

Intra-arterial Prourokinase for Acute Ischemic Stroke

The PROACT II Study: A Randomized Controlled Trial

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INTRAVENOUS (IV) TISSUE-TYPE PLASMINOGEN activator (tPA) improves outcomes after acute ischemic stroke but must be given within 3 hours of onset.¹ Six randomized trials have failed to show an overall benefit for IV thrombolytic therapy initiated within 6 hours of stroke onset.²⁻⁷ A number of factors have contributed to this failure, but stroke heterogeneity has been cited as a main cause.^{8,9} A focused trial of a homogeneous stroke population provides an alternative to the traditional large, randomized clinical trial.⁹ Intra-arterial (IA) thrombolysis lends itself to such a design in selected patients with acute ischemic stroke.¹⁰⁻¹⁶

The recanalization efficacy and safety of IA recombinant prourokinase (r-proUK) in patients with acute ischemic stroke of less than 6 hours' dura-

Context Intravenous tissue-type plasminogen activator can be beneficial to some patients when given within 3 hours of stroke onset, but many patients present later after stroke onset and alternative treatments are needed.

Objective To determine the clinical efficacy and safety of intra-arterial (IA) recombinant prourokinase (r-proUK) in patients with acute stroke of less than 6 hours' duration caused by middle cerebral artery (MCA) occlusion.

Design PROACT II (Prolyse in Acute Cerebral Thromboembolism II), a randomized, controlled, multicenter, open-label clinical trial with blinded follow-up conducted between February 1996 and August 1998.

Setting Fifty-four centers in the United States and Canada.

Patients A total of 180 patients with acute ischemic stroke of less than 6 hours' duration caused by angiographically proven occlusion of the MCA and without hemorrhage or major early infarction signs on computed tomographic scan.

Intervention Patients were randomized to receive 9 mg of IA r-proUK plus heparin (n = 121) or heparin only (n = 59).

Main Outcome Measures The primary outcome, analyzed by intention-to-treat, was based on the proportion of patients with slight or no neurological disability at 90 days as defined by a modified Rankin score of 2 or less. Secondary outcomes included MCA recanalization, the frequency of intracranial hemorrhage with neurological deterioration, and mortality.

Results For the primary analysis, 40% of r-proUK patients and 25% of control patients had a modified Rankin score of 2 or less ($P = .04$). Mortality was 25% for the r-proUK group and 27% for the control group. The recanalization rate was 66% for the r-proUK group and 18% for the control group ($P < .001$). Intracranial hemorrhage with neurological deterioration within 24 hours occurred in 10% of r-proUK patients and 2% of control patients ($P = .06$).

Conclusion Despite an increased frequency of early symptomatic intracranial hemorrhage, treatment with IA r-proUK within 6 hours of the onset of acute ischemic stroke caused by MCA occlusion significantly improved clinical outcome at 90 days.

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tion caused by middle cerebral artery (MCA) occlusion were demonstrated in the first Prolyse in Acute Cerebral Thromboembolism (PROACT I) trial.¹⁷ Prolyse (narsuplase beta) is a glycosylated 411-amino acid single-chain proenzyme precursor of urokinase (UK) derived from transfected murine SP2/0

Author Affiliations and a complete list of the PROACT Investigators are given at the end of this article.

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hybridoma cells.¹⁸ Single-chain r-proUK is activated to 2-chain UK at the thrombus surface by fibrin-associated plasmin.¹⁹ The thrombolytic effect of r-proUK is augmented by heparin, possibly through thrombin neutralization or by stimulating tPA release from the endothelium.^{20,21}

Based on PROACT I, we performed a multicenter, randomized trial to determine the clinical efficacy and safety of IA r-proUK in patients with acute ischemic stroke of less than 6 hours duration caused by MCA occlusion. In PROACT II, we increased the total dose of r-proUK from 6 mg to 9 mg given over 2 hours while using the same low heparin dose as in PROACT I in an attempt to improve recanalization while limiting symptomatic brain hemorrhages.

METHODS

Between February 1996 and August 1998, 54 North American centers screened patients with suspected acute stroke for the study. The study protocol and all amendments were approved by the institutional review board at each center.

The clinical inclusion criteria were (1) new focal neurological signs in the MCA distribution allowing initiation of treatment within 6 hours of the onset of symptoms; (2) a minimum National Institutes of Health Stroke Scale (NIHSS)²² score of 4, except for isolated aphasia or hemianopia; and (3) age 18 through 85 years. Clinical exclusion criteria included an NIHSS score greater than 30; coma; rapidly improving neurological signs at any point prior to administration of study drug; history of stroke within the previous 6 weeks; seizures at onset; clinical presentation suggestive of subarachnoid hemorrhage; previous history of intracranial hemorrhage at any time, neoplasm, or subarachnoid hemorrhage; septic embolism; suspected lacunar stroke; surgery, biopsy of a parenchymal organ, trauma with internal injuries or lumbar puncture within 30 days; head trauma within 90 days; active or recent hemorrhage within 30 days; known hemorrhagic diathesis, baseline international normalized ratio

greater than 1.7, activated partial thromboplastin time more than 1.5 times normal, or baseline platelet count less than $100 \times 10^9/L$ ($100 \times 10^3/\mu L$); known contrast sensitivity; and uncontrolled hypertension defined by a blood pressure greater than 180 mm Hg systolic or greater than or equal to 100 mm Hg diastolic on 3 separate occasions at least 10 minutes apart or requiring continuous IV therapy.

Computed tomographic (CT) scan exclusion criteria were intracranial tumors except small meningioma, hemorrhage of any degree or location, significant mass effect with midline shift, and acute hypodense parenchymal lesion or effacement of cerebral sulci in more than one third of the MCA territory (European Cooperative Acute Stroke Study [ECASS] criteria²³).

Patients who met all clinical and CT scan criteria and for whom signed informed consent was obtained underwent diagnostic cerebral angiography of the symptomatic MCA territory. Angiographic inclusion criteria were complete occlusion (TIMI [Thrombolysis in Myocardial Infarction] grade 0)²³ or contrast penetration with minimal perfusion (TIMI grade 1) of either the M₁ segment or an M₂ division of the MCA. Angiographic exclusion criteria were arterial dissection, arterial stenosis precluding safe passage of a microcatheter into the MCA, nonatherosclerotic arteriopathy, no visible occlusion, or occlusion of an artery other than the M₁ or M₂ MCA. All patients with an angiographic exclusion were observed for 24 hours or until an alternative stroke therapy was initiated, whichever came first.

Eligible patients were randomized to receive 9 mg total of IA r-proUK over 2 hours plus IV heparin or IV heparin alone, in a ratio of 2:1. Randomized treatment was to be initiated within 6 hours of stroke onset. The randomization was stratified by baseline stroke severity into 3 NIHSS strata: (1) 4 through 10, (2) 11 through 20, and (3) 21 through 30. A blinded randomization code was assigned via telephone independent of the sponsor by Paragon Bio-

medical Inc, Irvine, Calif. A computer-generated master randomization schedule using a random block size ranging from 3 to 12 was used. The schedule was not stratified by clinical center to preclude knowledge of the distribution of future treatment assignments at a given center.

All randomized patients received a 2000 U bolus and a 500 U/hr infusion of IV heparin for 4 hours beginning at the time of angiography.¹⁷ Heparin flush solutions for angiography contained 1 U/mL heparin in 0.9% sodium chloride and were infused at 60 mL/h. Otherwise, antithrombotic agents were prohibited for the first 24 hours.

An infusion microcatheter (<3.0 F) with a single end hole was placed into the proximal one third of the MCA thrombus using a steerable microguidewire. If intrathrombus positioning of the infusion catheter was not possible, the tip of the catheter was to be placed as close to the proximal face of the thrombus as possible for r-proUK infusion. A superselective angiogram was performed through the microcatheter to document catheter placement (FIGURE 1). Mechanical disruption of the clot was not permitted. Recombinant prourokinase was infused at a rate of 30 mL/h. After 1 hour of r-proUK infusion (4.5 mg), another angiogram was performed through the microcatheter. If any of the proximal thrombus had dissolved, the interventionalist advanced the microcatheter tip into the proximal portion of any remaining clot in the MCA. Even if complete lysis occurred in the first hour, the remaining 4.5 mg of r-proUK was infused into the proximal MCA over the subsequent 1 hour. Another diagnostic carotid angiogram was performed at 2 hours in both r-proUK and control patients to assess final vessel patency.

All CT scans and 2-hour angiograms were assessed by a neuroradiologist at a core facility who was blinded to treatment assignment and clinical status. Computed tomographic scans were obtained at baseline, 24 hours, and 7 to 10 days after initial treatment. Hemorrhagic infarction was defined as any

area of petechial or small confluent hemorrhages within larger regions of hypodense ischemic injury. Parenchymatous hematoma was defined as more homogeneous areas of hemorrhage, with or without mass effect or intraventricular extension. Complete recanalization was defined as complete (TIMI 3) flow in both the M_1 segment and M_2 divisions of the MCA. Partial recanalization was defined as partial (TIMI 2) flow in either MCA segment.

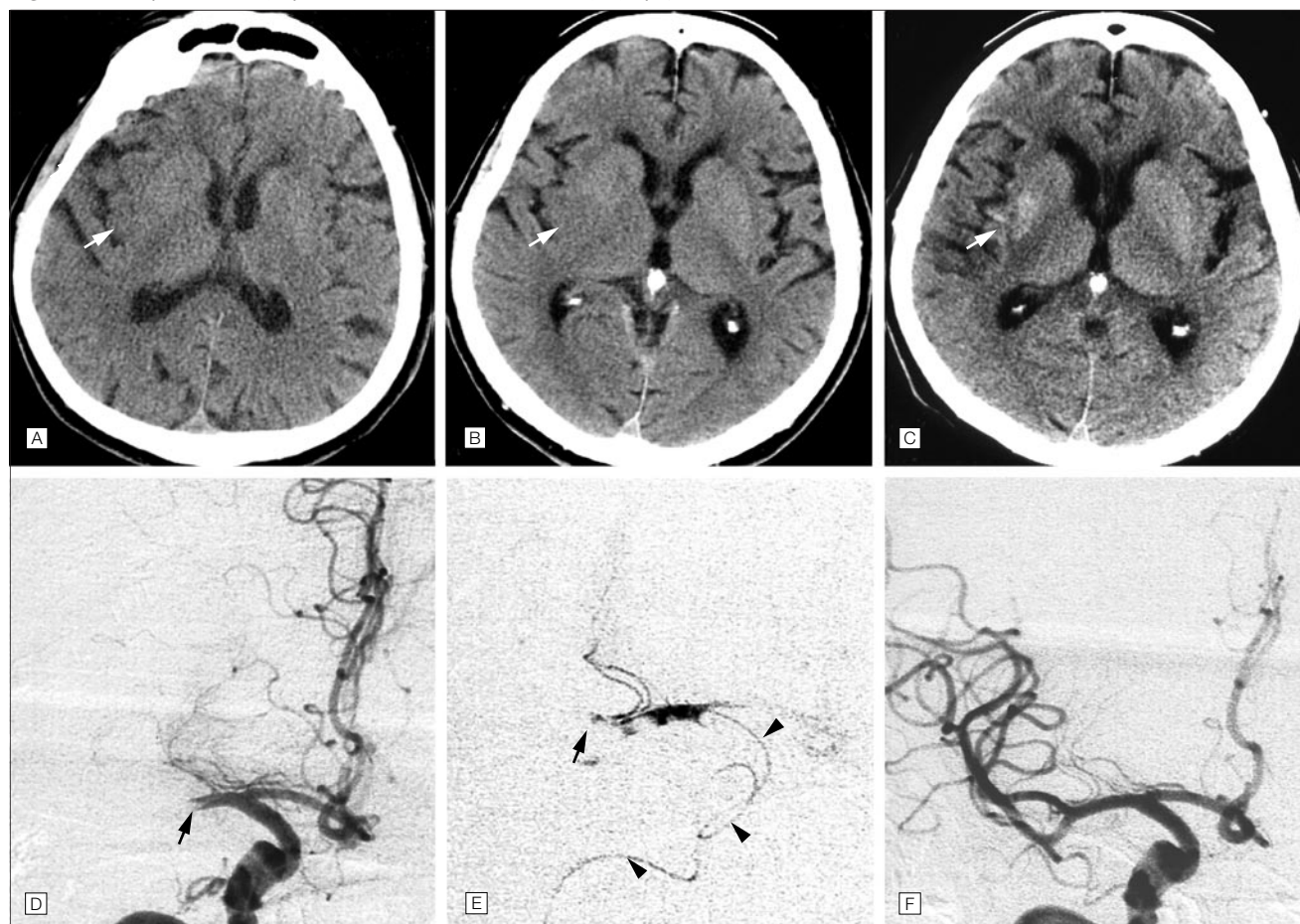
Clinical efficacy was assessed at 7 to 10 days, 30 days, and 90 days following initial treatment based on the modified Rankin scale, NIHSS score, and Barthel index.²⁴ Follow-up examinations

were standardized and blinded. All follow-up examinations were to be performed by the same board-certified or eligible blinded neurologist. At the time of randomization, centers were required to designate a neurologist who was to remain blinded to treatment assignment and angiographic results for the duration of the trial. The principal investigator at each site was responsible for ensuring the integrity of the blinded follow-up examinations. All examiners were required to pass certifying tests for both the NIHSS and Barthel index. An NIHSS recertification examination had to be passed after approximately 6 months.

The primary efficacy outcome was the percentage of patients achieving a modified Rankin score of 2 or less at 90 days following the initial therapy; this score signifies slight or no disability. The interobserver agreement for differences of 1 grade on the modified Rankin scale is 0.56 and for 2 grades, 0.91.²⁵

The secondary efficacy outcomes were the percentage of patients reaching an NIHSS score of 1 or less at 90 days and the rate of angiographic recanalization. Other preplanned analyses included the percentage of patients achieving a 50% or greater reduction from baseline NIHSS score at 90 days, and the percentage of patients achieving a Barthel index score

Figure 1. Computed Tomographic (CT) Scans and Cerebral Angiography With Recombinant Prourokinase Infusion



Computed tomographic scans (A-C) and angiography (D-F) in an 80-year-old man with acute left hemiparesis. A, Baseline CT scan shows a suggestion of very early edema in the posterior aspect of the right putamen and insular cortex (arrow). B, Follow-up CT at 24 hours shows a small amount of edema in the posterior putamen only. C, By 8 days this has evolved to a small petechial hemorrhagic infarction. D, Angiography (frontal view, right carotid artery injection) confirms a proximal right M_1 occlusion (arrow). E, A microcatheter is introduced (arrowheads), and clot is confirmed by hand contrast injection (arrow). Recombinant prourokinase infusion was begun via microcatheter 4.8 hours after symptom onset. F, After 120 minutes, carotid artery injection shows complete clot lysis with normal distal flow.

of 60 or greater and a Barthel index score of 90 or greater at 90 days.

The primary and secondary clinical efficacy analyses were performed on an intent-to-treat basis. For living patients who missed the 90-day assessment, the most recent assessment prior to 90 days was used. The upper limit for the 90-day visit data was prospectively set at 120 days. For living patients with no data, the scale value corresponding to failure was imputed. The principal analyses of the NIHSS and Barthel index total scores were performed with imputations for mortality of 42 for the NIHSS and 0 for the Barthel index.

Modified Rankin score, Barthel index, and NIHSS score analyses were performed using the Cochran-Mantel-Haenszel method with baseline stroke severity as the stratification factor. The analysis for the primary end point,

stratified by center, revealed no significant treatment by center interaction and is not presented.

Procedural complications were analyzed for all randomized patients. All other safety analyses were performed on patients treated as randomized, ie, r-proUK patients who received the drug and control patients who did not receive a thrombolytic agent. The primary safety outcome was hemorrhagic transformation causing neurological deterioration within 24 hours of treatment. Guidelines for neurological deterioration were a 4-point or greater increase in the NIHSS score or a 1-point deterioration in level of consciousness. An external safety committee was commissioned to recommend termination of the trial if predefined rates of hemorrhagic transformation with neurological deterioration were reached. The percentage of patients experiencing

hemorrhagic transformation with neurological deterioration within 24 hours of treatment was compared between treatment groups using the Fisher exact test for 2 × 2 tables. Adverse events and nonintracranial bleeding complications were analyzed using the Fisher exact test for 2 × 2 tables.

Based on the results of PROACT I,¹⁷ 100 r-proUK patients and 50 control patients provided a power of 80% at the 2-sided .05 α level for detecting a difference in the primary efficacy outcome between r-proUK and control. To adjust for patients who were randomized but who might not receive the study drug, approximately 120 r-proUK and 60 control patients needed to be enrolled.

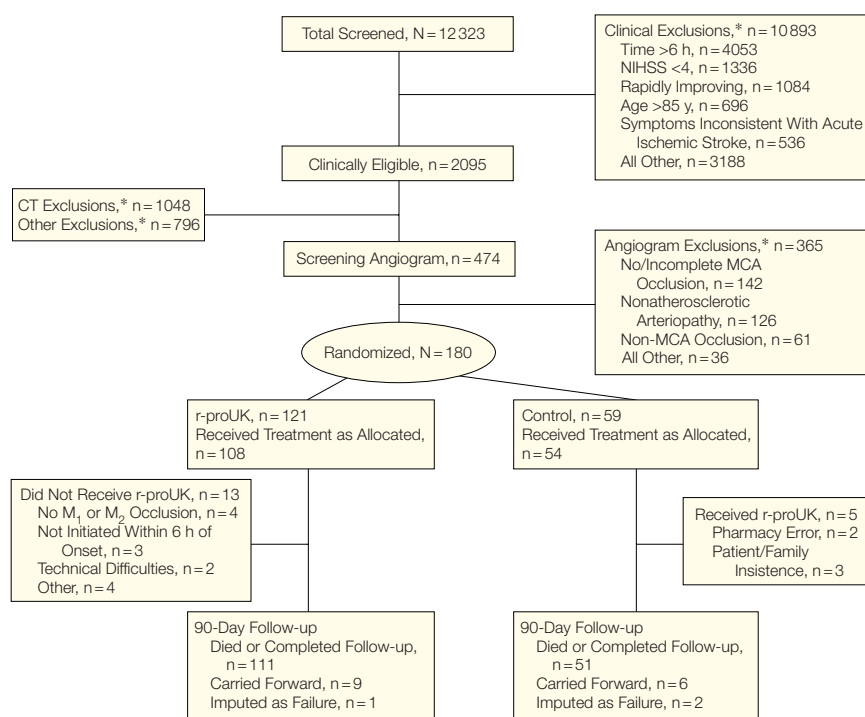
Site management, data monitoring, and data management were performed independently of the sponsor by ClinTrials Research Inc, Cary, NC. A preplanned futility assessment was performed after the first 75 patients completed the 90-day follow-up. The futility assessment and the analyses in this report were performed independently of the sponsor by the Clinical Trials Methodology Group, Hamilton Civic Hospitals Research Centre, McMaster University, Hamilton, Ontario.

RESULTS

During the study, 12 323 patients with acute stroke were screened, of whom 474 (4%) underwent diagnostic cerebral angiography at a median of 4.5 hours from stroke onset. There were angiographic exclusions in 294 patients. The remaining 180 patients were randomized (FIGURE 2).

The 121 r-proUK and 59 control patients were generally well-matched for medical history (TABLE 1) and baseline characteristics (TABLE 2). There was an excess history of diabetes among control patients and more ECASS CT scan protocol violations among r-proUK patients. A total of 20% (11/54) of control patients vs 8% (9/108) of r-proUK patients received some heparin within 5 to 23 hours after the start of the initial protocol-specified 4-hour infusion. The total rate of ECASS CT scan protocol violations was 8% (14/177).

Figure 2. Patient Selection and Follow-up



Stroke patients were screened over a 30-month period resulting in exclusion based on protocol criteria: clinical exclusion (83%), computed tomographic (CT) scan exclusion (8%), other exclusions (6%), and cerebral angiography exclusions (3%). Screening resulted in a randomized patient population of 180 (2% of screened patients). Asterisk indicates number of exclusion reasons; because subjects could have multiple reasons for exclusion, number of reasons is greater than total number of patients screened. NIHSS indicates National Institutes of Health Stroke Scale; r-proUK, recombinant prourokinase; and MCA, middle cerebral artery.

The median baseline NIHSS score was 17 in both groups. The median time to initiation of r-proUK treatment was 5.3 hours.

For the primary efficacy analysis, 40% of r-proUK patients and 25% of control patients had a modified Rankin score of 2 or less at 90 days after stroke onset ($P = .04$; absolute benefit, 15%; relative benefit, 58%; number needed to treat to benefit, 7 (TABLE 3 and FIGURE 3).

All secondary clinical outcome trends favored r-proUK at all time points, although there were no statistically significant differences between treatment groups at 90 days (TABLE 4). Patients treated with r-proUK achieved independence in activities of daily living earlier as measured by a Barthel index score of 90 or higher at 7 to 10 days (22% vs 10%, $P = .04$), although this difference did not maintain statistical significance at 90 days ($P = .24$).

Among all randomized patients, 13 r-proUK patients did not receive any r-proUK for the following reasons: no M_1 or M_2 occlusion (4); treatment not initiated within 6 hours of onset of symptoms (3); technical difficulties (2); and agitation, neurological deterioration, pharmacy error, and improper informed consent (1 each). Five control patients received thrombolytic agent (2 received r-proUK by pharmacy error;

3, at patient/family insistence), 3 of whom experienced intracranial hemorrhage with neurological deterioration. If these 18 patients are removed from the intention-to-treat analysis there is still a 15% absolute benefit (42% vs 27%, $P = .053$) for the primary outcome in favor of r-proUK.

Procedural complications for randomized patients in the r-proUK and control groups included worsening of neurological symptoms, 1% (1/121) vs 0%; anaphylaxis, 1% (1/121) vs 0%; and systemic hemorrhage (primarily minor hemorrhages at the catheter site), 7% (9/121) vs 17% (4/59).

Among patients treated as randomized, intracranial hemorrhage within 24 hours occurred in 35% (38/108) of the r-proUK patients and 13% (7/54) of control patients ($P = .003$). By 10 days, the rates for all intracranial hemorrhages were 68% (73/108) and 57% (31/54), respectively ($P = .23$).

Intracranial hemorrhage with neurological deterioration within 24 hours occurred in 10% (11/108) of r-proUK patients and 2% (1/54) of control patients (number needed to treat to harm, 12) (FIGURE 4). All symptomatic intracranial hemorrhages occurred in patients with a baseline NIHSS score of 11 or higher (NIHSS 11-20, 11%; NIHSS >20, 13%). The median activated partial thromboplastin time at the end of the 4-hour heparin infusion was 34.9 seconds for r-proUK patients and 36.5 seconds for control patients.

There was no difference in the NIHSS stratum-adjusted 90-day mortality rate, which was 25% for r-proUK patients and 27% for control patients (intention-to-treat analysis, Table 4, Figure 3).

For patients treated as randomized, the NIHSS stratum-adjusted recanalization rates (TIMI 2 + 3) on the 2-hour angiogram were 66% in r-proUK patients and 18% in control patients

Table 1. Medical Histories of Randomized Patients*

Variable	No. (%)	
	r-proUK Group (n = 121)	Control (n = 59)
Cerebrovascular disease	24 (20)	8 (14)
Aspirin therapy	32 (26)	18 (31)
Diabetes	16 (13)	18 (31)
Blood glucose†		
mmol/L	7.2 (2.5)	8.6 (4.0)
mg/dL	132 (45)	156 (73)
Hypertension	78 (64)	36 (61)
Myocardial infarction‡	29 (24)	14 (24)
Arrhythmia‡	50 (41)	24 (41)
Ischemic heart disease‡	29 (24)	15 (25)
Congestive heart failure‡	25 (21)	18 (31)
Valvular heart disease‡	18 (15)	9 (15)
Cigarette smoking‡	54 (45)	30 (51)
Cancer	11 (9)	9 (15)

*r-proUK indicates recombinant prourokinase.
 †N = 114 for r-proUK group; 56 for control. Data are presented as mean (SD).
 ‡N = 120 for r-proUK group; 59 for control.

Table 2. Baseline Characteristics of Randomized Patients*

Characteristic	r-proUK Group (n = 121)	Control (n = 59)
Age, mean (SD), y	64 (14)	64 (14)
White, No. (%)	92 (76)	52 (88)
Women, No. (%)	51 (42)	23 (39)
Weight, mean (SD), kg†	79 (16)	81 (19)
NIHSS score, median (range)	17 (5-27)	17 (4-28)
Stroke subtype, No. (%)		
Angiogram complication	1 (1)	2 (3)
Cardiogenic embolism	72 (60)	30 (51)
Carotid atheroembolism	11 (9)	7 (12)
Unknown	33 (27)	20 (34)
Other	4 (3)	0 (0)
Blood pressure, mean (SD), mm Hg		
Systolic	150 (22)	144 (19)
Diastolic	78 (16)	78 (17)
Coagulation factor I, mean (SD), g/L‡	3.4 (0.2)	3.4 (0.9)
M, MCA occlusion, No. (%)	74 (61)	37 (63)
Left hemisphere stroke, No. (%)	67 (55)	32 (54)
CT scan early infarction signs, No. (%)§	88 (76)	37 (67)
ECASS violations, No. (%)	12 (10)	2 (4)
Hypodensity mean volume, mL	16.6	9.1
Hyperdense MCA, No. (%)¶	40 (33)	20 (36)
Time from stroke onset to randomization, median (interquartile range), h	4.7 (4.0-5.3)	5.1 (4.2-5.5)

*r-proUK indicates recombinant prourokinase; NIHSS, National Institutes of Health Stroke Scale; MCA, middle cerebral artery; CT, computed tomographic; and ECASS, European Cooperative Acute Stroke Study.
 †N = 108 for r-proUK group; 53 for control.
 ‡N = 91 for r-proUK group; 41 for control.
 §N = 116 for r-proUK group; 55 for control.
 ||N = 120 for r-proUK group; 57 for control.
 ¶N = 120 for r-proUK group; 55 for control.

Table 3. Modified Rankin Scale (mRS) Scores ≤ 2 at 90-Day Follow-up Assessment*

NIHSS Strata	r-proUK Group		Control		Absolute Difference, %	Odds Ratio (95% CI)
	No.	mRS ≤ 2 No. (%)	No.	mRS ≤ 2 No. (%)		
4-10	16	10 (63)	8	5 (63)	0	1.00 (0.17-5.77)
11-20	75	34 (45)	37	9 (24)	21	2.58 (1.07-6.21)
21-30	30	4 (13)	14	1 (7)	6	2.00 (0.20-19.75)
Total	121	(40)†	59	(25)†	15‡	2.13 (1.02-4.42)

*The upper limit for the 90-day follow-up assessment was prospectively set at 120 days. NIHSS indicates National Institutes of Health Stroke Scale²²; r-proUK, recombinant prourokinase; mRS, modified Rankin scale; and CI, confidence interval.

†NIHSS stratum adjusted.

‡P = .04 and is based on stratum-adjusted rates.

Table 4. Secondary Clinical Outcomes at 90-Day Follow-up Assessment*

Outcome (90-Day Follow-up)*	r-proUK Group (n = 121), %†	Control (n = 59), %†	Absolute Difference, %	P Value
mRS ≤ 1	26	17	9	.16
Barthel index ≥ 90	41	32	9	.24
Barthel index ≥ 60	54	47	7	.39
NIHSS score ≤ 1	18	12	6	.30
NIHSS score $\geq 50\%$ decrease	50	44	6	.46
Mortality‡	25	27	-2	.80

*The upper limit for the 90-day follow-up assessment was set prospectively at 120 days. r-proUK indicates recombinant prourokinase; mRS, modified Rankin scale; and NIHSS, National Institutes of Health Stroke Scale.

†NIHSS stratum adjusted.

‡Two deaths in the r-proUK group occurred after 90 days but within 120 days.

($P < .001$). The 2-hour complete (TIMI 3) recanalization rates were 19% and 2%, respectively ($P < .003$) (FIGURE 5).

COMMENT

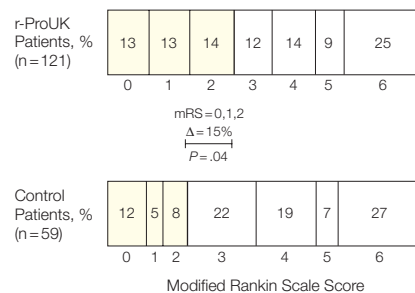
PROACT II is the first randomized multicenter trial to demonstrate the clinical efficacy of IA thrombolysis in patients with acute stroke of less than 6 hours' duration caused by MCA occlusion. Compared with patients receiving low-dose IV heparin only, patients with ischemic stroke caused by MCA occlusion treated with 9 mg of IA r-proUK plus low-dose heparin a median of 5.3 hours from symptom onset were 58% more likely to have slight or no neurological disability at 90 days. The 15% absolute increase in favorable outcome with IA r-proUK ($P = .04$) means that, on average, for every 7 patients treated with IA r-proUK, 1 will benefit.

PROACT I and PROACT II are the only randomized, multicenter stroke trials to restrict patient selection to MCA occlusion. We selected MCA occlusion because of its poor natural history²⁶ and because the MCA is the most frequent site of arterial occlusion in patients with

severe stroke of less than 6 hours' duration.²⁷ To further increase homogeneity between the 2 study arms, PROACT II prospectively stratified for initial stroke severity. In contrast to the National Institute of Neurological Disorders and Stroke (NINDS) tPA trial,¹ we chose slight or no neurological disability (modified Rankin score ≤ 2) as the primary outcome measure rather than complete recovery (modified Rankin score ≤ 1) because of the anticipated high baseline stroke severity in patients with MCA occlusion. A modified Rankin score of 2 or less has been used as an indicator of functional independence in other thrombolysis stroke trials.^{4,5}

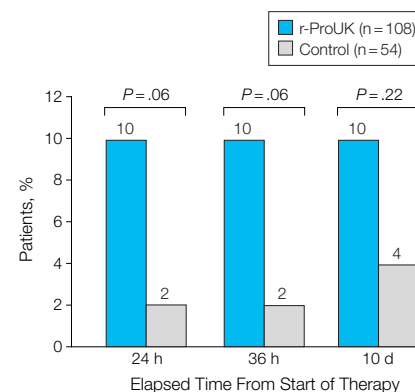
Intra-arterial thrombolysis poses other unique stroke trial design issues.^{28,29} PROACT I used a double-blind design; control patients received IA saline placebo. In PROACT II we changed to an open design with blinded follow-up because of ethical concerns about infusing a placebo into the MCA through a microcatheter for 2 hours with little likelihood of any benefit and to create a control group more

Figure 3. Distribution of NIHSS-Stratum Adjusted Modified Rankin Scores at 90-Day Follow-up Assessment



A score of ≤ 2 (yellow) on the modified Rankin scale (mRS) indicates a favorable outcome of slight or no disability. A score of 6 represents death. r-proUK indicates recombinant prourokinase.

Figure 4. Intracranial Hemorrhage With Neurological Deterioration in Patients Treated as Randomized



Data are based on adjudicated results by an external safety committee blinded to treatment and clinical outcome. Neurological deterioration was defined as a 4-point or more increase on the total National Institutes of Health Stroke Scale (NIHSS) score or a 1-point increase in level of consciousness on the NIHSS. Time-points were based on the onset of symptoms relative to the initiation of randomized therapy. r-proUK indicates recombinant prourokinase.

closely reflecting the natural history of MCA occlusion.

We demonstrated a benefit with IA r-proUK despite the use of a conservative interventional technique. To demonstrate the pharmacological effect of r-proUK and to standardize delivery technique across centers, we prohibited mechanical clot manipulation in PROACT I and PROACT II. The low TIMI 3 recanalization rate in PROACT II indicates that residual thrombus was

frequently present 2 hours after IA r-proUK thrombolysis. Advances in catheter technology, imaging techniques, mechanical clot removal, and thrombolytic agents should lead to faster and more complete recanalization and potentially even better patient outcomes.

Although the treatment groups were generally well-balanced, the small sample size resulted in some differences in baseline variables by chance. Two of these, baseline CT hypodensity^{30,31} and diabetes,³² have been correlated with stroke outcome, but we have limited our initial report to the pre-specified analysis plan.

The higher r-proUK dose in PROACT II improved recanalization efficacy by 26% compared with PROACT I, but the symptomatic brain hemorrhage rate also increased by 4%. It is not clear if low-dose heparin contributed to the intracranial hemorrhage risk in either group. The median activated partial thromboplastin times were not prolonged by low-dose heparin, and symptomatic brain hemorrhage was not clinically apparent until several hours after it was discontinued.

Treatment with IA r-proUK was beneficial despite an increased risk of early intracranial hemorrhage with neurological deterioration. There was no significant difference in the rates of total intracranial hemorrhage by day 10. This may reflect delayed recanalization in the control group with hemorrhagic transformation, whereas the higher early rate with r-proUK reflected drug-induced recanalization and reperfusion hemorrhage. The total intracranial hemorrhage rates were consistent with those previously reported in patients with embolic stroke.³³⁻³⁵ Most of these hemorrhages were small and clinically irrelevant and were detected only because of the protocol-mandated CT scans.

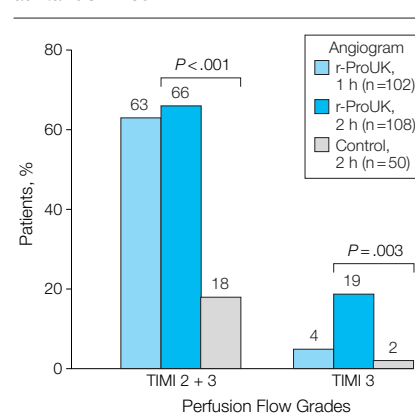
The higher rate of intracranial hemorrhage with neurological deterioration with IA r-proUK (10.2%) compared with IV tPA in NINDS (6.4%),¹ Alteplase Thrombolysis for Acute Non-interventional Therapy in Ischemic Stroke (ATLANTIS) (7.2%),⁷ and ECASS II (8.8%)⁶ reflects the greater baseline

stroke severity and time to treatment in PROACT II. Baseline stroke severity was first associated with intracranial hemorrhage risk in ECASS I² and NINDS.³⁶ The patients in PROACT II had the greatest baseline stroke severity of any randomized acute stroke trial. The median baseline NIHSS score of 17 in PROACT II contrasts with a median NIHSS score of 11 in both ECASS II⁶ and ATLANTIS,⁷ and 14 in the NINDS trial.¹

Direct comparisons of hemorrhage rates and clinical outcomes between PROACT II and the IV thrombolysis trials are difficult. Patients with acute ischemic stroke have a variety of arterial occlusion sites despite similar clinical presentations.³⁷ Since neither the sites of arterial occlusion nor the recanalization rates are known in the IV thrombolysis trials, including NINDS, the efficacy of IV thrombolysis in patients with MCA occlusion cannot be specifically determined from those trials. While the NINDS study supports the use of IV tPA in a less than 3-hour window, limited data suggest that IV tPA may be relatively ineffective in the subset of patients with MCA occlusion. The Thrombolytic Therapy of Acute Thrombotic/Thromboembolic Stroke Study (TTATTS)³⁸ suggests a recanalization rate of no more than 30% for large vessel occlusion with 0.8 mg/kg or 1.0 mg/kg of IV tPA. Tomsick et al³⁹ reported that a baseline NIHSS score greater than 10 and a hyperdense MCA sign on CT scan (signifying MCA occlusion) predicted a poor clinical outcome for patients treated with IV tPA given less than 3 hours from stroke onset.

Although MCA recanalization rates may be superior with IA thrombolysis, there was an average 3-hour delay between patient arrival at hospital and initiation of the IA r-proUK infusion. We treated only 1 patient with r-proUK less than 3 hours from stroke onset. When the 2-hour drug infusion time is added, up to 5 hours elapsed in some patients during which brain infarction continued. A door-to-drug time of 1 hour similar to that recommended for IV tPA⁴⁰ is more difficult to achieve with IA thrombolysis but was met in a few

Figure 5. Recanalization of Occluded Middle Cerebral Artery in Patients Treated as Randomized



Determination of 2-hour recanalization was made by a neuroradiologist at a core facility who was blinded to treatment and clinical outcome. One-hour recanalization was determined unblinded by the neuroradiologist. TIMI indicates Thrombolysis in Myocardial Infarction trial. TIMI 2 is partial flow in the middle cerebral artery; TIMI 3 is complete flow in both the M₁ and M₂ segments of the middle cerebral artery.

patients in PROACT II. It may also be feasible to give IA thrombolysis to patients with persistent MCA occlusion after IV tPA.⁴¹⁻⁴³

There has been significant controversy over the therapeutic window in acute human ischemic stroke.^{44,45} Recent diffusion and perfusion magnetic resonance studies suggest that as many as two thirds of patients with acute MCA distribution stroke have brain tissue at risk even 24 hours after stroke onset, but the clinical relevance of these observations is uncertain.^{46,47} PROACT II has demonstrated that the therapeutic window for a significant number of patients with major stroke due to MCA occlusion may extend to at least 6 hours. The challenge is to build on the results of PROACT II and other thrombolysis trials by refining patient selection, reducing the risk of hemorrhage, optimizing delivery techniques, and combining treatment strategies to further improve outcomes for patients with acute stroke.

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