Intravenous Ancrod for Treatment of Acute Ischemic Stroke

The STAT Study: A Randomized Controlled Trial

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Context Approved treatment options for acute ischemic stroke in the United States and Canada are limited at present to intravenous tissue-type plasminogen activator, but bleeding complications, including intracranial hemorrhage, are a recognized complication.

Objective To evaluate the efficacy and safety of the defibrinogenating agent ancrod in patients with acute ischemic stroke.

Design The Stroke Treatment with Ancrod Trial (STAT), a randomized, parallel-group, double-blind, placebo-controlled trial conducted between August 1993 and January 1998.

Setting Forty-eight centers, primarily community hospitals, in the United States and Canada.

Patients A total of 500 patients with an acute or progressing ischemic neurological deficit were enrolled and included in the intent-to-treat analysis.

Interventions Patients were randomly assigned to receive ancrod (n=248) or placebo (n=252) as a continuous 72-hour intravenous infusion beginning within 3 hours of stroke onset, followed by infusions lasting approximately 1 hour at 96 and 120 hours. The ancrod regimen was designed to decrease plasma fibrinogen levels to 1.18 to 2.03 μmol/L.

Main Outcome Measures The primary efficacy end point was functional status, with favorable functional status defined as survival to day 90 with a Barthel Index of 95 or more or at least the prestroke value, compared by treatment group. Primary safety variables included symptomatic intracranial hemorrhage and mortality.

Results Favorable functional status was achieved by more patients in the ancrod group (42.2%) than in the placebo group (34.4%; $P=.04$) by the prespecified covariate-adjusted analysis. Mortality was not different between treatment groups (at 90 days, 25.4% for the ancrod group and 23% for the placebo group; $P=.62$), and the proportion of severely disabled patients was less in the ancrod group than in the placebo group (11.8% vs 19.8%; $P=.01$). The favorable functional status observed with ancrod vs placebo was consistent in all subgroups defined for age, stroke severity, sex, prestroke disability, and time to treatment (≤3 or >3 hours after stroke onset). There was a trend toward more symptomatic intracranial hemorrhages in the ancrod group vs placebo (5.2% vs 2.0%; $P=.06$), as well as a significant increase in asymptomatic intracranial hemorrhages (19.0% vs 10.7%; $P=.01$).

Conclusion In this study, ancrod had a favorable benefit-risk profile for patients with acute ischemic stroke.

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ANCROD, A PURIFIED FRACtion of venom from the Malaysian pit viper (*Calloselasma rhodostoma*), induces rapid defibrinogenation in humans by splitting fibrinopeptide A from fibrinogen.[1,2] Monitoring fibrinogen levels permits control of defibrinogenation. Although ancrod does not directly affect any other coagulation factors or hematological components, rapid defibrinogenation does.[1,3] Defibrinogenation produces anticoagulation by depleting the substrate needed for thrombus formation. Depletion of fibrinogen also decreases blood viscosity, resulting in improved blood circulation.[4] Products of defibrinogenation may also enhance local clot-specific thrombolysis by stimulating endogenous plasminogen activators.[5]

Ancrod has been used in Europe and Canada since the 1970s as reperfusion therapy for clinical conditions such as

For editorial comment see p 2440.

Author Affiliations and **Financial Disclosure** are listed at the end of this article.
A complete list of the STAT Participants appears at the end of this article.

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Table 1. Study Entry Criteria*

Inclusion Criteria
Ischemic stroke (any vascular territory)
Symptoms lasting at least 30 minutes
Treatment to begin within 3 hours of stroke onset
Adult patients (≥18 years old)
Exclusion Criteria
Clinical or CT evidence of brain hemorrhage
CT evidence of potentially progressive lesion (eg, neoplasm)
Very mild stroke (pretreatment SSS score, excluding gait, ≥40)
Coma
Prior stroke within 6 weeks
Deficit from TIA within 3 hours
Ipsilateral neurological deficit from prior stroke interfering with evaluation
Deficit attributed to migraine, hypoglycemia, or sequelae of recent seizure
Recent or anticipated surgery
Hypertension (systolic BP >185 mm Hg or diastolic BP >105 mm Hg) or hypotension (systolic BP <90 mm Hg) on any of 2 measurements taken within approximately 30 minutes before treatment
Labile BP (systolic BP differing by >30 mm Hg) on 2 BP measurements taken within approximately 30 minutes before treatment
Antihypertensive medication given within 15 minutes before treatment
Thrombolytic therapy within 1 week or anticipated
Coagulation disorder (patients taking anticoagulants were eligible if their pretreatment prothrombin time was <14 seconds [or INR was <1.3] and if aPTT was <45 seconds)
Thrombocytopenia (platelet count $<100 \times 10^9$/L)
Prior treatment with ancrod

*CT indicates computed tomography; SSS, Scandinavian Stroke Scale; TIA, transient ischemic attack; BP, blood pressure; INR, international normalized ratio; and aPTT, activated partial thromboplastin time.

peripheral vascular disease, deep vein thrombosis, and central retinal venous thrombosis.[1,6-11] Ancrod also has been used prophylactically for thromboembolism and as an alternate anticoagulant in the setting of heparin-induced thrombocytopenia.[12-16] At present, ancrod is being marketed only in Canada.

Evaluation of ancrod for acute ischemic stroke began with 2 studies published in the 1980s.[17,18] These randomized trials of 20 and 30 patients suggested that ancrod was both safe and beneficial in stroke patients. This experience led to a double-blind, randomized, placebo-controlled study of ancrod in 132 patients treated within 6 hours of stroke onset.[19] In that study, patient-weighted analysis demonstrated significant benefit favoring ancrod ($P=.04$) for the prespecified primary end point of neurological function, measured by the Scandinavian Stroke Scale (SSS; patient-weighted analysis not reported); no patient who received ancrod had a symptomatic intracranial hemorrhage. Trends favoring ancrod also were seen on the Barthel Index (BI) of functional capability and for mortality.

The Stroke Treatment with Ancrod Trial (STAT) was designed to investigate the efficacy and safety of ancrod in patients treated within 3 hours of acute ischemic stroke. Treatment effects also were assessed in subpopulations based on important pretreatment variables, including age, sex, pretreatment SSS score, and time to treatment.

METHODS

Study Design and Patients

STAT was a multicenter, parallel-group, double-blind, randomized, placebo-controlled study with a 5-day treatment period and a 3-month follow-up period. Patients with an acute or progressing ischemic neurological deficit in any vascular territory were eligible. Treatment was to begin between 30 minutes and 3 hours after symptom onset; because of safety observed previously in patients starting ancrod up to 6 hours after stroke onset,[19] the 3-hour limit was sometimes relaxed.

To eliminate patients with probable transient ischemic attack, patients with rapidly improving neurologic deficits or mild deficits (pretreatment SSS score, excluding gait, ≥40) were excluded. The SSS (range, 0 [worst] to 46 [best]) primarily evaluates motor function and speech[20] and has been used in other stroke studies with high levels of interobserver agreement.[21] Postural hypotension associated with standing may worsen the stroke deficit; therefore, standing is discouraged in patients with acute stroke and evaluation of gait was excluded from these analyses. Patients with prior strokes were eligible if residual deficits did not interfere with evaluation of their acute stroke. Computed tomographic (CT) evidence of the acute stroke did not exclude patients, and there was no upper age limit. Study entry criteria are listed in TABLE 1.

The study was approved by the institutional review board at each participating hospital. Signed written informed consent was obtained from all patients or their representatives. An unblinded safety committee received reports of all deaths and serious adverse events. In addition to this ongoing review of safety, the committee reviewed 2 prespecified interim analyses to ensure that futility or efficacy bounds had not been exceeded. On US approval of tissue-type plasminogen activator (tPA) for stroke in 1996, the safety committee issued a letter to investigators supporting continued participation in the study, and consent forms were modified to acknowledge the availability of an approved treatment.

Treatment and Randomization

Identical-appearing supplies containing 1-mL (70-IU) ampules of ancrod or isotonic sodium chloride solution (placebo) in sequentially numbered prepacks were prepared by the supplier (Knoll Pharmaceutical Co, Mount Olive, NJ) for patients at each site, following a 1:1 randomization program in block sizes of 4 generated by a statistician.

Patients received ancrod or placebo as a continuous 72-hour infusion, followed by infusions lasting approximately 1 hour, given at approximately 96 (range, 90-102) and 120 (range, 114-126) hours after treatment was started. The target fibrinogen level in ancrod pa-

tients was 1.18 to 2.03 µmol/L. Ancrod was administered at initial infusion rates of 0.167, 0.125, and 0.082 IU/kg per hour based on pretreatment fibrinogen levels of more than 13.23, 10.29 to 13.20, and 2.94 to 10.26 µmol/L, respectively. Fibrinogen levels were measured before treatment and at prespecified and increasing intervals during treatment. More frequent fibrinogen measurements were advised for patients with fibrinogen levels outside the target range after 12 hours. The 96- and 120-hour infusions were calculated to deliver a full day's dose.

While receiving ancrod or placebo, patients were not to receive aspirin, anticoagulants, thrombolytic agents, dextran, or other drug therapies that might affect the fibrinolytic system (eg, ϵ-aminocaproic acid, tranexamic acid). After completion of intravenous treatment, patients were permitted to receive standard prophylactic therapy (eg, aspirin or warfarin) throughout the 3-month follow-up.

To preserve the blind, patients' treatment assignments were known only by the supplier's clinical packaging group and were kept in a sealed envelope by the statistician until database lock. The clinical staffs received no information about the method used to generate the randomization, the randomization itself, or the block size. Fibrinogen measurement results were provided only to an unassociated, unblinded dosing supervisor at each site (usually a research pharmacist), who calculated adjustments to the infusion rate based on a dosing algorithm provided by the supplier. Laboratories reporting results by computer were required by the supplier to restrict results to computers in the laboratory and pharmacy. The safety committee provided unblinded dosing supervisors with schedules for fibrinogen level determinations and infusion rate adjustments in placebo patients that matched the actual changes in dosing used at other sites for individual ancrod patients. Investigators were informed that bruising and minor bleeding had occurred in both the ancrod and placebo arms of a previous study.[19]

Primary Efficacy and Safety Measures

The primary efficacy variable was favorable functional status, defined as survival to follow-up day 90 with a BI score (range, 0 [worst] to 100 [best]) of 95 or more (implying a need for little or no help in daily activities) or at least equal to the prestroke value. The BI is a validated measure of performance of activities of daily living that has been used in studies of stroke patients.[22-25] Because patients with prior disabilities from strokes or other illnesses were included in the study to reflect more accurately the patient population at risk for stroke, patients with prestroke disabilities were required to improve only to at least their prestroke BI score, which was assessed by interview at study enrollment. The 90-day evaluation was conducted by each site's blinded investigative team in person (so that the SSS score also could be obtained) or, less often, by telephone.

Safety variables included deaths, adverse events within 3 months, and laboratory measurements. Particular attention was paid to bleeding events, including symptomatic and asymptomatic intracranial hemorrhage and retroperitoneal hematoma.

A follow-up CT scan was performed 7 to 10 days after stroke (or within 48 hours of hospital discharge, if earlier) to determine infarction volume (to be reported subsequently) and incidence of asymptomatic intracranial hemorrhage; individuals analyzing CT scan results were blinded to treatment. Symptomatic intracranial hemorrhage was defined as a documented intracranial hemorrhage (by autopsy, CT, or magnetic resonance imaging performed because of clinical worsening) considered by the local investigative staff to be causally related to clinical deterioration; asymptomatic intracranial hemorrhages were documented intracranial hemorrhages identified by the local investigative staff as causally unrelated to clinical worsening. Thrombotic adverse events were tabulated to determine if rebound coagulopathy occurred.

Statistical Analysis

Sample size was based on an absolute difference in favorable functional outcomes of 15% and a placebo rate of 34%,[19] with 90% power and a 2-sided significance level of .05. Two prespecified interim analyses[26] were conducted by the unblinded statistician on the safety committee after one third and two thirds of the patients had been followed up for 3 months; critical P values were $<.001$ and .02. The adjusted critical level required for an overall α level of .05 was $P=.047$ for the final analysis of the primary end point and $P=.05$ for all other analyses. Except where indicated, all statistical tests were conducted on the intent-to-treat population and were 2-tailed.

The primary efficacy analysis compared proportions of favorable functional outcomes between treatment groups using logistic regression analysis.[27] Included in the model were prespecified terms for treatment group, pooled study center, age category (<65, 65-74, 75-84, and ≥ 85 years), and pretreatment SSS score category (<20, 20-29, and 30-39); these latter 2 terms (covariates) were included because of their known prognostic importance. Logistic regression, excluding pooled study center, was used in evaluating the occurrence of symptomatic intracranial hemorrhage and mortality. Scandinavian Stroke Scale scores were evaluated as a secondary efficacy end point using a general linear model with normal transformation and, except for the pretreatment value, terms for age category, pretreatment SSS score category, study center, center-by-treatment interaction, and treatment. Differences in pretreatment characteristics were evaluated using the Cochran-Mantel-Haenszel test. The relationship between clinical outcome (favorable functional status, mortality, and symptomatic intracranial hemorrhage) and fibrinogen levels was explored by applying descriptive statistics to early defibrinogenation (fibrinogen levels ≤ 3.82 µmol/L at 6 hours) and mean time-weighted fibrinogen levels during treatment between 9 and 72 hours (effectively integrating fibrinogen levels over time).

RESULTS

Demographic and Pretreatment Patient Characteristics

Patients were recruited for STAT between August 1993 and January 1998, predominantly from community hospitals in the United States and Canada. A total of 2613 patients were screened, most within 3 hours of stroke onset, and from this group, 500 patients were enrolled at 48 study sites and were randomly assigned to receive ancrod or placebo (FIGURE 1); 248 received ancrod and 252 received placebo, and all were included in the intent-to-treat analysis. A similar proportion of patients in the ancrod group (77.0%) and the placebo group (83.3%) completed treatment; most discontinuations resulted from adverse events or death.

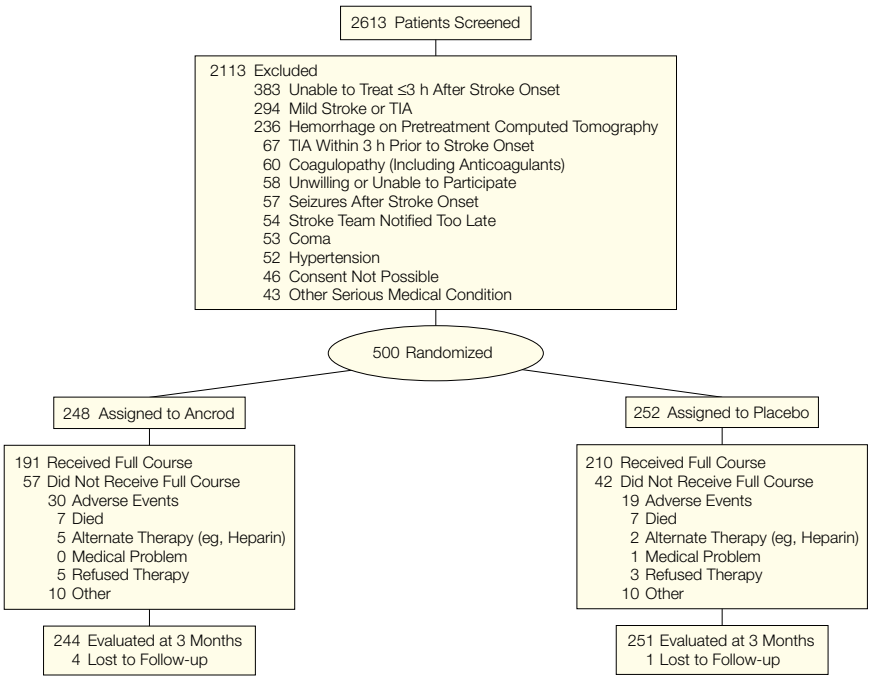
The mean age of the patients in the study was 72.8 years, and similar proportions of men (51.2%) and women (48.8%) were enrolled. No significant differences were identified between treatment groups for patient sex, race, age, weight, or height (TABLE 2). The mean pretreatment SSS score was 23.8 for the ancrod group and 24.4 for the placebo group. Although not statistically significant, milder strokes (SSS scores 30-39) occurred more often (>5%) in the placebo group than in the ancrod group.

The mean time between stroke onset and treatment initiation in the ancrod group was 2.7 (SD, 0.4; range, 1.5-3.9) hours; in the placebo group, it was 2.7 (SD, 0.5; range, 1.5-4.0) hours. Treatment began in 5.2% of ancrod and placebo group patients (n=13 in both groups) within 2 hours of stroke onset; in 77.8% (n=193) of ancrod and 79.0% (n=199) of placebo group patients at 2 to 3 hours; and in 16.9% (n=42) of ancrod and 15.9% (n=40) of placebo group patients after 3 hours. Six patients in each group began treatment more than 3.5 hours after stroke onset.

Functional Status

Ancrod treatment resulted in a significantly ($P=.04$) greater proportion of favorable functional outcomes than placebo; 102 ancrod-treated patients (41.1%) achieved favorable functional status vs 89 placebo group patients (35.3%) (odds ratio [OR] by logistic regression analysis, 1.55; 95% confidence interval [CI], 1.02-2.36). In view of the uneven distribution of pretreatment SSS scores, covariate-adjusted proportions were calculated to obtain a more accurate estimate of the true treatment effect. For ancrod, the covariate-

Figure 1. Trial Profile



Reasons for exclusion that did not account for 2% or more of the total exclusions are not shown. TIA indicates transient ischemic attack.

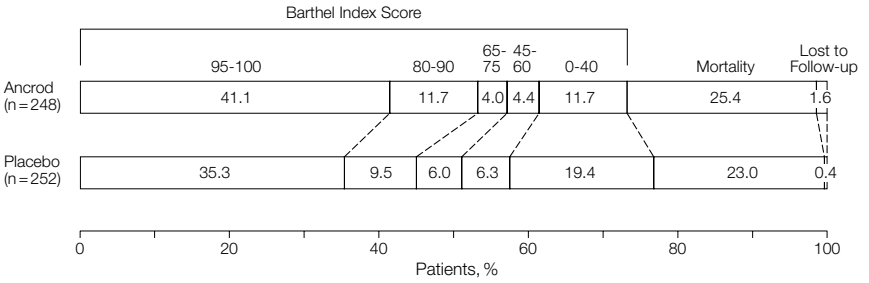
Table 2. Demographic and Pretreatment Patient Characteristics*

Characteristics	Ancrod Group (n = 248)	Placebo Group (n = 252)
Age, mean (SD) [range], y	72.6 (11.8) [34-95]	73.1 (11.6) [39-98]
Age group, y, %		
<65	22.6	20.2
65-74	28.2	31.0
75-84	33.1	34.1
≥85	16.1	14.7
Male, %	49.2	53.2
Weight, mean (SD) [range], kg	76.1 (16.5) [37-151]	77.2 (20.4) [40-181]
Pretreatment SSS score, mean (SD)	23.8 (10)	24.4 (11)
SSS score category, %		
<20	31.5	30.2
20-29	35.1	31.0
30-39	33.5	38.9
Stroke type, %		
Craniocervical large vessel	36.7	42.5
Intracranial small vessel	18.1	18.3
Infracervical embolism†	29.4	28.2
Other	0.8	1.2
Unknown	14.9	11.1
Prior stroke, %	17.7	21.0
Systolic BP, mean (SD), mm Hg	157 (21)	157 (20)
Diastolic BP, mean (SD), mm Hg	84 (12)	84 (13)
Fibrinogen, mean (SD), µmol/L	10.55 (2.97)	10.70 (3.09)
Glucose, mean (SD), mg/dL‡	147 (71)	144 (70)

*Not all columns sum to 100% due to rounding. SSS indicates Scandinavian Stroke Scale (excluding gait); BP, blood pressure.
†Emboli originating in the heart or aorta.
‡To convert glucose from mg/dL to mmol/L, multiply by 0.05551.

adjusted proportion of patients achieving favorable functional status was 42.2% compared with 34.4% for placebo, yielding a 22.7% relative increase in the likelihood of achieving favorable functional status for ancrod-treated patients ($P=.04$). The overall distribution of functional outcomes at 3 months (FIGURE 2) shows that treatment with ancrod also reduced the proportion of severely disabled patients. The covariate-adjusted proportion of severely disabled patients, with BI scores of 40 or less, was 40.4% lower for ancrod patients (11.8%) than for placebo patients (19.8%; $P=.01$ by logistic regression analysis), and the covariate-adjusted proportion of patients with complete recovery (BI score = 100 or at least equal to prestroke value) was 27.1% higher for ancrod (36.1%) relative to placebo (28.4%; $P=.02$ by logistic regression analysis).

Figure 2. Overall Distribution of Functional Responses at 3 Months by Treatment Group



The primary efficacy end point was defined as survival with a Barthel Index score of 95 or more or at least equal to the prestroke value at 3 months. Results may differ from text because text results are covariate-adjusted.

Functional Status Categorized by Pretreatment Variables

The robustness of the treatment effect was evaluated by determining the proportion of favorable functional outcomes in different subpopulations based on important pretreatment variables, including overall predictors of stroke outcome such as age and pretreatment stroke severity (TABLE 3). Across both treatment groups, patients with more severe strokes (ie, lower pretreatment SSS scores), older patients, women, those with prior disabilities (prestroke BI score ≤90), and patients who had a longer time to treatment had lower probabilities of favorable functional status. However, more ancrod-treated patients achieved favorable functional status than placebo group patients, regardless of pretreatment SSS score category, age, sex, prestroke disability, or time to treatment. The greatest relative improvements were observed in patients with the lowest pretreatment SSS scores (35.6%) and in the oldest patient group (45.5%). Among the 242 ancrod and 246 placebo group patients whose treatment began within 3.5 hours of stroke onset, significantly more ancrod group patients (n = 101; 41.7%) achieved favorable functional status than placebo group patients (n = 88; 35.8%; $P=.03$ by logistic regression analysis).

Neurological Recovery

Patients in the ancrod group began treatment with worse mean SSS scores than those in the placebo group. This was reversed within 24 hours of treatment (FIGURE 3). Although not significant ($P=.07$ by analysis of variance), SSS scores increased 2.6 points for ancrod-treated patients compared with 0.4 points for patients in the placebo group. The difference in neurological function favoring ancrod was maintained throughout the treatment and follow-up periods.

Safety

Adverse events occurred with similar frequency in the ancrod (n = 244; 98.4%) and placebo (n = 250; 99.2%) groups.

Mortality was also similar in the 2 treatment groups. A Kaplan-Meier survival curve censored at 90 days showed no significant difference between the 2 groups ($P=.62$ by log-rank test). At 7 days, 22 ancrod-treated patients (8.9%) died compared with 24 placebo group patients (9.5%). At 1 month, mortality was 19.0% for ancrod-treated patients and 19.8% for placebo group patients; at 3 months, mortality was 25.4% in the ancrod group and 23.0% in the placebo group; and at the last observation (median, 364 days), mortality was 33.5% in the ancrod group and 32.5% in the placebo group. Up to 30 days after stroke onset, the primary cause of death was stroke, but thereafter, cardiac and pulmonary causes of death predominated. Causes of death at 3 months in the ancrod and placebo groups, respec-

Table 3. Proportion of Favorable Functional Outcomes by Pretreatment Variables*

Variables	Proportion of Favorable Functional Outcomes, No. (%)	
	Ancrod Group (n = 248)	Placebo Group (n = 252)
Pretreatment stroke severity, SSS score†		
<20	14/78 (17.9)	10/76 (13.2)
20-29	30/87 (34.5)	23/78 (29.5)
30-39	58/83 (69.9)	56/98 (57.1)
Age category, y		
<65	32/56 (57.1)	26/51 (51.0)
65-74	34/70 (48.6)	31/78 (39.7)
75-84	25/82 (30.5)	25/86 (29.1)
≥85	11/40 (27.5)	7/37 (18.9)
Sex		
Male	54/122 (44.3)	51/134 (38.1)
Female	48/126 (38.1)	38/118 (32.2)
Prestroke disability, Barthel Index		
≤90	7/27 (25.9)	3/21 (14.3)
95-100	95/221 (43.0)	86/231 (37.2)
Time to treatment, h		
<2	6/13 (46.2)	5/13 (38.5)
2-3	82/193 (42.5)	74/199 (37.2)
>3	14/42 (33.3)	10/40 (25.0)

*Interactions between treatment and age, pretreatment stroke severity, and time to treatment were all nonsignificant; in addition, the treatment effect was not statistically significant in any of the individual subgroups.
†Measured by pretreatment Scandinavian Stroke Scale (SSS) score, excluding gait. Lower scores represent more severe deficits; patients with SSS scores of 40 or more were excluded.

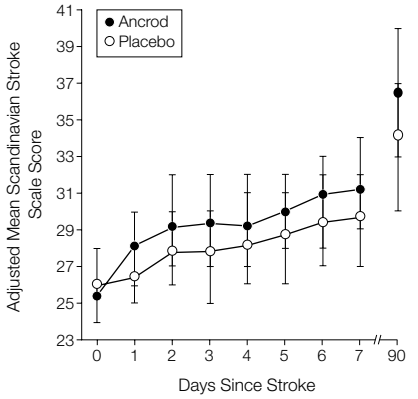
tively, were stroke (n=32 and n=28), cardiac arrest (n=10 and n=8), pneumonia (n=5 and n=2), myocardial infarction (n=1 and n=3), pulmonary embolism (n=0 and n=3), other cardiovascular events (n=5 and n=4), intracranial hemorrhage (n=1 for both), and other (n=9 for both).

Symptomatic intracranial hemorrhages occurred in 13 ancrod-treated patients (5.2%) and 5 placebo group patients (2%) (OR by logistic regression analysis, 2.58; 95% CI, 0.95-8.21; $P=.06$; TABLE 4). Seven of the 13 symptomatic intracranial hemorrhages in ancrod-treated patients occurred within 36 hours of starting treatment, and all occurred within the first 72 hours of ancrod or placebo administration. Ten of the 13 ancrod-treated patients and 3 of the 5 placebo group patients with symptomatic intracranial hemorrhage died within 1 week; an additional 2 ancrod-treated patients died by the end of 3 months. No patient with a symptomatic intracranial hemorrhage achieved favorable functional status. The incidence of symptomatic intracranial hemorrhage was independent of the interval to treatment; symptomatic intracranial hemorrhage occurred in 11 (5.7%) of 193 ancrod-treated patients and 4 (2%) of 199 placebo group patients with treatment initiated within 2 to 3 hours after stroke onset compared with 2 (4.8%) of 42 ancrod-treated patients and 1 (2.5%) of 40 placebo group patients with treatment initiated more than 3 hours after stroke onset.

Asymptomatic intracranial hemorrhage occurred significantly more often in the ancrod group (n=47; 19.0%) than in the placebo group (n=27; 10.7%; OR by logistic regression analysis, 1.92; 95% CI, 1.14-3.27; $P=.01$). Intracranial hemorrhage, whether symptomatic or asymptomatic, was identified within the first 72 hours in 17 ancrod-treated patients (6.9%) and 11 placebo group patients (4.4%; $P=.28$ by logistic regression analysis). Retroperitoneal hemorrhages occurred in 2 placebo group patients (0.8%) but in no ancrod-treated patients; both patients had received heparin after placebo was discontinued. No intraocular hemorrhages were reported.

Within 3 months of study enrollment, arterial thrombotic events occurred in 20 ancrod-treated patients (8.1%) and 22 placebo group patients (8.7%; OR by logistic regression analysis, 0.93; 95% CI, 0.49-1.76; $P=.82$). Venous thrombotic events occurred in 13 ancrod-treated patients (5.2%) and 24 placebo group patients (9.5%; OR by logistic regression analysis, 0.50; 95% CI, 0.24-1.00; $P=.05$), including thrombophlebitis in 10 ancrod-treated and 17 placebo group patients and pulmonary embolism/infarction in 2 ancrod-treated and 9 placebo group patients.

Figure 3. Scandinavian Stroke Scale Total Score During the First Week of Treatment and at 3 Months



Scores are adjusted mean total scores (error bars indicate 95% confidence intervals), excluding gait, based on an analysis of variance with pooled study center, age category, pretreatment Scandinavian Stroke Scale score category (for all times except pretreatment), treatment, and treatment-by-center interaction in the model, following a normal score transformation.

Fibrinogen Levels, Efficacy, and Safety in Ancrod-Treated Patients

Plasma fibrinogen concentrations in ancrod-treated patients decreased rapidly, reaching the lowest levels 12 to 24 hours after initiation of treatment. In placebo group patients, fibrinogen levels increased gradually for the first several days after stroke onset.

Rapid initial defibrinogenation was related to treatment success in ancrod-treated patients; success was achieved by 70 (45.8%) of 153 patients with 6-hour fibrinogen levels of 3.82 µmol/L or less compared with 28 (34.6%) of 81 patients with higher 6-hour fibrinogen levels (TABLE 5). A logistic regression analysis of ancrod-treated patients including terms for pretreatment SSS and age categories showed that the effect of 6-hour fibrinogen levels on favorable functional status was not statistically significant ($P=.08$ by logistic regression analysis), and did not appear related to subsequent maintenance of the mean, time-weighted, 9- to 72-hour fibrinogen level during treatment in the range of 1.18 to 2.06 µmol/L ($P=.97$ by logistic regression analysis). Safety, by contrast, appeared to be related less to initial than to subsequent defibrinogenation. Based on 9- to 72-hour fibrinogen levels, symptomatic intracranial hemorrhages occurred in 4 (13.3%) of 30 patients with levels of less than 1.18

Table 4. Incidence of Clinically Significant Bleeding and Thrombotic Events*

	No. (%)		
	Ancrod Group (n = 248)	Placebo Group (n = 252)	*P* Value
Intracranial hemorrhage			
Symptomatic	13 (5.2)	5 (2.0)	.06
Asymptomatic	47 (19.0)†	27 (10.7)	.01
Retroperitoneal hemorrhage	0	2 (0.8)	.50
Arterial thrombotic events‡	20 (8.1)	22 (8.7)	.82
Venous thrombotic events§	13 (5.2)	24 (9.5)	.05

*Events occurring in each patient through 28 days after the last day of study drug administration were counted.
†One ancrod patient with a subarachnoid hemorrhage (symptomatic intracranial hemorrhage) also had a small area of hemorrhagic conversion noted on computed tomography scan that was considered by the investigator to be asymptomatic.
‡Arterial thrombotic events included myocardial infarction, new stroke, and systemic arterial embolism.
§Venous thrombotic events included deep venous thrombosis, phlebitis, and pulmonary embolism.

µmol/L and 9 (4.4%) of 204 patients with levels of at least 1.18 µmol/L. There were too few patients with symptomatic intracranial hemorrhage, however, to permit a logistic regression analysis.

Table 5. Relationship of Defibrinogenation in Ancrod-Treated Patients to Efficacy and Safety

Fibrinogen Levels, µmol/L	No.	Favorable Functional Status, No. (%)*	90-Day Mortality, No. (%)	90-Day Symptomatic Intracranial Hemorrhage, No. (%)
6-Hour levels				
≤3.82	153	70 (45.8)	35 (22.9)	7 (4.6)
>3.82	81	28 (34.6)	24 (29.6)	6 (7.4)
9- to 72-Hour levels				
<1.18	30	9 (30.0)	4 (13.3)	4 (13.3)
1.18-2.06	167	72 (43.1)	9 (5.4)	9 (5.4)
>2.06	37	17 (45.9)	0 (0)	0 (0)
Nonevaluable†	7	2 (28.6)	2 (28.6)	0
Missing	7	2 (28.6)	0	0

*Favorable functional status was defined as survival to day 90 of follow-up with a Barthel Index of 95 or higher or equal to prestroke value.
†Ancrod or placebo was stopped early at the sponsor's request in 11 patients (7 in ancrod group and 4 in placebo group) when violations of entry criteria exposing patients to potential risk (eg, thrombocytopenia, anemia) became known, leaving 489 evaluable patients.

COMMENT

In this study, treatment with ancrod significantly increased the proportion of patients with ischemic stroke who achieved favorable functional status at 3 months compared with placebo. The covariate-adjusted proportions of patients achieving favorable functional status were 42.2% for ancrod and 34.4% for placebo, a 22.7% relative treatment effect that is clinically meaningful.[28] Significantly more ancrod-treated than placebo group patients achieved complete functional recovery, and the proportion of severely disabled patients was significantly less with ancrod than placebo. Ancrod-treated patients had a similar mortality rate and a trend for more symptomatic intracranial hemorrhage compared with the placebo group.

The primary end point of favorable functional status used in this study incorporates both benefit and risk of drug treatment, with any death or disability potentially resulting from adverse events counting as failure. Logistic regression analysis was used to analyze the primary end point because it adjusts for age and pretreatment stroke severity, known powerful predictors of outcome in untreated stroke.[29] Thus, we believe logistic regression provides improved estimates of success based on drug treatment alone and also compensates for imbalances in the distribution of predictive factors across treatment groups, such as the greater proportion of patients with milder strokes in the placebo vs ancrod group of this study.

The favorable response associated with ancrod was consistent across patient subgroups based on pretreatment stroke severity, age, sex, prestroke disability, and time to treatment after stroke onset. Although not statistically significant, ancrod-treated patients achieved a higher proportion of favorable functional status than placebo patients in each patient subgroup.

The greater-than-4-year duration of this study, during which tPA was approved for stroke treatment, potentially influenced the results as investigators gained experience evaluating and managing cases of hyperacute stroke. Major efforts to preserve the blind, such as restricting information about randomization and laboratory results, were incorporated into the study design to limit the potential for unblinding implicit in the necessity for on-site pharmacodynamic measurements for dosing (fibrinogen levels). Although several of the *P* values did not reach statistical significance, we believe the strength of this trial resides in its internal consistency across the outcome measures and among the subgroups based on pretreatment prognostic factors.

The effect of time to treatment after the onset of stroke symptoms has been addressed in several clinical trials. Extending the use of intravenous tPA to within 6 hours of stroke onset has been associated with a further increase in the occurrence of large parenchymal hemorrhages compared with placebo,[22,23] and when given within a 3- to 5-hour time window after stroke onset, tPA was found in the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study to be ineffective.[30] Moreover, reanalysis of the National Institute of Neurological Disorders and Stroke (NINDS) data has shown decreasing efficacy with increased interval from stroke onset to treatment, even within the 3-hour window.[31] Locally administered therapy (eg, intra-arterial prourokinase) may extend the treatment window to 6 hours in a population restricted by the availability of interventional radiology.[32]

When patients enrolled in STAT were grouped by time to treatment, those treated up to 3.5 hours after stroke onset had a statistically significantly higher rate of favorable treatment outcome with ancrod compared with placebo, and this was reflected across all 3 time-to-treatment intervals assessed (Table 3). In addition, the incidence of symptomatic intracranial hemorrhage did not increase in patients who started ancrod more than 3 hours after stroke onset, indicating no increase in the relative risk of ancrod treatment. However, the numbers of patients who received treatment more than 3 hours after symptom onset were small, and the power to detect important differences in these groups is limited.

While these results are consistent with the 1994 Ancrod Stroke Study, which randomized 132 patients to ancrod or placebo within 6 hours of stroke onset and yielded evidence of efficacy and safety with a mean interval to treatment of 5 hours,[19] enrollment in the European Stroke Treatment with Ancrod Trial,[33] in which patients were treated up to 6 hours after symptom onset, was terminated March 27, 2000, because of

a failed futility assessment at a preplanned interim analysis. A 90-day mortality analysis of patient data from this interim data set showed that mortality was higher in ancrod patients than placebo patients. Further safety and efficacy analyses from the European study are ongoing, and consideration of the use of ancrod in the treatment of acute stroke should await this full analysis.

Although the difference was not statistically significant, symptomatic intracranial hemorrhages occurred more often in STAT ancrod-treated than placebo group patients. The increased incidence of symptomatic intracranial hemorrhage with ancrod (2.6 times that of placebo), however, was less than the 4-fold increase reported for thrombolytic agents in a recent review by the Cochrane Collaboration[34] or in individual trials of thrombolytic agents.[22,23,25,35,36] While the wide CI warrants caution in interpreting the ancrod results, the apparently lower relative risk of symptomatic intracranial hemorrhage with ancrod might reflect predominantly nonthrombolytic actions of ancrod.[37]

Compared with the 1995 NINDS tPA trial,[25] a similarly sized, 3-hour acute stroke trial, patients in STAT were older (mean age, 73 vs 67 years), had more prior strokes (18% vs 12%), and were sicker (ie, there was a smaller proportion of favorable functional outcomes in STAT placebo patients [34%] vs NINDS trial placebo patients [38%]). Although these are not the only differences between the 2 trials, they may explain the higher rate of symptomatic intracranial hemorrhage among STAT placebo group patients (2.0%) compared with those in the NINDS trial (0.6%). Only 2 of the 13 symptomatic intracranial hemorrhages in the ancrod group were in patients younger than 70 years. Yet the rate of symptomatic intracranial hemorrhage in ancrod-treated patients (5.2% or 2.6 times the placebo rate) was lower than that for NINDS patients treated with tPA (6.4% or 10 times the placebo rate),[25] Prolyse in Acute Cerebral Thromboembolism II (PROACT-II) patients treated with intra-arterial prourokinase (10% or 5 times the placebo rate),[32] and patients treated with streptokinase, even in the absence of aspirin or heparin, more than 3 hours after stroke onset (6.0% or 10 times the placebo rate).[36]

Although favorable functional status was achieved with fibrinogen levels targeted at 1.18 to 2.03 µmol/L, it was clear from this and the earlier ancrod study[19] that rapid defibrinogenation was important to success and did not increase mortality. Mean maintenance fibrinogen levels below the target range at 9 to 72 hours were, however, associated with a greater likelihood of symptomatic intracranial hemorrhage. This association suggests that further research on fibrinogen control with ancrod is necessary to reduce such events. Adjusting ancrod infusions based on monitored fibrinogen levels adds minimal cost and inconvenience while suggesting better efficacy and safety from individually optimized dosing.

In conclusion, this study demonstrates a favorable benefit-risk profile for use of ancrod in treatment of acute ischemic stroke. Therapeutic benefits and a favorable safety profile of ancrod appear to be related to achieving controlled defibrinogenation.

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