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NXY-059 for the Treatment of Acute Stroke
Pooled Analysis of the SAINT I and II Trials

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Background and Purpose—In animal models of acute ischemic stroke (AIS), the free radical–trapping agent NXY-059 showed promise as a neuroprotectant. SAINT I and II were randomized, placebo-controlled, double-blind trials to investigate the efficacy of NXY-059 in patients with AIS.

Methods—Patients with AIS received an infusion of intravenous NXY-059 or placebo within 6 hours from the onset of stroke symptoms. A pooled individual patient analysis was prespecified to assess the overall efficacy and to examine subgroups. The primary end point was the distribution of disability scores measured on the modified Rankin scale (mRS) at 90 days. Neurologic and activities of daily living scores were investigated as secondary end points. We also evaluated whether treatment with NXY-059 would reduce alteplase-related intracranial hemorrhages. Finally, we evaluated possible predictors of good or poor outcome.

Results—An intent-to-treat efficacy analysis was based on 5028 patients. Baseline parameters and prognostic factors were well balanced between treatment groups. The distribution of scores on the mRS was not different in the group treated with NXY-059 (n=2438) compared with the placebo group (n=2456): odds ratio for limiting disability=1.02; 95% CI, 0.92 to 1.13 (P=0.682, Cochran-Mantel-Haenszel test). Comparisons at each level of the mRS confirmed an absence of benefit. There was no evidence of efficacy in prespecified subgroups or from the secondary outcome analyses. Mortality was equal in the 2 groups (16.7% vs 16.5%), and adverse event rates were similar. Among patients treated with alteplase, there was no decrease in rates of symptomatic or asymptomatic hemorrhage associated with NXY-059 treatment versus placebo. Subgroup analyses identified National Institutes of Health Stroke Scale score, age, markers of inflammation, blood glucose, and right-sided infarct as predictors of poor outcome.

Conclusions—NXY-059 is ineffective for treatment of AIS within 6 hours of symptom onset. This is also true for subgroups and the prevention of alteplase-associated hemorrhage. **(*Stroke*. 2008;39:1751-1758.)**

Key Words: ischemic stroke ■ neuroprotective therapy ■ pooled analysis ■ thrombolysis ■ predictors of outcome

Thrombolysis with alteplase (recombinant tissue-type plasminogen activator) is the only approved drug treatment for acute stroke in a 3-hour time window.[1] There is an urgent need for new therapies that are safer and can be offered to a higher percentage of patients over a longer time period after the event. Cerebral tissue can be protected in animal models by a variety of medications that attenuate neuronal injury after ischemia,[2] but no neuroprotective drug has been approved for use in humans. NXY-059, a potent free radical–trapping agent, has been extensively tested in small- and large-animal models of focal ischemic stroke and has been shown to improve functional recovery and reduce the size of the cerebral infarction.[3] A first study showed that NXY-059 was significantly better than placebo in improving outcome when tested in patients with ischemic stroke treated within 6 hours from the onset of symptoms.[4,5] Suggesting a biologic signal, post hoc analysis of the data also revealed that treatment with NXY-059 significantly reduced the incidence of intracranial hemorrhages among patients in whom alteplase was also used.[4] The second phase III study with a larger sample, however, was neutral for the primary and all secondary outcomes.[6] Pooled individual patient analysis of the 2 trials was prespecified to examine efficacy and especially to consider subgroups. This article reports the pooled analysis of the 2 studies and investigated possible baseline predictors of poor or good outcome.

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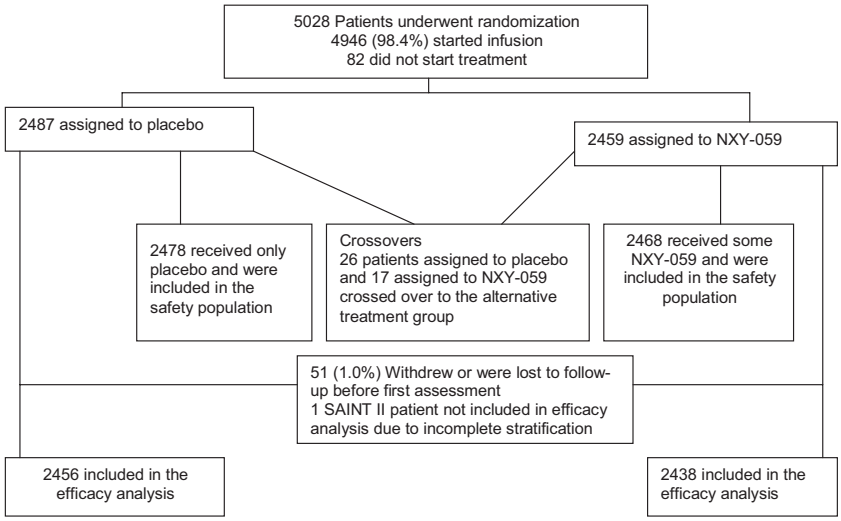

Figure 1. Allocation of patients for this study (combined SAINT II and II).

Patients and Methods

Study Design

SAINT I and II were 2 randomized, double blind, placebo-controlled studies that enrolled patients from May 2003 through June 2006. The trials included 498 centers from 38 countries, with local or national institutional ethics review board approval as appropriate. Patients were randomized only if informed consent was obtained from the patient or, if the patient was unable to consent, from an acceptable surrogate.

The design and conduct of the 2 SAINT studies were developed by a steering committee comprising stroke experts from Europe, North America, and Australia. The steering committee had complete access to all data and was responsible for writing the manuscript. An independent data safety monitoring committee was responsible for safety reviews and futility analysis. The sponsor, AstraZeneca, was responsible for operational aspects of the trial, including collecting and storing the data and performing the analysis according to the approved statistical analysis plan.

Patients

Patients were eligible for enrollment if they were 18 years or older and had a clinical diagnosis of acute ischemic stroke within 6 hours of symptom onset. They had to score at least 6 on the National Institutes of Health Stroke Scale (NIHSS)[7] with at least 2 points for limb weakness. All patients received appropriate routine stroke care as per local treatment practices, including alteplase for eligible patients presenting <3 hours from onset; patients receiving alteplase had to commence the study drug within 30 minutes of completion of the alteplase infusion.

Table 1. Demographic Characteristics of Patients Included in the Safety Analysis (SAINT I and II)

Parameter	NXY-059 n=2468	Placebo n=2478
Sex		
Male	1373 (55.6%)	1342 (54.2%)
Female	1095 (44.4%)	1136 (45.8%)
Age, y		
Median	71.0	71.0
Race		
White	2120 (85.9%)	2141 (86.4%)
Black	93 (3.8%)	75 (3.0%)
Oriental	213 (8.6%)	210 (8.5%)
Other	42 (1.7%)	52 (2.1%)
BMI, kg/m^2		
Median	26.4	26.3
Weight, kg		
Median	75.0	75.0

Study Intervention

Patients were randomly assigned by a computer-generated coding system to receive an intravenous infusion of either NXY-059 or placebo. Sites were required to maintain an average time to start of the study drug infusion of <4 hours. Randomization was stratified according to country, NIHSS score at baseline, side of infarction, and intention to treat with alteplase. AstraZeneca supplied the study drug as a concentrate to be diluted to 15 mg/mL in 500 mL of 0.9% saline solution. Matching placebo was handled similarly. The initial infusion rate (bolus) was 2270 mg/h and was reduced after 1 hour to 480 to 960 mg (32 to 64 mL) per hour for a further 71 hours, with the aim of maintaining a target serum concentration of 260 μmol unbound study drug per liter. The infusion rate was guided by the estimated rate of creatinine clearance based on the serum creatinine concentration[8] and was adjusted to 32 mL/h for a clearance of 30 to 50 mL/min, 44 mL/h for a clearance of 51 to 80 mL/h, and 64 mL/h for values >80 mL/h. Patients with a creatinine clearance of <30 mL/h were withdrawn from treatment.

Clinical Assessment

Patients were assessed at the time of enrollment; 24 and 72 hours after start of the study drug; and on days 7, 30, and 90. Initial assessments included physical examination, neuroimaging, and a NIHSS assessment to determine stroke severity. Examiners were trained and certified in the use of the NIHSS examination (scores range from 0 to 42, with a higher score indicating greater stroke severity).[9]

Assessments after completion of the study drug infusion were primarily functional or neurologic, including the modified Rankin scale (mRS)[10] (days 7, 30, and 90), the NIHSS (days 7 and 90), and the Barthel Index[11] (days 7, 30, and 90). Additional outcome measures included the Stroke Impact Scale and the Euro-QoL 5D. The mRS is a global disability scale with a range from 0, indicating no residual symptoms, to 5, for patients who are bedridden and require constant care. In this study, patients who died were assigned a score of 5 on the mRS. Investigators were trained, tested, and certified in use of the mRS by using a DVD method developed specifically in preparation for this trial.[12] The NIHSS quantifies the level of neurologic deficit, with higher scores at 90 days predictive of dependence.[13] The Barthel Index is an activities-of-daily-living scale ranging from 0 to 100, with 100 indicating independence and 0 indicating complete dependence.

Table 2. Baseline Characteristics of Patients Included in the Safety Analysis (SAINT I and II)

Parameter	NXY-059 n=2468	Placebo n=2478
History of diabetes mellitus	547 (22.2%)	588 (23.7%)
History of hypertension	1834 (74.3%)	1831 (73.9%)
History of and/or atrial fibrillation at admission	678 (27.5%)	768 (31.0%)
History of congestive heart failure at admission	243 (9.8%)	224 (9.0%)
History of ischemic heart disease	806 (32.7%)	820 (33.1%)
History of myocardial infarction	321 (13.0%)	320 (12.9%)
History of arrhythmia	264 (10.7%)	244 (9.8%)
History of previous stroke	482 (19.5%)	497 (20.1%)
History of ischemic stroke	482 (19.5%)	497 (20.1%)
History of transient ischemic attack	288 (5.7%)	133 (5.4%)
Subclassification of stroke*		
Cardioembolic	1098 (44.7%)	1153 (46.7%)
Noncardioembolic	1357 (55.3%)	1316 (53.3%)
History of smoking†		
Nonsmoker	1348 (54.8%)	1419 (57.3%)
Ex-smoker	512 (20.8%)	547 (22.1%)
Occasional smoker	75 (3.0%)	54 (2.2%)
Habitual smoker	526 (21.4%)	455 (18.4%)
Prior use of antiplatelet agent	830 (33.6%)	839 (33.9%)
Prior use of anticoagulants	247 (10.0%)	260 (10.5%)
Plasma glucose at admission, mmol/L‡		
0–2.5	2 (0.1%)	1 (0.0%)
>2.5 to <3.9	14 (0.7%)	17 (0.8%)
≥3.9 to ≤6.1	716 (33.8%)	734 (33.9%)
>6.1 to ≤8.0	823 (38.8%)	805 (37.2%)
>8.0 to ≤10.0	282 (13.3%)	302 (14.0%)
>10.0	283 (13.3%)	304 (14.1%)
Total NIHSS score at baseline¶		
Mean	12.9	12.8
SD	5.5	5.5
Median	12.0	12.0
6–9	877 (35.5%)	892 (36.0%)
10–14	697 (28.2%)	711 (28.7%)
15–19	539 (21.8%)	523 (21.1%)
≥20	355 (14.4%)	352 (14.2%)
Side of infarct		
Right	1318 (53.4%)	1308 (52.8%)
Left	1150 (46.6%)	1169 (47.2%)
Alteplase treatment		
No	1518 (61.5%)	1513 (61.1%)
Yes	950 (38.5%)	965 (38.9%)
Time from onset of stroke to start of infusion, h:min		
Mean	03:46	03:48
SD	00:55	00:57
Median	03:45	03:45
Time from onset of stroke to start of infusion		
0 to ≤2 hours	50 (2.0%)	55 (2.2%)
>2 to ≤3 hours	482 (19.5%)	492 (19.9%)
>3 to ≤4 hours	1137 (46.1%)	1083 (43.7%)
>4 to ≤5 hours	534 (21.6%)	574 (23.2%)
>5 to ≤6 hours	265 (10.7%)	268 (10.8%)
>6 hours	0 (0.0%)	6 (0.2%)

*Based on 2455 patients treated with NXY-059 and 2469 treated with placebo.

†Based on 2461 (NXY-059) and 2475 (placebo) patients.

‡Based on 2120 (NXY-059) and 2163 (placebo) patients.

¶Scores on the NIHSS range from 0, indicating normal functioning, to 42, indicating most severe impairment.

Safety Assessments

Vital signs were recorded at enrollment and at specified times throughout the infusion and follow-up periods. Routine laboratory data and ECGs were performed at the time of enrollment, at 24 and 72 hours, and on day 7 and were analyzed centrally (ECGs at day 7 were performed only if abnormal at 72 hours). To assess any effect of NXY-059 on hemorrhagic transformation after alteplase administration, brain imaging was repeated after 72 hours in patients who were receiving concomitant treatment with alteplase. Symptomatic hemorrhagic transformation was defined as an increase in the NIHSS score of at least 4 points within 36 hours, plus evidence of any blood on neuroimaging after treatment with alteplase. Patients meeting criteria for progressive stroke (NIHSS increase of ≥4 points within 72 hours) or new stroke in the first week were also reimaged. Follow-up scans were read centrally, and readers were blinded to treatment allocation.

Statistical Analysis

The pooled analyses were prespecified and followed the intention-to-treat principle, except that only those patients who commenced any investigational infusion were considered. For efficacy purposes, patients were analyzed according to the intended treatment group. The primary outcome measure was the mRS score at 90 days or on last rating, analyzed across the whole distribution of scores by the Cochran-Mantel-Haenszel test with a modified ridit score, with adjustment for baseline variables of NIHSS score, side of infarct, and alteplase use,[14] the preferred scoring system that produces van Elteren's extension of the Wilcoxon rank-sum test for stratified analyses. Dichotomized and trichotomized mRS results were also analyzed.

The sample size estimations for the 2 SAINT trials were reported previously.[4,6] Deaths were included within the worst outcome category (mRS score=5). Neurologic function was assessed by the total NIHSS score, the first secondary end point, at 90 days or on last rating, and was analyzed with the Cochran-Mantel-Haenszel test with a modified ridit score and adjusted for baseline variables of NIHSS score, side of infarct, and alteplase use.

Analysis of efficacy outcomes was ordered hierarchically. This avoided the need for further adjustment for multiplicity because formal statistical testing was performed only when the preceding end point was significant. The primary end point mRS score was the first

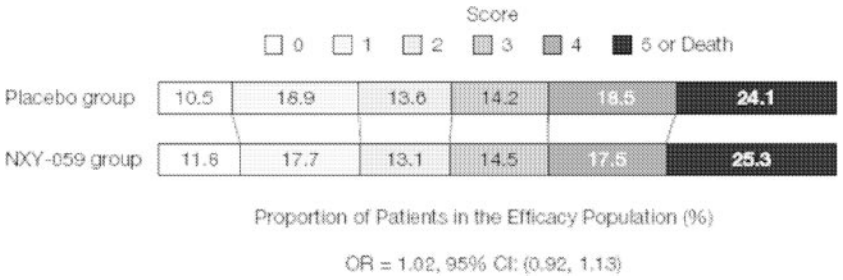

Figure 2. Primary outcome at 90 days, according to scores on the mRS, in the intention-to-treat analysis.

in the hierarchy of outcomes, and a positive result would have been declared if this was significant, irrespective of end points lower in the hierarchy.

Safety end points included mortality, serious and nonserious adverse events, laboratory parameters, vital signs, and neuroimaging data. The incidence of intracranial hemorrhage in patients who were treated concomitantly with alteplase was prospectively analyzed by the χ^2 test. Descriptive statistics (number and frequency) were summarized for all intracranial hemorrhages for each treatment group.

Prospectively identified prognostic/risk factors were entered into a logistic-regression model with mRS score at day 90 as the response variable. With the stepwise selection method within the PROC LOGISTIC computational environment in SAS, predictors of the response variable were retained in the model if the 0.05 significance level criterion was met. The selected model was refitted with the addition of a main effects interaction, and goodness of fit was assessed with the deviance criterion calculated from the observed and expected frequencies of the response variable. Odds ratios (ORs) and 95% CIs were obtained from exponents of the parameter estimates. Percent change was calculated from 100(OR−1) for interpretation of the ORs.

Results

Baseline Characteristics

Of the 5028 patients randomized, 4946 patients received study treatment, with 2468 patients treated with NXY-059 and 2478 treated with placebo (Figure 1). The numbers of crossovers and of patients who withdrew from the study are shown in Figure 1. Demographic and baseline characteristics are shown in Tables 1 and 2. The mean time from onset of symptoms to start of study drug infusion was 3 hours, 47 minutes. One thousand nine hundred fifteen patients (38.7%) received treatment with alteplase. Of the 1876 NXY-059–treated patients with plasma concentration data, 1803 (96.1%) reached a plasma concentration of 150 μmol/L or greater, well above the levels that were shown to be neuroprotective in animal models of stroke.

Clinical Outcomes

The distribution of scores on the mRS at 90 days was similar in both groups (P=0.682, n=4894, Cochran-Mantel-Haenszel test; OR for favorable outcome=1.02; 95% CI, 0.92 to 1.13; Figure 2). Analysis of the per-protocol group, patients who completed at least 75% of the infusion and who complied fully with the protocol, also did not show any significant difference between the 2 groups (Cochran-Mantel-Haenszel test, P=0.733; OR=1.02; 95 CI, 0.91 to 1.13). There were no significant effects noted at 7 and 30 days between the NXY-059– and placebo-treated groups.

There was no effect of NXY-059 on any of the prespecified secondary end points. The total NIHSS score at last rating in the NXY-059 group was not significantly different from that in the placebo-treated group (Cochran-Mantel-Haenszel test, P=0.726; Mann-Whitney rank statistic, 0.50; 95% CI, 0.48 to 0.52). In addition, there was no difference in the percentage of patients who made a complete recovery (NIHSS score of 0 vs 1 to 42: 18.2% in the NXY-059– vs 16.9% in the placebo-treated group). There was no difference in the proportion of patients attaining a Barthel Index score of 95 or more between the NXY-059–treated and the placebo treated group (43.3% NXY-059 vs 40.8% placebo). Finally, there was no difference in mortality (Figure 3).

In our prespecified analysis of patients treated with alteplase, there were no significant differences in the percentage of patients who developed symptomatic (4.1% vs 5.6%,

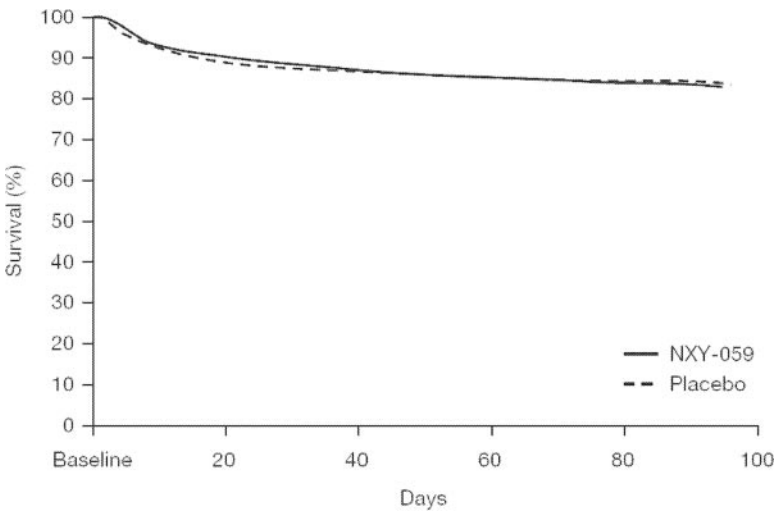

Figure 3. Survival curves. The number of deaths in the NXY-059 group (267, or 16.6%) was virtually identical to that among placebo-treated patients (266, or 16.4%).

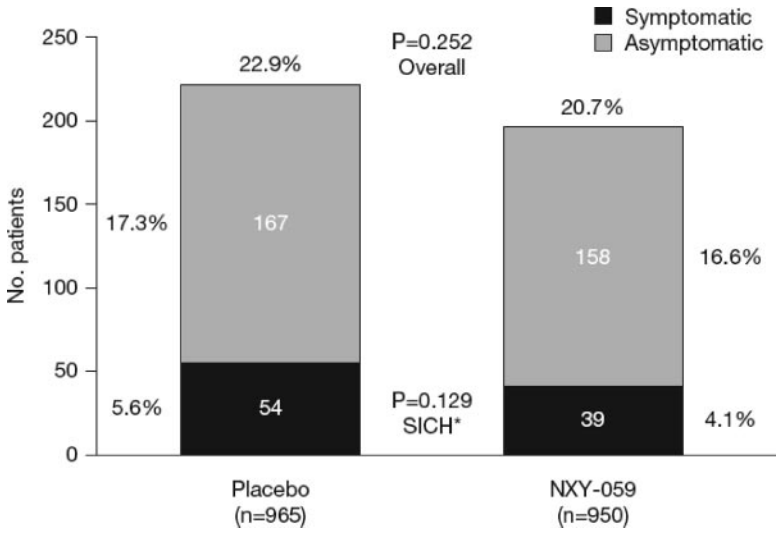

Figure 4. Occurrence of symptomatic (SICH) and asymptomatic intracranial hemorrhages in patients treated with alteplase, depending on assignment to NXY-059 or placebo.

NXY-059 vs placebo, $P=0.129$), asymptomatic (16.6% vs 17.3%, NXY-059 vs placebo, $P=0.694$), or overall combined (20.7% vs 22.9%, NXY-059 vs placebo, $P=0.252$; Figure 4) cerebral hemorrhages. There were no interactions between the treatment effect of NXY-059 and the time from stroke onset to treatment (<4 hours vs ≥4 hours), the severity of stroke (based on NIHSS score), or the use of alteplase (Figure 5).

Subgroup Analyses

Logistic-regression analysis identified 6 baseline characteristics as predictors of outcome. These are shown in Table 3. As expected, an increase in the severity of stroke and age were the most important factors for poor outcome. Left-sided infarcts had a better prognosis. Increased neutrophil count as a sign of ongoing inflammation predicted poor outcome. Higher glucose values also predicted poor outcome.

Intake of antiplatelet medication has been associated with a better outcome in some studies or case-control series. Therefore, we compared stroke severity at baseline, measured by the NIHSS, between patients on (n=1669) and off (n=3266) antiplatelet treatment at randomization. The analysis took possible confounders into consideration. There was no difference between the patient categories (OR=0.80; 95% CI, −1.68 to 0.08; $P=0.08$).

We analyzed whether very high or very low blood pressure (BP) had an influence on outcome. Low BP was defined as <120/80 mm Hg or >160/100 mm Hg, and the outcome considered was the mRS score. There were 689 patients (15.1%) whose BP fell outside the normal range and 3880 (84.9%) whose BPs were within the normal range. Five hundred sixty (12.4%) had an increase in systolic BP of >20 mm Hg in the first 48 hours. The marginally better outcome with a normal-range BP (OR=1.16; 95% CI, 0.97 to 1.38) was not significant ($P=0.095$).

We considered whether during the first 48 hours increases in BP of >20 mm Hg or decreases of >30 mm Hg had an influence on outcome. The estimated effect on the final mRS score, adjusted for the baseline predictors, indicated a numerically better outcome in patients not experiencing a BP increase, but the effect was not statistically significant (OR=1.17; 95% CI, 096 to 1.41; $P=0.12$).

Finally, we dichotomized patients according to admission blood glucose, with 160 mg/dL (8.8 mmol/L) as the cutpoint. The 846 patients who had blood glucose levels above the cutpoint had a poorer prognosis than did the 3397 patients who had normal blood glucose values (OR=1.46; 95% CI, 1.26 to 1.71).

Safety Analysis

There was no difference in mortality for patients treated with NXY-059 (413/2468 (16.7%) compared with placebo (408/2478, or 16.5%) as shown in Figure 4. The most common causes of death were neurologic damage from the initial stroke (NXY-059 n=123 [25.4%] vs placebo n=153 [32.5%]) and bronchopneumonia (NXY-059 n=68 [14.0%] vs placebo n=61 [13.0%]). Adverse events were reported in 81.8% of patients in the NXY-059–treated group compared with 82.6% of patients in the placebo-treated group. Serious adverse events were reported in 37.8% of NXY-059–treated and in 39.1% of placebo-treated patients. The proportion of patients who discontinued medication due to adverse events was 4.7% for NXY-059 and 6.6% for placebo. The only adverse event seen more frequently in the NXY-059–treated group was hypokalemia (10.1% vs 7.5%, NXY-059 vs placebo), but this was not associated with cardiac or other complications and resolved by 7 days.

Discussion

The pooled analysis of the SAINT trials presented here confirms neutral results, not only in the overall population but now also in important prespecified subgroups, such as those treated early after stroke or those who were offered alteplase. The trial program for NXY-059 in ischemic stroke was extensive and rigorous. Despite adequate power with a considerable sample size for an acute stroke trial and use of an accepted primary outcome, the mRS score, we failed to confirm the efficacy of NXY-059.

SAINT I showed promising results, with a reduction in global disability,[4,5] and showed benefit in some of the secondary end points. SAINT II with more patients was neutral for the primary and key secondary outcomes. In SAINT I, patients treated with alteplase and NXY-059 had

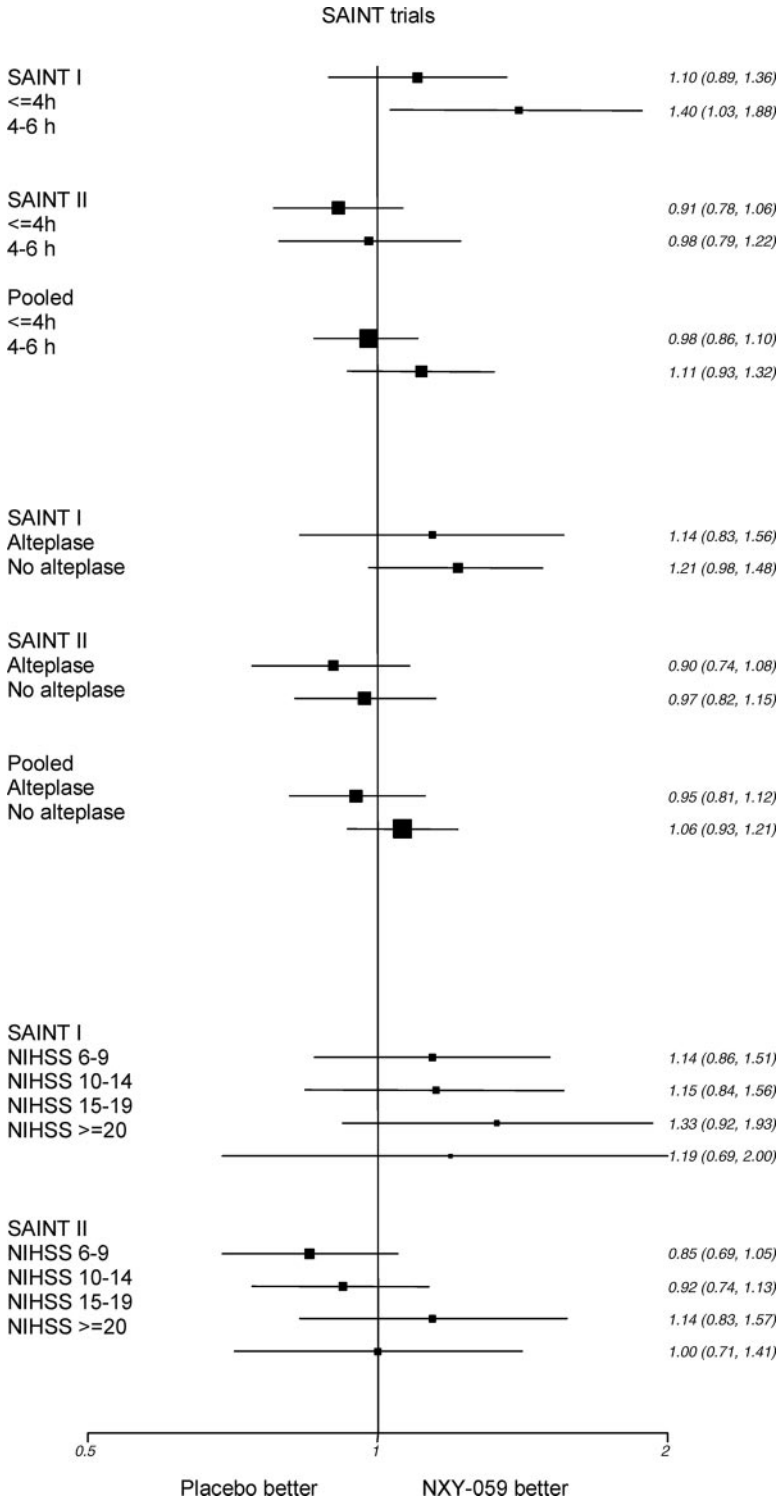

Figure 5. Forest plot of baseline variables, with possible influence on outcome (mRS score), time interval from stroke onset to onset of treatment, use or nonuse of recombinant tissue-type plasminogen activator, and NIHSS score at baseline.

fewer cerebral hemorrhages than did those given placebo,[4] an effect we failed to confirm in SAINT II[6] or in this pooled analysis. NXY-059 had a good safety profile with no difference in mortality and, with the exception of hypokalemia, no other relevant adverse events were observed.

Large clinical trials offer an opportunity to explore subgroups of patients or comorbidities influencing outcome. This is important for the design of future clinical trials.[15,16] We prospectively identified predictors of poor outcome, finding that age and severity of stroke measured by the NIHSS were the most important predictors,[17] followed by neutrophil count and blood glucose value. Systemic and local inflammation[18] is a risk factor for stroke and a predictor of poor outcome.[19] Elevated glucose level and diabetes mellitus are well-known predictors of poor outcome.[20,21] In contrast to earlier studies,[22,21] we were not able to show a protective effect of antiplatelet therapy at the time of the qualifying stroke. We found a trend for poor outcome with both very low and increased

Table 3. Baseline Parameters That Were Identified as Significant Predictors of Outcome (Final mRS, Noncategorized) at 90 Days Based on a Stepwise Search

Baseline Factor	OR Estimate	95% CI	*P* Value
Baseline NIHSS total	0.814	0.80–0.83	<0.0001
Age in years at date of consent	0.964	0.96–0.97	<0.0001
Neutrophils at baseline*	0.944	0.92–0.96	<0.0001
Baseline glucose value, mmol/L	0.934	0.91–0.95	<0.0001
Time from stroke onset to study drug, min	0.997	1.00–1.00	<0.0001
Side of infarction, left	1.277	1.13–1.44	<0.0001

ORs are based on proportional odds across the full mRS. An OR <1 indicates a decrease in the predicted odds of a favorable outcome.

*Continuous variable with 10^9 as the unit.

BP, which was not significant. Other trials have shown a clear influence of BP and BP changes on outcome.[23–25]

The NXY-059 trial program shows how difficult it is to perform trials with neuroprotective substances in acute ischemic stroke. The partly positive result of the first trial, SAINT I, could not be confirmed by the larger SAINT II trial, suggesting that the initially favorable result in SAINT I was likely a chance finding. Other than the larger sample size, the most obvious difference in SAINT II was the higher frequency of alteplase use (44% vs 28.7%).[6] The higher rate of alteplase use in SAINT I is unlikely to explain the different results in the 2 SAINT trials because there was no interaction between alteplase use and NXY-059 effect in either trial. The most probable explanation is an imbalance in baseline factors in SAINT I that favored the active treatment group. Analyzing the known predictors of outcome, we could not identify which baseline variables might have influenced the outcome, and the possibility that the different recombinant tissue-type plasminogen activator use rates explains the difference in the 2 trials cannot be conclusively excluded.

The reduced rate of hemorrhagic transformation associated with NXY-059 after thrombolysis in SAINT I indicated a neuroprotective action of NXY-059.[4] This observation also could not be replicated in SAINT II. Experimental data support the notion that free radicals play an important role in blood–brain barrier damage after stroke by activating matrix metalloproteinases and other proteases.[26,27]

What are the lessons to be learned? Despite following STAIR criteria[28–31] in the development of NXY-059 and using up-to-date study design and statistical methods, the pooled analysis showed no benefit of the active drug. Perhaps data gained from rats and small primates cannot be transferred to the treatment of human stroke. It is not enough simply to move on: rigorous reexamination of the experimental models and data should now be undertaken to explore the role of preclinical data for future candidate treatments. For the time being, the STAIR criteria do not offer a validated means of predicting the results of a neuroprotective trial. Second, we have seen that even a trial of 1700 patients can produce misleading results: we need to consider whether our attention to outcome assessment, though strictly controlled, was sufficiently rigorous. For example, perhaps video recording of outcomes with central adjudication is now required to limit interobserver variation, drift, and bias. We need to explore our management of patients beyond the crucial first few days of acute care to discover whether wide variations in rehabilitation practices conceals useful treatment benefits, not only because we may be abandoning useful approaches unnecessarily but also because such variations may be having a profound adverse effect on outcomes of some groups of patients. Perhaps we need to concentrate less on acute neuroprotection and more on controlling other aspects of care. Third, because even larger trials of acute stroke are required, we need to find ways to limit the paperwork and costs involved so that we can afford to involve more centers, include more patients, and recruit more quickly to trials. Fourth, we might need outcome measures in phase II studies in humans that more resemble the models used in animals, eg, 30-day fluid-attenuated inversion recovery/baseline diffusion-weighted imaging ratio in magnetic resonance imaging. Finally, we should consider whether our selection criteria for trials are allowing the inclusion of patients whose outcomes are not amenable to treatment. Penumbral imaging is being studied elsewhere and offers 1 potential tool. With large patient numbers in the SAINT trials and an onset-to-treatment time of <4 hours, we consider that selection by penumbral imaging would not have concentrated our sample by >30% to 40% and that we should therefore not have diluted a useful treatment effect to undetectable levels.

Most of the preclinical data on NXY-059, as with other neuroprotective drugs evaluated to date, assessed histologic rather than behavioral outcome. The decision to move from phase II to phase III in the NXY-059 program, however, was based on long-term behavioral outcomes in marmosets.[32] Although it is unlikely that this explains the entire discrepancy between preclinical animal studies and the results of clinical trials in stroke patients, it does suggest that we should make the outcome measures in preclinical and clinical trials more congruent. For instance, perhaps we might be able to detect a biologic effect of a drug in humans with more sensitivity by using reduction in infarct size as an outcome measure in phase II studies.[33] The diffusion-weighted imaging/perfusion-weighted imaging concept was not developed enough at the time when phase II of NXY was being conducted. In addition, at that time very few centers in the world had the ability to perform stroke magnetic resonance imaging in the acute setting.

In summary, the clinical program for NXY-059 has reached its conclusion: the treatment had a good safety profile but was ineffective, and we claim no glimmers of hope among subgroups. The field of neuroprotection has suffered a major setback from which it can only recover through rigorous examination of all aspects of the development process. In the meantime, stroke care can still be improved through early restoration of perfusion and consistent application of high standards of care throughout the period of hospitalization and beyond.

Appendix

Steering Committee: K.R. Lees, Glasgow, Scotland (chair; principal investigator of SAINT I); A. Shuaib (principal investigator of SAINT II), Edmonton, Canada; T. Ashwood, Södertälje, Sweden (sponsor representative); A. Davalos, Barcelona, Spain; S. Davis, Melbourne, Australia; H.C. Diener, Essen, Germany; J. Grotta, Houston, Tex; P. Lyden, San Diego, Calif; W. Wasiewski, Wilmington, Del (sponsor representative).

Data and Safety Monitoring Board: S. Pocock, London, England (chair); H. Adams, Iowa City, Iowa; P. Bath, Nottingham, England; D. Oakes, Rochester, NY; N.G. Wahlgren, Stockholm, Sweden; T. Collier (Data and Safety Monitoring Board statistician).

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Disclosures

K.R.L., J.G., and S.M.D. have received fees and expenses from AstraZeneca for steering committee work and lectures but have no financial or related interest in AstraZeneca, Renovis, or NXY-059. A.D. is or has been a consultant or speaker for AstraZeneca, Boehringer Ingelheim, Pfizer, MSD, Sanofi-Synthelabo, BMS, Bayer, Paion, Forest, Daiichi Asubio, Lily, Fujisawa, Novonordisk, and Ferrer International. H.C.D. is or has been a consultant or speaker for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, BASF, Abbott, Novartis, Parke-Davis, MSD, Servier, Sanofi-Synthelabo, Bayer, Fresenius, and Janssen Cilag. P.L. is or has been a consultant or speaker for AstraZeneca, Bayer, Mitsubishi, Pfizer, Lily, and Merck and has held research contracts with AstraZeneca and Bayer. J.G. has received research support from AstraZeneca, NovoNordisk, and Boehringer Ingelheim. A.S. is or has been a consultant or speaker for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Pfizer, Roche, Merck, and Sanofi-Synthelabo. T.A., H.-G.H., V.A., and W.W. are employees of AstraZeneca and hold stock in AstraZeneca. The SAINT trials were sponsored by AstraZeneca. NXY-059 is subject to a partnership agreement between AstraZeneca and Renovis. Renovis had no influence on the conduct, analysis, or interpretation of the study but was permitted to comment on manuscripts. The principal investigators (Profs Lees and Shuaib) assume full responsibility for the integrity and interpretation of the data. The sponsor, AstraZeneca, was responsible for operational aspects of the trial, including collecting and storing the data and performing the analysis according to the approved plan.

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