 2 patients (14.3%) in the placebo group ($2P=1.00$). One patient in each treatment group suffered a fatal intracerebral hemorrhage. Overall, within the study period there was no significant difference in the frequency of intracerebral hemorrhage between the rpro-UK (13; 50.0%) and placebo (5; 35.7%) groups ($2P=.51$).

During the early course of the study the frequency of cerebral hemorrhage that caused neurological worsening, while not in excess of the prospectively established stopping limits, was considered worrisome. The frequency of hemorrhagic transformation within 24 hours of treatment was 72.7% in the rpro-UK and 20.0% in the placebo groups exposed to the initial heparin regimen (Table 3). A recommendation by the External Safety Committee that the heparin dose be decreased was accepted, following which the frequency of brain hemorrhage at 24 hours fell to 20% (3 patients) in the rpro-UK group and 0% in the placebo group (Table 3).

TABLE 2. Recanalization vs Heparin Dose

| Heparin Dose | Treatment Group | n | Partial/Complete Recanalization at 120 min | |
|--------------|-----------------|----|--|-------|
| | | | | 2P |
| High* | rpro-UK | 11 | 9 (81.8%) | <.001 |
| | Placebo | 5 | 0 (0.0%) | |
| Low* | rpro-UK | 15 | 6 (40.0%) | .657 |
| | Placebo | 9 | 2 (22.2%) | |
| All | rpro-UK | 26 | 15 (57.7%) | .017 |
| | Placebo | 14 | 2 (14.3%) | |

*High dose=100 IU/kg bolus+1000 IU/h×4 h; Low dose=2000 IU bolus+500 IU/h×4 h.

TABLE 3. Intracranial Hemorrhage

| Heparin Dose | Treatment Group | n | HI and/or PH Within 24 h | | HI and/or PH Within 90 d | |
|--------------|-----------------|----|--------------------------|---|--------------------------|---|
| | | | All Hemorrhages | Hemorrhages With Clinical Deterioration | All Hemorrhages | Hemorrhages With Clinical Deterioration |
| High* | rpro-UK | 11 | 8 (72.7%) | 3 (27.3%) | 8 (72.7%) | 3 (27.3%) |
| | Placebo | 5 | 1 (20.0%) | 1 (20.0%) | 2 (40.0%) | 1 (20.0%) |
| Low* | rpro-UK | 15 | 3 (20.0%) | 1 (6.7%) | 5 (33.3%) | 1 (6.7%) |
| | Placebo | 9 | 0 (0.0%) | 0 (0.0%) | 3 (33.3%) | 1 (11.1%) |
| All | rpro-UK | 26 | 11 (42.3%)† | 4 (15.4%) | 13 (50.0%) | 4 (15.4%) |
| | Placebo | 14 | 1 (7.1%)† | 1 (7.1%) | 5 (35.7%) | 2 (14.3%) |

HI indicates hemorrhagic infarction; PH, parenchymatous hematoma.

*High dose=100 IU/kg bolus+1000 IU/h×4 h; Low dose=2000 IU bolus+500 IU/h×4 h.

† $P=.030$; all other pairwise comparisons $2 P>.100$.

Among patients treated with rpro-UK the frequency of recanalization was 81.8% for the “high-heparin” group and 40.0% for the “low-heparin” group ($2P=.051$).

Although the number of patients was too small to establish statistical significance, there appeared to be a 10% to 12% absolute increase in excellent neurological outcome in the rpro-UK group over placebo at 90 days (Table 4). Overall, 6 angiographic responders (35.3%) had a modified Rankin score of 0 or 1 at 90-day follow-up compared with 5 nonresponders (21.7%) ($2P=.48$). The 90-day cumulative mortality was 26.9% in the rpro-UK group and 42.9% in the placebo group ($2P=.48$). Death was attributed to medical complications accompanying the initial stroke in 7 patients, while 4 deaths were due to cardiac causes (Table 5).

Sixteen adverse events occurred in 14 of the 105 patients who underwent diagnostic angiography. One patient had three events. Three patients (2.9%) experienced worsening of their clinical condition. Adverse clinical events following angiography were reported in 5 patients. In 1 patient, transient vasospasm of the catheterized cavernous internal carotid artery was attributed to the catheterization, but neurological deterioration was attributed to the signal stroke. Of the remaining 4 patients, 1 suffered a seizure during the screening angiogram, worsened neurologically, and ultimately died. A second patient, who also suffered two injection site hemorrhages, had a 2-point change in the NIHSS after the 120-minute angiogram. None of these patients received treatment. Among 2 patients who received rpro-UK, 1 suffered acute worsening of chronic renal insufficiency due to the radiocontrast agent. A second

patient was unable to handle oral secretions during the infusion and developed an aspiration pneumonia but subsequently improved. Injection site hemorrhages occurred in 10 patients, two of which were severe, justifying transfusion in 1 patient. These affected 3 patients each who received placebo, rpro-UK, or were not randomized and 1 patient who did not receive treatment. Symptomatic intracerebral hemorrhage within 24 hours was not reported in any of the 65 patients who did not receive study treatment.

Discussion

This trial is the first double-blinded, randomized, placebo-controlled study of a plasminogen activator delivered intra-arterially by microcatheter in acute thrombotic stroke. The frequency of recanalization of documented M1 or M2 MCA occlusions in patients receiving direct intra-arterial rpro-UK within 6 hours of stroke onset was greater than with placebo, when the use of heparin was not considered. Recanalization could not be ascribed to mechanical disruption of the thrombus. There was no significant difference in frequency of cerebral hemorrhage causing neurological deterioration between the rpro-UK and placebo groups at 24 hours or 90 days. However, a contribution of adjunctive intravenous heparin, accompanying the arteriographic and delivery procedures, to the frequency of all intracerebral hemorrhages and to recanalization seemed likely, as suggested by the respective reductions in both events when the heparin dose was reduced. However, no relationship between recanalization and intracerebral hemorrhage was demonstrable in post hoc analyses, owing to the small number of patients.

TABLE 4. Clinical Outcomes at 90 Days

| Scores | Treatment Group | | |
|-----------------------|-----------------|----------------|-----|
| | rpro-UK (n=26) | Placebo (n=14) | 2P |
| Barthel Index | | | |
| 9 and 10 | 11 (42.3%) | 5 (35.7%) | .75 |
| Modified Rankin Scale | | | |
| 0 and 1 | 8 (30.8%) | 3 (21.4%) | .72 |
| NIHSS | | | |
| 0 and 1 | 5 (19.2%) | 1 (7.1%) | .40 |

TABLE 5. Mortality Within 90 Days

| | Treatment Group | | |
|--------------------------|-----------------|----------------|-----|
| | rpro-UK (n=26) | Placebo (n=14) | 2P |
| All mortality | 7 (26.9%) | 6 (42.9%) | .48 |
| Intracerebral hemorrhage | 1 | 1 | |
| Stroke | 4 | 3 | |
| Cardiac origin | 2 | 2 | |

To evaluate the contribution of the plasminogen activator alone to thrombus lysis, mechanical disruption of the thrombus was proscribed and catheter delivery of the placebo was used. To limit the exposure of patients to the placebo and still assess the risks of the delivery system, a 2:1 randomization scheme was employed. The ethical basis for the use of a placebo in this context has been described elsewhere.²⁰ This was based primarily on the desire to evaluate properly the efficacy of intra-arterial thrombolysis by the plasminogen activator alone, in which patient safety was carefully monitored.

rpro-UK is the 411 amino acid single-chain zymogen precursor of u-PA derived and purified from stably transfected murine SP2/0 hybridoma cells.¹¹ The zymogen remains inactive in the absence of fibrin, is not inhibited by circulating plasminogen activator inhibitors (eg, α_2 -antiplasmin, α_2 -macroglobulin), and is not activated in plasma. pro-UK (single chain urokinase plasminogen activator, or scu-PA) is converted to two-chain u-PA by plasmin and thereby amplifies plasminogen activation.²¹ The implication, confirmed by experimental work,²²⁻²⁴ is that rpro-UK is activated at the thrombus surface by plasmin associated with the fibrin network, in a surface-controlled process.²⁵ The thrombolytic potential remains confined to the thrombus but is apparently augmented by the concomitant use of heparin.^{21,26} In a canine femoral artery thrombosis model, rpro-UK plus heparin produced a significant increase in thrombus lysis compared with rpro-UK, vehicle plus heparin, and vehicle alone²⁶ and minimized further thrombus accretion. Other experimental data suggest that heparin doses sufficient to increase the activated partial thromboplastin time by 1.5 times control markedly increase the recanalization efficacy of rpro-UK.²⁷ The combination of rpro-UK and heparin would therefore be expected to enhance thrombus lysis by direct intra-arterial infusion. The enhanced thrombus dissolution and overall benefit in recanalization compared with placebo seen in this study was dependent on the effect of the higher heparin dose together with the fixed rpro-UK dose.

The potential contribution of concomitant heparin therapy to hemorrhagic transformation was also examined. Although the high-dose heparin regimen nearly doubled the recanalization frequency, it was also associated with a substantial increase in clinically significant brain hemorrhages (Table 3). However, no significant relationship between recanalization and hemorrhage was seen by post hoc analyses. Limited experience at the time of study termination suggested that the lower heparin dose regimen might decrease both recanalization frequency and hemorrhage risk.

This study did not exclude patients with early signs of ischemic injury on the entry CT scan as defined by the ECASS group.¹⁹ Somewhat more than one half of the 40 patients treated had evidence of subtle effacement or loss of gray-white matter distinction. Of those patients, all five who displayed evidence of ischemic injury exceeding one third of the affected hemisphere developed hemorrhage at the ischemic site within 24 hours after treatment with rpro-UK. This experience was consistent with that noted in ECASS.¹⁹ There was no difference in the frequency of hemorrhage with clinical deterioration between the rpro-UK and placebo groups by the end of this study, however.

Recent trials of intravenous thrombus lysis in acute ischemic stroke place this impression into perspective. Three placebo-controlled trials of intravenous streptokinase were abandoned because of an unacceptably high frequency of hemorrhagic complications or early mortality.²⁸⁻³⁰ Although dose rates of streptokinase were not tested before those trials, at least one was complicated by treatment of patients with extraordinarily severe neurological deficits.²⁹ The ECASS and the NINDS intravenous rt-PA trials both included large numbers of patients selected primarily on the basis of time from symptom onset, degree of neurological deficit, and CT criteria.^{19,31} In ECASS, intravenous rt-PA (alteplase, 1.1 mg/kg) provided no apparent clinical benefit when given to patients with evidence of hemispheric injury within 6 hours of stroke onset limited by CT scan criteria. The study confirmed the relevance of severe tissue injury on entry CT scan to parenchymal hematoma formation (19.4%, rt-PA versus 6.8%, placebo) after treatment with rt-PA. In the NINDS trial, despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with rt-PA (0.9 mg/kg, alteplase) within 3 hours of the onset of ischemic stroke resulted in an 11% to 13% absolute increase in full or nearly full recovery at 3 months. In the present study, patients who received rpro-UK had a nonsignificantly better neurological outcome at 90 days (Table 4), although the study was not powered to test this relationship.

In nonangiographic trials of plasminogen activators in acute stroke, it is difficult to assess their effect in individual patients because ischemic stroke has diverse etiologies with highly variable natural histories.^{32,33} For example, the frequency of symptomatic parenchymal hematoma formation in the placebo groups differed markedly between ECASS and the NINDS trial (6.4% versus 0.6%, respectively), suggesting different patient populations. The distribution of key variables such as the site of arterial occlusion and recanalization efficacy was not determined in those intravenous studies. In the present study, 73% of patients undergoing angiography had occlusions in the carotid territory within 6 hours from symptom onset, confirming previous experience in this territory.^{1,34} One angiography-based trial demonstrated that complete internal carotid artery and M1 MCA occlusions were significantly less likely to undergo successful recanalization with intravenous infusion of rt-PA (duteplase) than peripheral lesions.¹ In the present study, proximal MCA stem occlusions were chosen to provide a vascular and therefore neurologically homogeneous subpopulation of smaller size for study. Ultimately, if recanalization efficacy could be safely shown in this subpopulation, clinical benefit in a larger population with distal occlusions would be testable.

Although cumulative experience suggests a much greater recanalization frequency from direct intra-arterial infusion than from intravenous infusion of several plasminogen activators, neither a pivotal clinical efficacy trial of intra-arterial thrombolysis nor a direct comparison between intravenous and intra-arterial thrombolysis has been completed to date.²⁰ The intravenous trials reported thus far do not obviate the direct intra-arterial delivery approach. Significant improvements in delivery systems since the earlier reports describing feasibility and safety of the overall approach, as well as the use of disability measures for clinical outcome,^{19,31,35,36} underscore an increased

sophistication in evaluating vascular therapies in stroke patients. Symptomatic hemorrhagic transformation remains a central concern, although this study shows that the frequency of such events can be manipulated by attention to concomitant anticoagulant therapies. Based on the 65 patients who underwent angiography but were not treated in this study, the angiographic procedure per se did not contribute to hemorrhagic transformation. In this regard, one large retrospective study has indicated that the relative risks of diagnostic angiography are low.³⁷⁻³⁹ Of the patients undergoing the interventional procedure in this study, five suffered adverse clinical events. The relationship of the events to the procedures, as well as whether the number of events was excessive, must await evaluation of larger treatment cohorts. Recent insights into the manner in which the severity of the initial neurological status may have an impact on hemorrhagic transformation and poor outcome,¹⁹ evidence of recanalization efficacy demonstrated here, and the safety of the delivery system support further investigations of the clinical efficacy and safety of intra-arterial thrombolysis in acute thrombotic stroke.

An exploratory study is now in progress in which 180 patients with an acute thrombotic or thromboembolic stroke of the isolated MCA are randomized in a 2:1 ratio to either intra-arterial rpro-UK (9 mg) or an intravenous control.

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