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Asundexian for Secondary Stroke Prevention

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ABSTRACT

BACKGROUND

Patients with noncardioembolic ischemic stroke or transient ischemic attack (TIA) are at risk for recurrent stroke. Low factor XI levels are associated with a reduced risk of ischemic stroke. Asundexian inhibits activated factor XI. Whether the addition of asundexian to antiplatelet therapy would be superior to antiplatelet therapy alone for the secondary prevention of ischemic stroke is unclear.

METHODS

In this phase 3, double-blind trial, we randomly assigned patients within 72 hours after the onset of a noncardioembolic ischemic stroke or high-risk TIA to receive asundexian (50 mg once daily) or placebo, in addition to planned dual or single antiplatelet therapy. Patients had at least one of the following: a nonlacunar infarct on imaging, a history of atherosclerosis, or evidence of atherosclerotic plaque at any location on cerebrovascular imaging. The primary efficacy outcome was ischemic stroke. The composite of death from cardiovascular causes, myocardial infarction, or stroke was a key secondary outcome. The primary safety outcome was major bleeding.

RESULTS

Among 12,327 patients who underwent randomization (6162 to the asundexian group and 6165 to the placebo group), the incidence of ischemic stroke was lower in the asundexian group than in the placebo group (6.2% vs. 8.4%; cause-specific hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.84; P<0.001). The incidence of the composite of death from cardiovascular causes, myocardial infarction, or stroke was lower in the asundexian group than in the placebo group. The incidence of major bleeding was similar in the asundexian group and the placebo group (1.9% and 1.7%, respectively; cause-specific hazard ratio, 1.10; 95% CI, 0.85 to 1.44). The incidence of adverse events was 69.3% in the asundexian group and 70.1% in the placebo group; the incidence of serious adverse events was 19.2% and 19.5%, respectively.

CONCLUSIONS

Among patients with noncardioembolic ischemic stroke or high-risk TIA treated with antiplatelet therapy, asundexian at a daily dose of 50 mg resulted in lower risks of ischemic stroke and major cardiovascular events than placebo, without a higher risk of major bleeding. (Funded by Bayer; OCEANIC-STROKE ClinicalTrials.gov number, NCT05686070.)

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*A list of the OCEANIC-STROKE investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Despite the use of secondary prevention strategies, 5.1% of patients with an ischemic stroke or transient ischemic attack (TIA) have a recurrent stroke within 1 year.[1] Five years after a minor stroke or TIA, approximately 22% of persons who had survived the event are dead or disabled.[2] The risk is incompletely reduced by antiplatelet therapy.[3,4] Dual antiplatelet therapy for 21 to 90 days is recommended for minor ischemic stroke or TIA, and antiplatelet monotherapy is recommended for moderate-to-severe stroke and long-term treatment.[5,6] Long-term use of dual antiplatelet therapy is associated with a higher risk of major hemorrhage than monotherapy, without a lower risk of stroke.[7]

Factor XI, a coagulation factor, is part of the intrinsic pathway and appears to have a minor role in hemostasis.[8] Genetic factor XI deficiency is associated with a reduced risk of ischemic stroke without an increase in intracerebral bleeding, and increased levels of factor XI are associated with a higher risk of ischemic stroke.[9,10] The apparent dissociation of hemostasis and pathologic thrombosis makes factor XI an attractive therapeutic target for stroke prevention. Asundexian is an inhibitor of activated factor XI; at a dose of 50 mg daily, it inhibits activated factor XI by more than 90%.[11] In a phase 2 trial involving patients with noncardioembolic ischemic stroke, asundexian added to antiplatelet therapy appeared to reduce the occurrence of symptomatic ischemic stroke without a significant increase in the incidence of major or clinically relevant nonmajor bleeding.[12] We designed the Oral Factor Eleven A Inhibitor Asundexian as Novel Antithrombotic Stroke (OCEANIC-STROKE) trial to evaluate the efficacy and safety of asundexian for secondary stroke prevention in patients with ischemic stroke or high-risk TIA.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this phase 3, double-blind, event-driven, randomized, placebo-controlled trial at 702 centers in 37 countries. Relevant health authorities and independent ethics committees approved the trial. Written informed consent was obtained from all the patients or their legally authorized representatives. An independent data and safety monitoring board monitored the trial. The trial was conducted according to the principles of the Declaration of Helsinki and the international ethical guidelines of the Council for International Organizations of Medical Sciences.

Bayer sponsored the trial. The first and last authors, along with representatives from the sponsor and with input from the steering committee, developed the protocol (available with the full text of this article at NEJM.org). Amendments to the protocol are described in the protocol and in Table S1 in the Supplementary Appendix (available at NEJM.org). The steering committee, which included Population Health Research Institute investigators, external experts, trial leaders in each country, and sponsor representatives, oversaw the conduct of the trial. A list of participating investigators and committee members is provided in the Supplementary Appendix. Data were entered by site personnel into an electronic case-record form. The trial database was maintained by the sponsor. Confidentiality agreements were in place between the sponsor and the authors and institutions. These agreements did not limit the authors' access to the data or their ability to analyze, interpret, and report the results independently.

All the data analyses were independently performed at the Population Health Research Institute. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The first draft of the manuscript was written by the first author. Editorial assistance with an earlier version of the manuscript was provided by Prime Group of Companies and supported by Bayer according to Good Publication Practice guidelines. All the authors agreed to submit the manuscript for publication.

ELIGIBILITY

Patients were eligible if they were at least 18 years of age with a noncardioembolic ischemic stroke or high-risk TIA within 72 hours after the onset of symptoms and there was a plan for treatment with dual or single antiplatelet therapy. Patients with ischemic stroke had a maximum score of 15 on the National Institutes of Health Stroke Scale (NIHSS; scores range from 0 to 42, with

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higher scores indicating more severe stroke), and high-risk TIA was defined as an ABCD^2 score of 6 or 7 (on a scale estimating the risk of stroke on the basis of age, blood pressure, clinical features, symptom duration, and the presence of diabetes; scores range from 0 to 7, with higher scores indicating a higher risk of stroke).[13] Patients who had been treated with intravenous thrombolysis or mechanical thrombectomy were permitted to undergo randomization only if at least 24 hours had elapsed since treatment. All the patients had at least one of the following: imaging of the head that showed an acute nonlacunar infarct; a history of atherosclerosis, defined as coronary artery disease, peripheral vascular disease, or documented carotid stenosis of at least 50%; or imaging evidence of cerebrovascular atherosclerosis of any degree involving extracranial or intracranial vessels or the aortic arch. Qualifying atherosclerosis on vascular imaging did not have to be causally or anatomically related to the index event. The stroke subtype was determined by investigators using previously established criteria.[14]

Patients were excluded if they had a history of atrial fibrillation or other condition with an indication for anticoagulation; active nontrivial bleeding, including parenchymal hematoma on cerebral imaging; or a qualifying stroke that was related to a procedure or other specific cause, such as bacterial endocarditis. Additional details of the inclusion and exclusion criteria are available in the protocol.

RANDOMIZATION AND TREATMENTS

Eligible patients were randomly assigned in a 1:1 ratio to receive asundexian (at a dose of 50 mg once daily) or matching placebo, in addition to planned dual or single antiplatelet therapy. Randomization was performed by means of an interactive Web-based system and was stratified according to planned antiplatelet treatment as determined by the treating physician (dual antiplatelet therapy with aspirin and a purinergic receptor Y12 [P2Y12] inhibitor or single antiplatelet therapy). The randomization scheme was generated by the sponsor. On the basis of new pharmacokinetic data, we verified that after protocol amendment 3, asundexian could be crushed before either oral administration or administration by feeding tube (see the Supplementary Appendix). The first dose of asundexian or placebo was to be given as soon as possible and within 4 hours after randomization. Patients who were found to have atrial fibrillation or another indication for anticoagulation after randomization were treated with open-label anticoagulants, and asundexian or placebo was stopped. Patients were followed at 1 month and 3 months and then at 3-month intervals. All the patients, regardless of medication status, were followed to trial completion.

OUTCOMES

The primary efficacy outcome was the first occurrence of ischemic stroke. Ischemic stroke was determined to have occurred if there was a new focal neurologic deficit or clinically meaningful worsening of an existing deficit that persisted for at least 24 hours or was associated with imaging evidence of infarction and was not attributable to a nonischemic cause. The primary safety outcome was major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH); this outcome included fatal bleeding, symptomatic bleeding in a critical area or organ, and clinically overt bleeding that resulted in a decrease in hemoglobin level of at least 2 g per deciliter or that led to the transfusion of at least 2 units of packed red cells or whole blood.[15]

Secondary efficacy outcomes included any stroke (ischemic or hemorrhagic); a composite of death from cardiovascular causes, myocardial infarction, or stroke; a composite of death from any cause, myocardial infarction, or stroke; ischemic stroke in the first 90 days; disabling or fatal stroke; death from any cause; and TIA. Secondary safety outcomes included ISTH major or clinically relevant nonmajor bleeding, symptomatic intracranial hemorrhage, hemorrhagic stroke, fatal bleeding, and minor bleeding. Death from cardiovascular causes was an exploratory outcome. Event definitions and a full list of the outcomes that are included in this article are provided in the Supplementary Appendix. An outcome adjudication committee, whose members were unaware of the trial-group assignments, classified all ischemic and hemorrhagic outcomes.

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STATISTICAL ANALYSIS

After protocol amendment 2, we planned on including 12,300 patients in this event-driven trial and continuing until at least 830 patients had an ischemic stroke confirmed by the adjudication committee. The required number of patients was determined on the basis of the assumption that 6.3% of the patients in the placebo group would have had an event at 12 months, a type I error rate of 5% (two-sided), and 90% power for the trial to achieve a hazard ratio of 0.80. We estimated a trial duration of approximately 30 months until the common end of the treatment period. The original sample size of 9300 was increased on the basis of a blinded review of data that suggested that the original assumptions were not met. An interim analysis for futility was added when 460 patients had had a primary efficacy event.

Analysis of the primary efficacy outcome included all the patients who underwent randomization. To reflect the actual probability of the event of interest over time in the presence of competing risks, Aalen–Johansen estimates of cumulative risk were generated that treated death as the competing event.[16] Cause-specific hazard ratios with 95% confidence intervals were derived from a stratified cause-specific Cox proportional-hazards regression model. The proportional-hazards assumptions of the Cox models were assessed by plots of weighted Schoenfeld residuals over time with the use of a chi-square test.[17] Comparisons were made by means of two-sided stratified log-rank tests. Results are reported as point estimates with 95% confidence intervals.

For efficacy outcomes, the type I error rate was controlled with the use of a hierarchical testing procedure in a prespecified order, as detailed in the protocol. If a test was deemed to be nonsignificant, no testing of subsequent outcomes was performed. All reported P values are two-sided. Subgroup analyses were conducted for the primary efficacy outcome, as prespecified in the protocol and statistical analysis plan.

The analyses of primary and secondary safety outcomes included all the patients who received at least one dose of asundexian or placebo (safety population); these analyses included all the events that occurred between the first intake of asundexian or placebo and up to 2 days after permanent discontinuation of the regimen. Aalen–Johansen estimates of cumulative risk were determined that treated death and premature discontinuation as competing events. No formal hypothesis testing was performed for the safety analyses. Adverse events were tabulated according to the affected system organ class, which was coded in accordance with the *Medical Dictionary for Regulatory Activities*, version 28.1. The widths of the confidence intervals for efficacy and safety outcomes have not been adjusted for multiplicity and should not be used to infer treatment effects.

RESULTS

PATIENTS

From January 2023 through February 2025, a total of 12,578 patients were assessed for eligibility, of whom 12,327 underwent randomization (6162 to the asundexian group and 6165 to the placebo group) (Fig. S1). Asundexian or placebo was never administered to 73 patients. A total of 45 patients withdrew consent, and 39 were lost to follow-up.

The characteristics of the patients at baseline were similar in the two treatment groups (Table 1 and Table S2). The trial population was representative of the population of patients with noncardioembolic stroke (Tables S3 and S4). The mean age of the patients was 68 years, with 3070 patients (24.9%) being older than 75 years of age and with 33.3% of the patients being women. Ischemic stroke was the event at presentation in 11,677 patients (94.7%), with the remaining patients having high-risk TIA. Among the patients who presented with stroke, 3201 (27.4%) received intravenous thrombolysis, endovascular therapy, or both. Dual antiplatelet therapy was planned at randomization in 7712 patients (62.6%). Large-artery atherosclerosis was the most common stroke subtype at presentation, in 4996 patients (42.8%), with 2639 patients (22.6%) having small-vessel occlusion and 3496 (29.9%) having stroke of undetermined cause.

The median follow-up in the trial was 567 days (interquartile range, 377 to 729) after randomization. A total of 1624 of 6124 patients (26.5%) permanently discontinued asundexian, and 1598 of 6130 (26.1%) permanently discontinued placebo (Table S5).

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Asundexian (N = 6162)	Placebo (N = 6165)
Age — yr	67.7±10.8	67.5±10.9
Female sex — no. (%)	2063 (33.5)	2047 (33.2)
Geographic region — no. (%)		
North America	783 (12.7)	782 (12.7)
South America	281 (4.6)	286 (4.6)
Australia, Europe, or Israel	3338 (54.2)	3329 (54.0)
Asia–Pacific	1760 (28.6)	1768 (28.7)
Race — no. (%)†		
White	4105 (66.6)	4078 (66.1)
Black	143 (2.3)	139 (2.3)
Asian	1721 (27.9)	1742 (28.3)
Other	193 (3.1)	206 (3.3)
Index event — no. (%)‡		
Ischemic stroke	5839 (94.8)	5838 (94.7)
High-risk TIA	323 (5.2)	325 (5.3)
Stroke subtype — no./total no. (%)§¶		
Large-artery atherosclerosis	2512/5839 (43.0)	2484/5838 (42.5)
Small-vessel occlusion	1290/5839 (22.1)	1349/5838 (23.1)
Stroke of other determined cause	161/5839 (2.8)	188/5838 (3.2)
Stroke of undetermined cause	1786/5839 (30.6)	1710/5838 (29.3)
Cardioembolism	89/5839 (1.5)	107/5838 (1.8)
Time from index event to randomization — hr	50.5±15.4	50.3±15.4
Intravenous thrombolysis, endovascular therapy, or both — no./total no. (%)¶	1608/5839 (27.5)	1593/5838 (27.3)
Intravenous thrombolysis only	1146/5839 (19.6)	1168/5838 (20.0)
Endovascular therapy only	202/5839 (3.5)	169/5838 (2.9)
Median NIHSS score at randomization (IQR)¶‖	2.0 (1.0–4.0)	2.0 (1.0–4.0)
Planned dual antiplatelet therapy with aspirin and P2Y12 inhibitor at randomization — no. (%)**	3859 (62.6)	3853 (62.5)

* Plus–minus values are means ±SD. IQR denotes interquartile range, P2Y12 purinergic receptor Y12, and TIA transient ischemic attack.
† Race was reported by the patient.
‡ Data on the index event were missing for two patients, both in the placebo group.
§ The stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[14] Data were available for 11,676 patients (5838 in the asundexian group and 5838 in the placebo group).
¶ Data are shown for patients who had ischemic stroke as the index event.
‖ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe stroke. The NIHSS score was available for 11,673 patients (5837 in the asundexian group and 5836 in the placebo group).
** Planned antiplatelet therapy (dual or single) at randomization was a stratification factor.

PRIMARY EFFICACY OUTCOME

Ischemic stroke (the primary outcome) occurred in 384 patients (6.2%) in the asundexian group and in 518 (8.4%) in the placebo group (cause-specific hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.84; P<0.001) (Table 2, Fig. 1A, and Fig. S2A). In the subgroup analysis, the effects of asundexian as compared with placebo were mostly consistent among the subgroups (Fig. 2).

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Table 2. Efficacy Outcomes.*

Outcome	Asundexian (N = 6162)			Placebo (N = 6165)			Cause-Specific Hazard Ratio (95% CI)†	P Value‡
	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)§ %	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)§ %		
Primary efficacy outcome								
Ischemic stroke	384 (6.2)	4.4 (4.0–4.9)	5.1 (4.6–5.7)	518 (8.4)	6.0 (5.5–6.5)	7.0 (6.3–7.6)	0.74 (0.65–0.84)	<0.001
Secondary efficacy outcomes								
Any stroke	404 (6.6)	4.6 (4.2–5.1)	5.3 (4.8–5.9)	545 (8.8)	6.3 (5.8–6.9)	7.3 (6.6–8.0)	0.74 (0.65–0.84)	<0.001
Death from cardiovascular causes, myocardial infarction, or stroke	568 (9.2)	6.6 (6.0–7.1)	7.3 (6.7–8.0)	685 (11.1)	8.0 (7.4–8.6)	9.0 (8.3–9.7)	0.83 (0.74–0.92)	<0.001
Death from any cause, myocardial infarction, or stroke	649 (10.5)	7.5 (6.9–8.1)	8.3 (7.6–9.0)	757 (12.3)	8.8 (8.2–9.4)	9.7 (9.0–10.5)	0.85 (0.77–0.95)	0.003
Ischemic stroke in the first 90 days¶	183 (3.0)	12.4 (10.7–14.2)	3.0 (2.6–3.4)	218 (3.5)	14.8 (12.9–16.8)	3.5 (3.1–4.0)	0.84 (0.69–1.02)	0.08
Disabling or fatal stroke‖	128 (2.1)	1.4 (1.2–1.7)	1.7 (1.4–2.0)	185 (3.0)	2.1 (1.8–2.4)	2.5 (2.1–2.9)	0.69 (0.55–0.87)	—
Death from any cause	248 (4.0)	2.7 (2.4–3.1)	2.8 (2.4–3.3)	253 (4.1)	2.8 (2.4–3.1)	2.7 (2.3–3.2)	0.98 (0.83–1.17)	—
Transient ischemic attack	124 (2.0)	1.4 (1.2–1.6)	1.6 (1.3–1.9)	145 (2.4)	1.6 (1.4–1.9)	1.9 (1.6–2.3)	0.86 (0.67–1.09)	—
Exploratory efficacy outcome								
Death from cardiovascular causes	148 (2.4)	1.6 (1.4–1.9)	1.6 (1.3–2.0)	163 (2.6)	1.8 (1.5–2.1)	1.8 (1.5–2.2)	0.91 (0.73–1.14)	—

* Ischemic stroke included undetermined stroke, any stroke included ischemic and hemorrhagic stroke, and death from cardiovascular causes included death from undetermined causes. Confidence intervals for secondary and exploratory efficacy outcomes are unadjusted for multiplicity and may not be used for inference.

† Cause-specific hazard ratios are estimated from a Cox proportional-hazards model, with stratification according to baseline intention of dual antiplatelet therapy use.

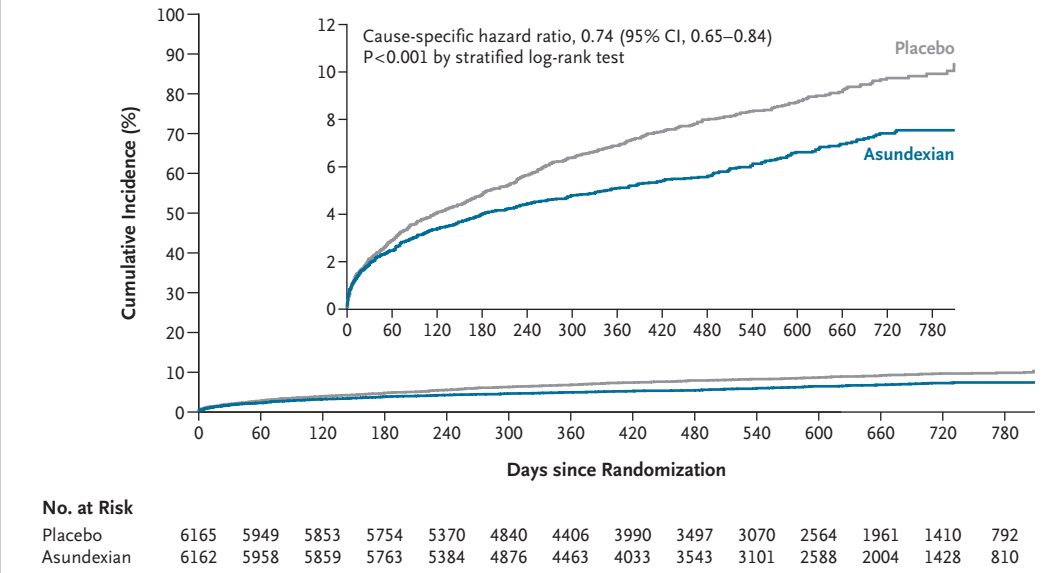
‡ P values were obtained from a log-rank test, with stratification according to baseline intention of dual antiplatelet therapy use. The statistical testing of the null hypotheses for the primary and secondary efficacy outcomes was carried out in a hierarchical order, as presented in the table. Hypothesis testing was to be stopped when a test in the sequence did not reach statistical significance; no P values are provided for outcomes lower in the hierarchy.

§ Cumulative-incidence functions were estimated with the use of Aalen–Johansen estimators, with death treated as the competing event. For death from cardiovascular causes and the composite of death from cardiovascular causes, myocardial infarction, or stroke, death from noncardiovascular causes was the competing event. For death from any cause and the composite of death from any cause, myocardial infarction, or stroke, there was no competing event, and the cumulative incidence is the same as 1 minus the survival function estimated by the Kaplan–Meier method.

¶ For this secondary outcome, the cumulative incidence of ischemic stroke was estimated at day 90.

‖ A disabling stroke was defined as a stroke of any type during the trial associated with a score on the modified Rankin scale of 3 or higher at 90 days after the stroke or an increase of 1 point if the last available modified Rankin scale score before the recurrent stroke event was 3 or higher. Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death).

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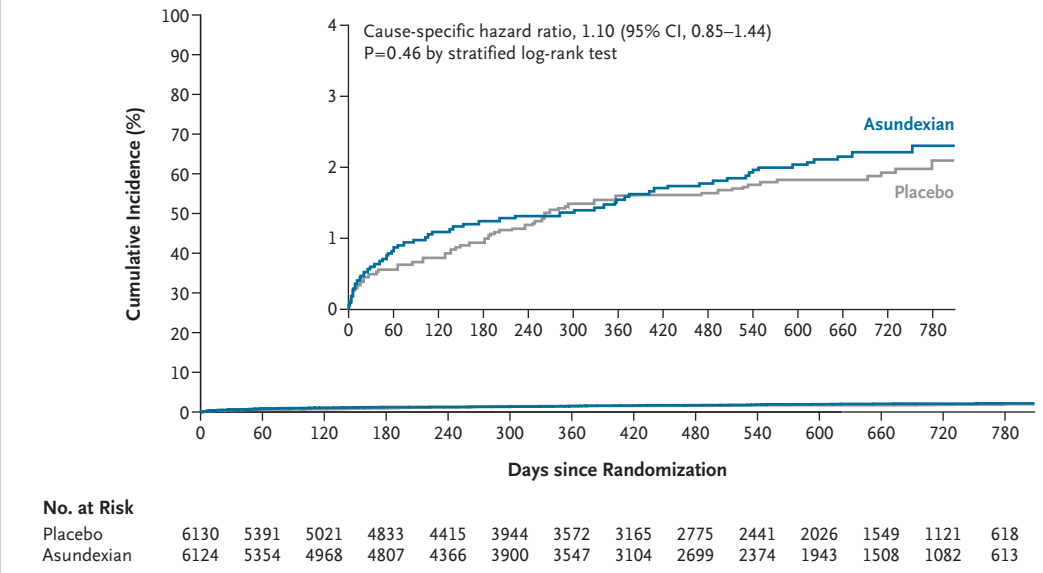
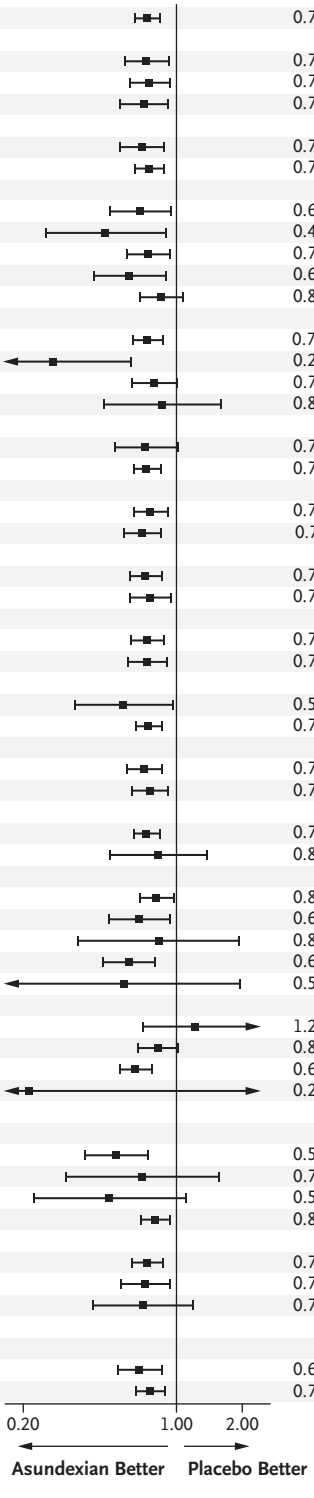


Figure 1. Cumulative Incidence of Ischemic Stroke and ISTH Major Bleeding.

Shown is the cumulative incidence of ischemic stroke (primary efficacy outcome) (Panel A) and of major bleeding defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria (primary safety outcome) (Panel B). Cause-specific hazard ratios are shown (with a competing risk of death for the primary efficacy outcome and competing risks of death and premature discontinuation for the primary safety outcome). P values were obtained from a log-rank test with stratification according to baseline intention of dual antiplatelet therapy use. Cumulative-incidence curves were estimated by the Aalen–Johansen method, with truncation at day 820. Analyses were performed for the full follow-up time; the maximum follow-up in the trial was 957 days for ischemic stroke and 958 days for major bleeding. In both panels, the inset shows the same data on an expanded y axis.

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Subgroup	Asundexian	Placebo	Cause-Specific Hazard Ratio (95% CI)
	no. of events/total no. of patients (%)		
Overall	384/6162 (6.2)	518/6165 (8.4)	0.74 (0.65–0.84)
Age			
<65 yr	128/2313 (5.5)	176/2308 (7.6)	0.73 (0.58–0.92)
65–75 yr	152/2318 (6.6)	197/2318 (8.5)	0.76 (0.61–0.94)
>75 yr	104/1531 (6.8)	145/1539 (9.4)	0.72 (0.56–0.92)
Sex			
Female	114/2063 (5.5)	159/2047 (7.8)	0.70 (0.55–0.89)
Male	270/4099 (6.6)	359/4118 (8.7)	0.75 (0.64–0.88)
Geographic region			
North America	60/783 (7.7)	86/782 (11.0)	0.69 (0.50–0.96)
South America	14/281 (5.0)	29/286 (10.1)	0.48 (0.25–0.91)
Australia, Israel, or western Europe	132/2425 (5.4)	175/2419 (7.2)	0.75 (0.60–0.94)
Eastern Europe	42/913 (4.6)	68/910 (7.5)	0.62 (0.42–0.91)
Asia–Pacific	136/1760 (7.7)	160/1768 (9.0)	0.86 (0.68–1.08)
Race			
White	235/4105 (5.7)	314/4078 (7.7)	0.74 (0.63–0.88)
Black	8/143 (5.6)	25/139 (18.0)	0.28 (0.13–0.62)
Asian	123/1721 (7.1)	156/1742 (9.0)	0.79 (0.63–1.01)
Other	18/193 (9.3)	23/206 (11.2)	0.86 (0.47–1.60)
Hypertension before randomization			
No	58/1225 (4.7)	84/1297 (6.5)	0.73 (0.52–1.02)
Yes	326/4937 (6.6)	434/4868 (8.9)	0.74 (0.64–0.85)
Diabetes before randomization			
No	214/4028 (5.3)	281/4050 (6.9)	0.77 (0.64–0.92)
Yes	170/2134 (8.0)	237/2115 (11.2)	0.70 (0.58–0.86)
History of stroke or TIA before index event			
No	238/4852 (4.9)	325/4820 (6.7)	0.73 (0.61–0.86)
Yes	146/1310 (11.1)	193/1345 (14.3)	0.77 (0.62–0.95)
Medical history of atherosclerosis			
No	224/4172 (5.4)	300/4165 (7.2)	0.74 (0.62–0.88)
Yes	160/1990 (8.0)	218/2000 (10.9)	0.74 (0.60–0.91)
Vascular imaging evidence of atherosclerosis			
No	23/528 (4.4)	40/550 (7.3)	0.58 (0.35–0.97)
Yes	361/5634 (6.4)	478/5615 (8.5)	0.75 (0.66–0.86)
Acute nonlacunar infarct on imaging of head			
No	193/3173 (6.1)	266/3158 (8.4)	0.72 (0.60–0.86)
Yes	191/2989 (6.4)	252/3007 (8.4)	0.76 (0.63–0.92)
Type of index event			
Ischemic stroke	358/5839 (6.1)	485/5838 (8.3)	0.73 (0.64–0.84)
TIA	26/323 (8.0)	33/325 (10.2)	0.83 (0.49–1.38)
Stroke subtype			
Large-artery atherosclerosis	203/2512 (8.1)	247/2484 (9.9)	0.82 (0.68–0.98)
Small-vessel occlusion	59/1290 (4.6)	90/1349 (6.7)	0.68 (0.49–0.94)
Stroke of other determined cause	9/161 (5.6)	13/188 (6.9)	0.84 (0.36–1.96)
Stroke of undetermined cause	83/1786 (4.6)	127/1710 (7.4)	0.61 (0.46–0.81)
Cardioembolism	4/89 (4.5)	8/107 (7.5)	0.58 (0.17–1.95)
Time from index event to randomization			
≤24 hr	27/335 (8.1)	24/356 (6.7)	1.22 (0.70–2.11)
>24–48 hr	152/2190 (6.9)	181/2150 (8.4)	0.83 (0.67–1.03)
>48–72 hr	204/3592 (5.7)	310/3630 (8.5)	0.66 (0.55–0.78)
>72 hr	1/45 (2.2)	3/29 (10.3)	0.22 (0.02–2.08)
Intravenous thrombolysis or endovascular therapy for index stroke			
Intravenous thrombolysis only	54/1146 (4.7)	99/1168 (8.5)	0.54 (0.39–0.75)
Endovascular therapy only	11/202 (5.4)	13/169 (7.7)	0.71 (0.32–1.57)
Intravenous thrombolysis and endovascular therapy	9/260 (3.5)	18/256 (7.0)	0.50 (0.22–1.11)
Neither intravenous thrombolysis nor endovascular therapy	284/4231 (6.7)	355/4245 (8.4)	0.80 (0.69–0.94)
NIHSS score for index stroke at randomization			
≤3	240/4087 (5.9)	321/4079 (7.9)	0.74 (0.63–0.87)
4–7	95/1385 (6.9)	130/1375 (9.5)	0.73 (0.56–0.95)
≥8	23/365 (6.3)	33/382 (8.6)	0.71 (0.41–1.20)
Planned dual antiplatelet therapy with aspirin and a P2Y12 inhibitor			
No	119/2303 (5.2)	174/2312 (7.5)	0.68 (0.54–0.86)
Yes	265/3859 (6.9)	344/3853 (8.9)	0.77 (0.65–0.90)



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SECONDARY EFFICACY OUTCOMES

Efficacy outcomes are shown in Table 2. Ischemic or hemorrhagic stroke occurred in 404 patients (6.6%) in the asundexian group, as compared with 545 patients (8.8%) in the placebo group (cause-specific hazard ratio, 0.74; 95% CI, 0.65 to 0.84; P<0.001). Death from cardiovascular causes, myocardial infarction, or stroke occurred in 568 patients (9.2%) in the asundexian group, as compared with 685 patients (11.1%) in the placebo group (cause-specific hazard ratio, 0.83; 95% CI, 0.74 to 0.92; P<0.001). Death from any cause, myocardial infarction, or stroke occurred in 649 patients (10.5%) in the asundexian group, as compared with 757 patients (12.3%) in the placebo group (cause-specific hazard ratio, 0.85; 95% CI, 0.77 to 0.95; P=0.003).

The risk of ischemic stroke in the first 90 days was not significantly lower in the asundexian group than in the placebo group (183 patients [3.0%] and 218 patients [3.5%], respectively; cause-specific hazard ratio, 0.84; 95% CI, 0.69 to 1.02; P=0.08). Consequently, further hypothesis testing was not conducted. The incidence of disabling or fatal stroke was 2.1% in the asundexian group and 3.0% in the placebo group (cause-specific hazard ratio, 0.69; 95% CI, 0.55 to 0.87). The risks of death from any cause and of death from cardiovascular causes were similar in the trial groups. The net clinical benefit outcomes are shown in Table S6.

BLEEDING AND ADVERSE EVENTS

ISTH major bleeding occurred in 117 of 6124 patients (1.9%) who received asundexian and in 107 of 6130 patients (1.7%) who received placebo (cause-specific hazard ratio, 1.10; 95% CI, 0.85 to 1.44; P=0.46) (Table 3, Fig. 1B, Fig. S2B, and Table S7). A total of 339 patients (5.5%) who received asundexian and 307 (5.0%) who received placebo had major or clinically relevant nonmajor bleeding (cause-specific hazard ratio, 1.12; 95% CI, 0.96 to 1.30; P=0.16). The incidence of other secondary safety outcomes, including symptomatic intracranial hemorrhage, hemorrhagic stroke, fatal bleeding, and minor bleeding, was similar in the two trial groups.

The incidence of adverse events was 69.3% in the asundexian group and 70.1% in the placebo group. Serious adverse events were reported in 1177 patients (19.2%) who received asundexian and in 1196 (19.5%) who received placebo. Details of serious adverse events and adverse events according to system organ class are shown in Tables S8 and S9, respectively.

Figure 2 (facing page). Subgroup Analyses of the Primary Efficacy Outcome: Ischemic Stroke.

Shown are subgroup analyses for the primary efficacy outcome, ischemic stroke. Cause-specific hazard ratios are shown (with a competing risk of death). Confidence intervals are not adjusted for multiplicity and may not be used for inference. Race was reported by the patient. The stroke subtype was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. National Institutes of Health Stroke Scale (NIHSS) scores range from 0 to 42, with higher scores indicating more severe stroke. Arrows indicate that the confidence interval extends outside the graphed area. P2Y12 denotes purinergic receptor Y12, and TIA transient ischemic attack.

DISCUSSION

Among patients with noncardioembolic stroke or high-risk TIA who were taking antiplatelet therapy and treated within 72 hours after symptom onset, the risk of ischemic stroke was lower with asundexian than with placebo (6.2% vs. 8.4%), without a higher risk of major bleeding. The annualized rate of ischemic stroke was approximately that expected in this population (6.0 events per 100 patient-years in the placebo group).[1] Patients in the asundexian group also had a lower risk of the composite of death from cardiovascular causes, myocardial infarction, or stroke than those in the placebo group. Our results are consistent with those of epidemiologic and mendelian randomization studies that have shown a correlation between factor XI levels and the occurrence of ischemic stroke, with lower levels of factor XI associated with a reduced risk.[9,10,18]

The risk of major bleeding was not higher with asundexian added to antiplatelet therapy than with placebo, and the risks of symptomatic intracranial hemorrhage, hemorrhagic stroke, and fatal bleeding were similar to those observed with placebo. Our findings are consistent with the results of a phase 2 stroke trial that showed no increase in the risk of major bleeding

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Table 3. Safety Outcomes.*

Outcome	Asundexian (N = 6124)			Placebo (N = 6130)			Cause-Specific Hazard Ratio (95% CI)†
	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)‡	No. of Patients (%)	No. of Events/ 100 Patient-Yr (95% CI)	Cumulative Incidence at 1 Yr (95% CI)‡	
Primary safety outcome							
ISTH major bleeding	117 (1.9)	1.6 (1.4–2.0)	1.6 (1.3–1.9)	107 (1.7)	1.5 (1.2–1.8)	1.6 (1.3–2.0)	1.10 (0.85–1.44)
Secondary safety outcomes							
ISTH major or clinically relevant nonmajor bleeding	339 (5.5)	4.9 (4.4–5.4)	4.8 (4.3–5.4)	307 (5.0)	4.4 (3.9–4.9)	4.4 (3.9–4.9)	1.12 (0.96–1.30)
Clinically relevant nonmajor bleeding	231 (3.8)	3.3 (2.9–3.8)	3.3 (2.9–3.8)	210 (3.4)	3.0 (2.6–3.4)	2.9 (2.5–3.4)	1.11 (0.92–1.34)
Symptomatic intracranial hemorrhage, including intracerebral hemorrhage	41 (0.7)	0.6 (0.4–0.8)	0.5 (0.4–0.7)	36 (0.6)	0.5 (0.3–0.7)	0.5 (0.4–0.7)	1.15 (0.74–1.80)
Hemorrhagic stroke	13 (0.2)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	20 (0.3)	0.3 (0.2–0.4)	0.3 (0.2–0.5)	0.66 (0.33–1.32)
Fatal bleeding	14 (0.2)	0.2 (0.1–0.3)	0.1 (0.1–0.3)	8 (0.1)	0.1 (0.0–0.2)	0.1 (0.1–0.2)	1.77 (0.74–4.23)
Minor bleeding	479 (7.8)	7.2 (6.5–7.8)	6.8 (6.1–7.4)	512 (8.4)	7.6 (7.0–8.3)	7.4 (6.7–8.0)	0.94 (0.83–1.07)

* Confidence intervals are unadjusted for multiplicity and may not be used for inference. ISTH denotes International Society on Thrombosis and Haemostasis.
† Cause-specific hazard ratios were estimated from a Cox proportional-hazards model, with stratification according to baseline intention for dual antiplatelet therapy use (dual or single antiplatelet therapy).
‡ Cumulative-incidence functions were estimated with the use of Aalen–Johansen estimators, with death and premature discontinuation treated as competing events. For fatal bleeding, death from non–bleeding-related events and premature discontinuation were treated as competing events.

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or clinically relevant nonmajor bleeding with asundexian added to antiplatelet therapy.[12] A pooled analysis of phase 2 trials of asundexian suggested that the risk of major bleeding with asundexian was similar to that seen with placebo.[19] Persons who are born with factor XI deficiency have a mild bleeding diathesis with infrequent spontaneous bleeding and no apparent increased risk of intracerebral bleeding as compared with those born without a deficiency.[20-22] The observed lower risk of ischemic stroke without a significant increase in bleeding validates factor XIa as a therapeutic target with the potential to uncouple pathologic thrombosis from hemostasis.

The inclusion of common stroke subtypes (including small-vessel occlusion) suggests that the results are broadly applicable to patients with noncardioembolic ischemic stroke. Our trial included patients with higher NIHSS scores and those treated with thrombolytic agents and mechanical thrombectomy, which broadens the generalizability of our results beyond that of trials examining dual antiplatelet therapy for TIA and minor stroke that excluded such patients.[6,23,24]

Previous attempts at combination antithrombotic therapy for long-term secondary stroke prevention have been unsuccessful because of a lack of efficacy, an increased risk of bleeding, or both.[7,25-27] One exception was the demonstration that low-dose rivaroxaban added to aspirin was associated with a lower rate of stroke than aspirin alone among patients with stable atherosclerosis but with an increased rate of major bleeding.[28,29] Although that trial was not a secondary stroke prevention trial, our results showed a similar benefit by combining a clotting factor inhibitor with antiplatelet therapy. Antiplatelet monotherapy is the most common long-term treatment at present. Our results showed that the addition of asundexian is an effective and safe therapeutic option for patients treated with antiplatelet therapy for secondary stroke prevention.

A few limitations of the trial should be considered. First, although the inclusion criteria for stroke severity were broad, the trial included relatively few patients with an NIHSS score of 8 or higher. Second, the percentage of patients who were enrolled after a high-risk TIA, although consistent with that in a prevention trial that enrolled in the early time window (within 72 hours after symptom onset),[23] was low, at approximately 5%. Asundexian or placebo was discontinued by approximately 26% of the patients; however, the percentages of patients who discontinued were similar in the two trial groups and correspond with percentages seen in similar trials.[24,30] The percentage of Black patients enrolled was small (2.3%).

In this placebo-controlled trial, patients with noncardioembolic ischemic stroke or high-risk TIA who had been assigned to receive asundexian with background antiplatelet therapy had a lower risk of subsequent ischemic stroke, without a higher risk of hemorrhagic stroke or major bleeding, than those treated with antiplatelet therapy alone.

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