ORIGINAL ARTICLE

Asundexian versus Apixaban in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Stroke prevention with direct-acting oral anticoagulant agents in patients with atrial fibrillation confers a risk of bleeding and limits their use. Asundexian, an activated factor XI (XIa) inhibitor, is an oral anticoagulant that may prevent strokes with less bleeding.

METHODS

In a phase 3, international, double-blind trial, we randomly assigned high-risk patients with atrial fibrillation in a 1:1 ratio to receive asundexian at a dose of 50 mg once daily or standard-dose apixaban. The primary efficacy objective was to determine whether asundexian is at least noninferior to apixaban for the prevention of stroke or systemic embolism. The primary safety objective was to determine whether asundexian is superior to apixaban with respect to major bleeding events.

RESULTS

A total of 14,810 randomly assigned patients were included in the intention-to-treat population. The mean (±SD) age of the patients was 73.9±7.7 years, 35.2% were women, 18.6% had chronic kidney disease, 18.2% had a previous stroke or transient ischemic attack, 16.8% had received oral anticoagulants for no more than 6 weeks, and the mean CHA_2DS_2-VASc score (range, 0 to 9, with higher scores indicating a greater risk of stroke) was 4.3±1.3. The trial was stopped prematurely at the recommendation of the independent data monitoring committee. Stroke or systemic embolism occurred in 98 patients (1.3%) assigned to receive asundexian and in 26 (0.4%) assigned to receive apixaban (hazard ratio, 3.79; 95% confidence interval [CI], 2.46 to 5.83). Major bleeding occurred in 17 patients (0.2%) who received asundexian and in 53 (0.7%) who received apixaban (hazard ratio, 0.32; 95% CI, 0.18 to 0.55). The incidence of any adverse event appeared to be similar in the two groups.

CONCLUSIONS

Among patients with atrial fibrillation at risk for stroke, treatment with asundexian at a dose of 50 mg once daily was associated with a higher incidence of stroke or systemic embolism than treatment with apixaban in the period before the trial was stopped prematurely. There were fewer major bleeding events with asundexian than with apixaban during this time. (Funded by Bayer; OCEANIC-AF ClinicalTrials.gov number, NCT05643573; EudraCT number, 2022-000758-28.)

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*A complete listing of the OCEANIC-AF steering committee and investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Atrial fibrillation can lead to thromboembolic events, which carry a high risk of permanent disability and death.[1,2] Treatment guidelines[3,4] recommend the use of oral anticoagulation in patients with atrial fibrillation, preferably with direct-acting oral anticoagulants (DOACs) owing to their greater safety and efficacy as compared with those of vitamin K antagonists. Despite these class I recommendations and the better safety profile of DOACs as compared with that of vitamin K antagonists, many patients do not receive anticoagulants owing to their anticipated risk of bleeding or the occurrence of actual bleeding events.[5,6] There is an unmet need for effective anticoagulation that prevents stroke but with a lower risk of bleeding among patients with atrial fibrillation.

Inhibition of factor XI or activated factor XI (XIa) represents a potentially favorable anticoagulation target with the promise of lower bleeding risk than other oral antigcoagulants. Factor XI is activated after initiation of the contact activation pathway by factor XIIa and during the amplification phase after activation by thrombin. Therefore, factor XIa contributes to clot progression and pathologic thrombosis and has less effect on hemostasis owing to its limited role in the initiation phase of the extrinsic pathway.[7] Most persons with factor XI deficiency do not have spontaneous bleeding, hemarthroses, or hematomas and have a lower incidence of cardiovascular events, especially cardioembolic stroke, than persons without factor XI deficiency.[8,9] Several compounds that inhibit factor XIa have been associated with a lower risk of bleeding than DOACs.[10]

Asundexian is a direct, selective inhibitor of factor XIa that is administered orally once daily and has a mean terminal half-life of 16 to 18 hours with less than 15% renal elimination.[11,12] In the phase 2 PACIFIC-AF trial, treatment with asundexian was associated with a lower incidence of bleeding than treatment with apixaban.[13] The primary objective of the OCEANIC-AF trial reported here was to determine whether asundexian at a dose of 50 mg once daily would be at least noninferior to apixaban for the prevention of stroke or systemic embolism, would be superior for bleeding avoidance, and would provide a net clinical benefit in persons with atrial fibrillation at risk for stroke.

METHODS

TRIAL DESIGN AND OVERSIGHT

The OCEANIC-AF trial was a phase 3, international, double-blind, double-dummy, parallel-group, randomized, active comparator–controlled trial that compared the efficacy and safety of the oral factor XIa inhibitor asundexian with apixaban for the prevention of stroke or systemic embolism. The primary efficacy objective was to test the hypothesis that asundexian (50 mg daily) will be at least noninferior to apixaban for prevention of stroke or systemic embolism in patients with atrial fibrillation at risk for stroke. The primary safety objective was to determine whether asundexian is superior to apixaban in reducing major bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH), and in providing a net clinical benefit with respect to a composite of stroke, systemic embolism, or ISTH major bleeding. The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org.

The trial was funded by Bayer. National regulatory authorities and ethics committees at participating centers approved the trial, and all the patients provided written informed consent. An independent data monitoring committee periodically reviewed unblinded trial data and oversaw interim analyses. An international executive committee, led by the second author and last author, and the Duke Clinical Research Institute in collaboration with the sponsor were responsible for trial oversight and the reporting of results (see the Supplementary Appendix, available at NEJM.org, for details). The first author wrote the first draft of the manuscript. All the authors take responsibility for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

TRIAL PATIENTS

Patients were eligible if they were 18 years of age or older, had atrial fibrillation documented by electrocardiography (at baseline or within the previous 12 months) with an indication for indefinite treatment with an oral anticoagulant, and had a CHA_2DS_2-VASc score (range, 0 to 9, with higher scores indicating a greater risk of stroke) of 3 or more for men or 4 or more for women. Patients with a CHA_2DS_2-VASc score of 2 for men or 3 for women were also eligible if they had at least one of the following: an age of 70 years or older; a

previous stroke, transient ischemic attack, or systemic embolism; renal dysfunction with an estimated glomerular filtration rate of less than 50 ml per minute per 1.73 m^2 of body-surface area, calculated with the use of the Chronic Kidney Disease Epidemiology Collaboration equation within 14 days before randomization; a previous episode of nontraumatic major bleeding; current single-agent antiplatelet therapy planned for at least the next 6 months; or no more than 6 consecutive weeks of treatment with an oral anticoagulant before randomization. Full eligibility criteria are detailed in Table S1 in the Supplementary Appendix.

TRIAL PROCEDURES

Eligible patients were screened and underwent randomization within 14 days after screening. Patients were randomly assigned in a 1:1 ratio to receive asundexian at a dose of 50 mg once daily or a standard dose of apixaban (5 mg twice daily with dose reduction to 2.5 mg twice daily in patients with at least two of the following: an age of ≥80 years, a body weight of ≤60 kg, and a serum creatinine level of ≥1.5 mg per deciliter [133 μmol per liter]). Patients in the asundexian group also received a placebo matching apixaban, and those in the apixaban group received a placebo matching asundexian.

Randomization was stratified according to participation in the conventional trial model as compared with a decentralized trial model and current use as compared with no current use of concomitant single-agent antiplatelet therapy planned to continue for at least 6 months after randomization. More information on the decentralized trial model is provided in the Supplementary Appendix. After stratification, patients were randomly assigned to receive asundexian or apixaban in a 1:1 ratio with the use of an interactive Web-response system.

Adherence was monitored by means of drug dispensing and return for each patient. The concomitant use of nonsteroidal antiinflammatory drugs during the trial was strongly discouraged because this has been shown to increase the risk of gastrointestinal bleeding. The use of aspirin, at doses of no more than 100 mg per day, was permitted. Dual antiplatelet therapy (e.g., aspirin with P2Y12 inhibitors) was allowed in instances of acute myocardial infarction or after percutaneous coronary intervention.

END POINTS

The primary efficacy end point was stroke or systemic embolism; the analysis was performed in randomly assigned patients on an intention-to-treat basis. The primary safety end point was ISTH major bleeding[14] in patients who had received at least one dose of asundexian, apixaban, or placebo. The primary measure of net clinical benefit was the composite of stroke, systemic embolism, or ISTH major bleeding.

Secondary efficacy end points included the composite of ischemic stroke or systemic embolism, death from any cause, ischemic stroke, death from cardiovascular causes, and the composite of stroke, myocardial infarction, or death from cardiovascular causes. Secondary safety end points included the composite of ISTH major or clinically relevant nonmajor bleeding, ISTH clinically relevant nonmajor bleeding, hemorrhagic stroke, intracranial hemorrhage, fatal bleeding, and minor bleeding. Gastrointestinal bleeding and Bleeding Academic Research Consortium bleeding classifications were included as exploratory end points. An independent clinical-events classification committee, whose members were unaware of the trial-group assignments, applied the protocol definitions and adjudicated all suspected strokes, systemic embolisms, myocardial infarctions, deaths, and bleeding events.

STATISTICAL ANALYSIS

This trial was event driven, with termination planned once approximately 340 patients had had a primary efficacy end-point event. We assumed that there would be at least the same number of patients with a primary safety end-point event during that time. For 340 events to occur, a total trial population of 18,000 randomly assigned patients was planned.

The trial was powered to assess the noninferiority of asundexian as compared with apixaban for the prevention of stroke or systemic embolism. The planned efficacy analyses assumed a noninferiority margin of 1.5 for the cause-specific hazard ratio (competing event of death) of asundexian as compared with apixaban for the primary end point with a type I error of 0.05 for a two-sided log-rank test and at least 90% power for the noninferiority test under the assumption of a true cause-specific hazard of 1.0. The noninferiority margin of 1.5 for the primary efficacy end point was chosen to preserve at least 50% of the

relative reduction in the risk of stroke or systemic embolism associated with apixaban. An interim analysis was planned when 85 patients were observed to have had a primary efficacy end-point event. There were no prespecified stopping rules.

The primary safety analysis (competing event of death or premature discontinuation) assumed a power of at least 90% for the superiority test with a type I error of 0.045 in a two-sided log-rank test, which reflected the division of superiority testing for safety and efficacy. The type I error for the safety and subsequent comparisons was controlled for multiplicity with the use of the graphical approach.[15] However, owing to early termination of the trial, no formal testing for safety or other end points was conducted.

To estimate the relative change in the instantaneous rate of the occurrence of primary efficacy end-point events among patients assigned to receive asundexian as compared with those assigned to receive apixaban according to the defined estimand, cause-specific hazard ratios and their associated confidence intervals were derived from a stratified cause-specific Cox proportional-hazards regression model. Missing data were assumed to be missing at random. In subgroup analyses, cause-specific hazard ratios were not calculated unless there was at least one event in each of the compared treatment groups. All adverse events were tabulated according to the affected system organ class and preferred term, as coded by the *Medical Dictionary for Regulatory Activities*. Final analyses were confirmed by the Duke Clinical Research Institute with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT RECRUITMENT AND FOLLOW-UP

Between December 5, 2022, and November 19, 2023, a total of 16,436 patients were enrolled and screened at 1035 sites in 38 countries. A total of 14,830 patients were randomly assigned to receive asundexian or apixaban. Owing to Good Clinical Practice violations, 20 patients from one site were excluded before the data were unblinded, leaving a total of 14,810 patients (7415 patients assigned to the asundexian group and 7395 to the apixaban group) available for the intention-to-treat population (Fig. S1), of whom 14,737 received at least one dose of asundexian, apixaban, or placebo.

On November 19, 2023, the independent data monitoring committee recommended to the sponsor and executive committee that the trial be stopped owing to more events involving stroke or systemic embolism in the asundexian group than in the apixaban group. On the same day, the sponsor and trial chairs reviewed the data and concurred, and sites were notified of the trial termination. From November 20, 2023, through February 19, 2024, patients were brought in for trial closeout procedures and to start open-label noninvestigational oral anticoagulation therapy. The efficacy outcome analyses are based on data collected up to November 19, 2023, and the full follow-up data were used for all safety analyses.

BASELINE CHARACTERISTICS

The baseline characteristics and representativeness of the trial population are detailed in Table 1 and Table S2. The mean (±SD) age of the patients was 73.9±7.7 years, 5214 (35.2%) were women, 2493 (16.8%) had previously received oral anticoagulants for no more than 6 weeks, 1485 (10.0%) were receiving concomitant antiplatelet therapy, and the mean CHA_2DS_2-VASc score was 4.3±1.3. A total of 76 patients (0.5%) participated in the decentralized trial program. Coexisting conditions were frequent in the trial population and included chronic kidney disease (2756 patients [18.6%]), heart failure (6929 patients [46.8%]), hypertension (13,123 patients [88.6%]), diabetes mellitus (5470 patients [36.9%]), and previous stroke or transient ischemic attack (2694 patients [18.2%]). Overall, 5401 patients (36.5%) had paroxysmal atrial fibrillation, and 9153 (61.8%) had persistent forms of atrial fibrillation. The median follow-up was 155 days.

EFFICACY END POINTS

Stroke or systemic embolism (the composite primary efficacy end point) occurred in 98 patients (1.3%) assigned to receive asundexian and in 26 (0.4%) assigned to receive apixaban (hazard ratio, 3.79; 95% confidence interval [CI], 2.46 to 5.83) (Fig. 1). Full results for the primary and secondary efficacy end points are presented in Table 2. Death from cardiovascular causes occurred in 48 patients (0.6%) in the asundexian group and in 44 (0.6%) in the apixaban group (hazard ratio, 1.09; 95% CI, 0.72 to 1.64). Death from any cause occurred in 60 patients (0.8%) in the asundexian group and in 71 (1.0%) in the apixaban group

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Asundexian, 50 mg (N=7415)	Apixaban (N=7395)	Total (N=14,810)
Age — yr	73.9±7.7	73.9±7.7	73.9±7.7
Female sex — no. (%)	2656 (35.8)	2558 (34.6)	5,214 (35.2)
Race — no. (%)†			
White	5216 (70.3)	5211 (70.5)	10,427 (70.4)
Asian	2035 (27.4)	2010 (27.2)	4,045 (27.3)
Black	88 (1.2)	95 (1.3)	183 (1.2)
Other	76 (1.0)	79 (1.1)	155 (1.0)
Geographic region — no. (%)			
Eastern Europe	1520 (20.5)	1515 (20.5)	3,035 (20.5)
North America	1405 (18.9)	1406 (19.0)	2,811 (19.0)
South America	400 (5.4)	401 (5.4)	801 (5.4)
Asia	2114 (28.5)	2108 (28.5)	4,222 (28.5)
Western Europe, Australia, or Israel	1976 (26.6)	1965 (26.6)	3,941 (26.6)
Previous use of oral anticoagulant for ≤6 wk — no. (%)‡	1238 (16.7)	1255 (17.0)	2,493 (16.8)
CHA_2DS_2-VASc score§	4.3±1.3	4.3±1.3	4.3±1.3
Type of atrial fibrillation — no. (%)			
First detected	118 (1.6)	134 (1.8)	252 (1.7)
Paroxysmal	2760 (37.2)	2641 (35.7)	5,401 (36.5)
Persistent	1773 (23.9)	1805 (24.4)	3,578 (24.2)
Long-standing persistent	436 (5.9)	428 (5.8)	864 (5.8)
Permanent	2327 (31.4)	2384 (32.2)	4,711 (31.8)
Missing data	1 (<0.1)	3 (<0.1)	4 (<0.1)
Coexisting conditions — no. (%)			
Hypertension	6558 (88.4)	6565 (88.8)	13,123 (88.6)
Hyperlipidemia	4747 (64.0)	4719 (63.8)	9,466 (63.9)
Heart failure	3456 (46.6)	3473 (47.0)	6,929 (46.8)
Coronary artery disease	2496 (33.7)	2452 (33.2)	4,948 (33.4)
Diabetes mellitus	2722 (36.7)	2748 (37.2)	5,470 (36.9)
Chronic kidney disease	1399 (18.9)	1357 (18.4)	2,756 (18.6)
Gastrointestinal bleeding	276 (3.7)	214 (2.9)	490 (3.3)
Anemia	1432 (19.3)	1346 (18.2)	2,778 (18.8)
Stroke or TIA	1389 (18.7)	1305 (17.6)	2,694 (18.2)

* Plus–minus values are means ±SD. The intention-to-treat population included all randomly assigned patients, with the exception of 20 patients from one trial site who were excluded owing to Good Clinical Practice violations. EU denotes European Union, and TIA transient ischemic attack.
† Race was reported by the patients.
‡ Oral anticoagulants included direct-acting oral anticoagulants and warfarin.
§ CHA_2DS_2-VASc scores range from 0 to 9, with higher scores indicating a greater risk of stroke.

(hazard ratio, 0.84; 95% CI, 0.60 to 1.19). Results for the comparison of primary end-point events between patients assigned to receive asundexian and those assigned to receive apixaban across subgroups, including concomitant single antiplatelet therapy, renal function, CHA_2DS_2-VASc score, sex, age, type of atrial fibrillation, previous stroke or transient ischemic

Table 2. Efficacy End Points (Intention-to-Treat Population).*

End Point	Asundexian, 50 mg (N=7415)	Apixaban (N=7395)	Total (N=14,810)	Cause-Specific Hazard Ratio (95% CI)†
Primary efficacy end point: stroke or systemic embolism				
No. of patients (%)	98 (1.3)	26 (0.4)	124 (0.8)	3.79 (2.46–5.83)
Events/100 patient-yr (95% CI)	3.85 (3.13–4.65)	1.02 (0.66–1.44)	2.43 (2.02–2.88)	
Ischemic stroke or systemic embolism				
No. of patients (%)	96 (1.3)	22 (0.3)	118 (0.8)	4.38 (2.76–6.96)
Events/100 patient-yr (95% CI)	3.77 (3.06–4.57)	0.86 (0.54–1.26)	2.31 (1.92–2.75)	
Death from any cause				
No. of patients (%)	60 (0.8)	71 (1.0)	131 (0.9)	0.84 (0.60–1.19)
Events/100 patient-yr (95% CI)	2.34 (1.78–2.97)	2.77 (2.17–3.45)	2.56 (2.14–3.01)	
Ischemic stroke				
No. of patients (%)	85 (1.1)	21 (0.3)	106 (0.7)	4.06 (2.52–6.54)
Events/100 patient-yr (95% CI)	3.34 (2.67–4.08)	0.82 (0.51–1.21)	2.08 (1.70–2.49)	
Death from cardiovascular cause				
No. of patients (%)	48 (0.6)	44 (0.6)	92 (0.6)	1.09 (0.72–1.64)
Events/100 patient-yr (95% CI)	1.87 (1.38–2.44)	1.72 (1.25–2.26)	1.79 (1.45–2.18)	
MI, stroke, or death from cardiovascular cause				
No. of patients (%)	155 (2.1)	77 (1.0)	232 (1.6)	2.02 (1.54–2.66)
Events/100 patient-yr (95% CI)	6.11 (5.18–7.11)	3.02 (2.38–3.73)	4.56 (3.99–5.16)	

* MI denotes myocardial infarction.
† Cause-specific hazard ratios and their associated 95% confidence intervals were derived from a stratified cause-specific Cox proportional-hazards regression model. These confidence intervals should not be used to reject or not reject the null hypothesis of a treatment effect.

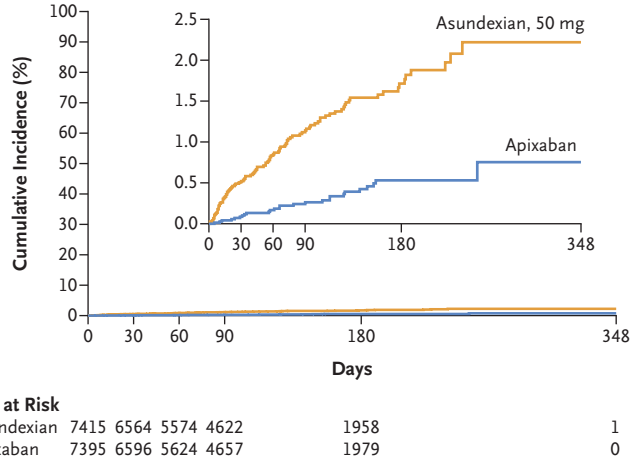

Figure 1. Cumulative Incidence of Stroke or Systemic Embolism.
The inset shows the same data on an expanded y axis.

attack, and no previous oral anticoagulation (≤6 weeks), are shown in Figure S2.

SAFETY END POINTS

In the safety population (at the end of treatment plus 2 days), ISTH major bleeding (the primary safety end point) occurred in 17 patients (0.2%) who received asundexian and in 53 (0.7%) who received apixaban (hazard ratio, 0.32; 95% CI, 0.18 to 0.55) (Fig. 2). The full safety end-point results are shown in Table 3. The composite of ISTH major or clinically relevant nonmajor bleeding occurred in 83 patients (1.1%) in the asundexian group and in 188 (2.6%) in the apixaban group (hazard ratio, 0.44; 95% CI, 0.34 to 0.57). A sensitivity analysis comparing the cumulative incidence of safety end-point events at 180 days had findings similar to those in the main safety analyses (Table S3).

ADVERSE EVENTS

In the full safety population at the end of follow-up (beyond the end of treatment), there were 73 deaths (1.0%) in the asundexian group and 85 (1.2%) in the apixaban group. Any adverse event occurred in 2573 patients (34.9%) in the asundexian group and in 2569 (34.9%) in the apixaban group. Any adverse event leading to discontinuation of the trial drug occurred in 147 patients (2.0%) in the asundexian group and in 118 (1.6%) in the apixaban group (Table S4).

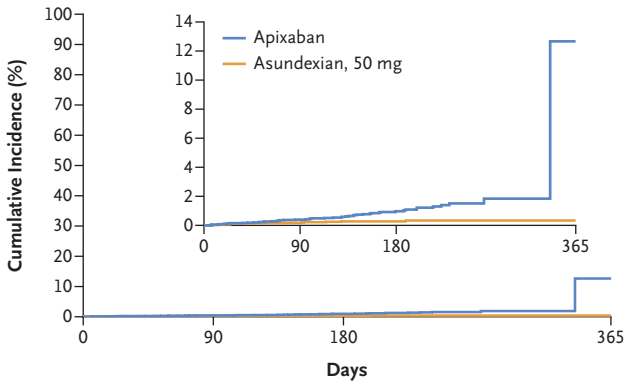

Figure 2. Cumulative Incidence of ISTH Major Bleeding.
The inset shows the same data on an expanded y axis. ISTH denotes International Society on Thrombosis and Haemostasis.

DISCUSSION

In this large, international, double-blind trial, more than 14,000 patients with atrial fibrillation at risk for stroke were randomly assigned to receive the factor XIa inhibitor asundexian or the factor Xa inhibitor apixaban. The trial was stopped prematurely when stroke or systemic embolism occurred in more than three times the number of patients in the asundexian group than in the apixaban group. There were fewer major bleeding events in patients who received asundexian than in those who received apixaban.

There are several notable findings from our trial. First, patients assigned to receive 50 mg of asundexian once daily had a higher incidence of stroke or systemic embolism than those assigned to receive apixaban before the trial was terminated prematurely. This difference was present early from the start of the trial and persisted during follow-up. Second, asundexian appeared to be associated with fewer bleeding events than apixaban. The relevance of this lower incidence of bleeding is unclear. Third, the trial patients, specifically those in the apixaban group, had a lower-than-expected incidence of stroke or systemic embolism on the basis of coexisting conditions and risk factors for stroke.

During the past several years, accumulating evidence has suggested that factor XIa inhibition could be a safer method of anticoagulation than other oral anticoagulants such as vitamin K antagonists and DOACs. Persons with factor XI deficiency have a relatively low incidence of spontaneous bleeding, hemarthroses, or hematoma formation.[16,17] When bleeding does occur in persons with factor XI deficiency, it is usually provoked by trauma, cancer, or surgery, a finding consistent with the role of factor XI in amplification (thrombus growth) but not initiation of clotting (hemostasis).[9,17] Moreover, population studies have shown that reduced factor XI levels are protective against cardiovascular events such as stroke or venous thromboembolism.[8,18] Subsequently, phase 2 trials have shown that inhibition of factor XI or XIa is associated with a lower risk of bleeding than DOAC therapy, including asundexian in the PACIFIC-AF trial and abelacimab in the AZALEA-TIMI 71 trial.[13,19] However, these trials were not designed to ascertain whether these drugs are as effective as DOACs for the prevention of stroke or systemic embolism — the main indication for therapy.

The OCEANIC-AF trial was designed to test the hypothesis that asundexian (50 mg daily) was at least noninferior to apixaban. There are several potential possibilities as to why asundexian at this dose was associated with a higher incidence of stroke or systemic embolism than apixaban. It is possible that factor XIa inhibition with asundexian does not lead to effective stroke prevention as compared with apixaban in patients with atrial fibrillation. Although epidemiologic data suggest that persons with factor XI deficiency have a lower incidence of thrombotic events than those without factor XI deficiency, escape mechanisms may play an important role, especially in patients with atrial fibrillation being transitioned from ongoing oral anticoagulation.

Table 3. Safety End Points (Safety Population).*

End Point	Asundexian, 50 mg (N=7373)	Apixaban (N=7364)	Total (N=14,737)	Cause-Specific Hazard Ratio (95% CI)†
Primary safety end point: ISTH major bleeding				
No. of patients (%)	17 (0.2)	53 (0.7)	70 (0.5)	0.32 (0.18–0.55)
Events/100 patient-yr (95% CI)	0.62 (0.36–0.95)	1.93 (1.45–2.48)	1.28 (1.00–1.60)	
ISTH major or clinically relevant nonmajor bleeding				
No. of patients (%)	83 (1.1)	188 (2.6)	271 (1.8)	0.44 (0.34–0.57)
Events/100 patient-yr (95% CI)	3.07 (2.44–3.76)	6.92 (5.97–7.94)	5.00 (4.42–5.61)	
ISTH clinically relevant nonmajor bleeding				
No. of patients (%)	67 (0.9)	140 (1.9)	207 (1.4)	0.48 (0.36–0.64)
Events/100 patient-yr (95% CI)	2.47 (1.92–3.10)	5.14 (4.32–6.03)	3.81 (3.31–4.35)	
Hemorrhagic stroke				
No. of patients (%)	1 (<0.1)	6 (0.1)	7 (<0.1)	0.17 (0.02–1.42)
Events/100 patient-yr (95% CI)	Not calculated	0.22 (0.08–0.42)	0.13 (0.05–0.24)	
Intracranial hemorrhage				
No. of patients (%)	3 (<0.1)	18 (0.2)	21 (0.1)	0.16 (0.05–0.55)
Events/100 patient-yr (95% CI)	0.11 (0.02–0.27)	0.65 (0.39–0.99)	0.38 (0.24–0.56)	
Fatal bleeding				
No. of patients (%)	0	4 (0.1)	4 (<0.1)	Not calculated
Events/100 patient-yr (95% CI)	Not calculated	0.15 (0.04–0.32)	0.07 (0.02–0.16)	
Minor bleeding				
No. of patients (%)	187 (2.5)	317 (4.3)	504 (3.4)	0.59 (0.49–0.70)
Events/100 patient-yr (95% CI)	7.00 (6.03–8.04)	11.90 (10.62–13.24)	9.44 (8.64–10.29)	
Stroke, systemic embolism, or ISTH major bleeding‡				
No. of patients (%)	120 (1.6)	75 (1.0)	195 (1.3)	1.61 (1.21–2.15)
Events/100 patient-yr (95% CI)	4.42 (3.66–5.24)	2.73 (2.15–3.38)	3.57 (3.09–4.09)	

* The safety population included all randomly assigned patients who had received at least one dose of asundexian, apixaban, or placebo. ISTH denotes International Society on Thrombosis and Haemostasis.
† Cause-specific hazard ratios and their associated 95% confidence intervals were derived from a stratified cause-specific Cox proportional-hazards regression model. These confidence intervals should not be used to reject or not reject the null hypothesis of a treatment effect.
‡ The net clinical benefit end point was a composite of stroke, systemic embolism, or ISTH major bleeding.

Another possibility is that 50 mg of asundexian once daily is not a high enough dose and does not adequately suppress factor XI activity to prevent thromboembolic events in patients with atrial fibrillation. In the PACIFIC-AF trial, asundexian at a dose of 50 mg once daily resulted in a 92% reduction in factor XI activity at trough concentrations and a 94% reduction at peak concentrations. However, to effectively prevent thrombus formation, complete or near complete (>99%) suppression of factor XIa may be required. Phase 2 efficacy-based dose-finding studies involving persons with atrial fibrillation are not possible owing to the low event rates for stroke and systemic embolism. Although persons at risk for venous thromboembolism have been recruited for dose finding with other agents in the past, this approach has had varying effectiveness. Asundexian is a small-molecule inhibitor of factor XIa; whether upstream or combined inhibition of factor XI and factor XIa would lead to effective stroke prevention is unknown.

Finally, it is worth noting that the incidence of ischemic stroke in the apixaban group was significantly lower than that predicted by the CHA_2DS_2-VASc score and that observed in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial performed more than 10 years ago.[20] This result is probably due to continued improvement in the medical treatment of coexisting conditions and use of oral anticoagulation, including a lower burden of atrial fibrillation in contemporary populations of patients with atrial fibrillation who receive more rhythm control than at the time of the DOAC trials. The findings of the OCEANIC-AF trial are probably attributable to a combination of these factors.

More research is needed to determine whether the concept of factor XIa inhibition may become an option for stroke prevention in patients with atrial fibrillation and, if so, in which population and what degree of factor XIa inhibition is necessary to effectively and safely achieve this. Multiple studies with different compounds, doses, and indications are under way, with ongoing oversight by independent data monitoring committees. The findings from these studies should help determine whether inhibition of factor XI or XIa can reduce the occurrence of stroke or systemic embolism in patients with atrial fibrillation.

Our trial has limitations. It was stopped prematurely, and although there were a substantial number of total patient-years of exposure, the follow-up was abbreviated. The number of patients approached for participation is unknown, so we cannot comment on the full generalizability to the overall population of patients with atrial fibrillation. The trial and hypothesis were focused on patients with atrial fibrillation who were at risk for both stroke and bleeding events and who had an indication for indefinite treatment with an oral anticoagulant. Whether asundexian is safe or effective in other populations cannot be determined from these data. Finally, only one dose of asundexian was tested in this phase 3 trial. Whether higher doses with greater degrees of factor XIa inhibition would yield similar results is unknown.

In this trial involving patients with atrial fibrillation at risk for stroke, treatment with asundexian at a dose of 50 mg once daily was associated with a higher incidence of stroke or systemic embolism than treatment with apixaban in the time period before the trial was stopped prematurely. There were fewer major bleeding events with asundexian than with apixaban during this time.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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