JAMA Cardiology | Original Investigation

Asundexian or Apixaban in Patients With Atrial Fibrillation According to Prior Oral Anticoagulant Use

A Subgroup Analysis of the OCEANIC-AF Randomized Clinical Trial

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IMPORTANCE In patients with atrial fibrillation (AF), oral anticoagulants (OACs) reduce the risk of stroke.

OBJECTIVE To investigate if patients with less prior OAC exposure respond differently to a new OAC than patients with more OAC exposure.

DESIGN, SETTING, AND PARTICIPANTS In this prespecified exploratory subgroup analysis of the Oral Factor 11a Inhibitor Asundexian as Novel Antithrombotic–Atrial Fibrillation (OCEANIC-AF) randomized clinical trial, patients enrolled in the OCEANIC-AF trial were categorized as OAC naive or OAC experienced based on whether they had 6 or fewer weeks or more than 6 weeks of prior OAC use. The effect of asundexian vs apixaban was then compared on outcomes among patients who were OAC naive and OAC experienced. The study setting included 1035 sites in 38 countries, and participants were those enrolled in the OCEANIC-AF trial. Data were analyzed from June to July 2024.

INTERVENTIONS Asundexian, a novel factor XIa inhibitor, was compared with apixaban in patients with AF.

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was stroke or systemic embolism. The main safety outcome was major bleeding.

RESULTS Of patients in the OCEANIC-AF trial, 2493 (17%) were OAC naive (mean [SD] age, 72.6 [8.6] years; 1464 male [59%]) and 12 317 (83%) were OAC experienced (mean [SD] age, 74.2 [7.5] years; 8132 male [66%]). In the asundexian arm, patients who were OAC naive had a stroke or systemic embolism rate of 0.8% (10 of 1238) compared with 1.4% (88 of 6177) in those who were OAC experienced. In the apixaban arm, patients who were OAC naive had a stroke or systemic embolism rate of 0.6% (7 of 1255) compared with 0.3% (19 of 6140) in those who were OAC experienced. Thus, patients who were OAC naive had a smaller increase in stroke or systemic embolism with asundexian compared with apixaban (hazard ratio [HR], 1.42; 95% CI, 0.54-3.73) than patients who were OAC experienced (HR, 4.66; 95% CI, 2.84-7.65; *P* for interaction =.03). Bleeding rates were lower among both OAC-naive patients (0.2% [2 of 1228]) and OAC-experienced patients (0.2% [15 of 6145]) assigned asundexian than among OAC-naive patients (1.0% [13 of 1249]) and OAC-experienced patients (0.7% [40 of 6115]) assigned apixaban.

CONCLUSIONS AND RELEVANCE In the OCEANIC-AF randomized clinical trial, patients with AF who were OAC naive had a smaller increase in stroke or systemic embolism and a similar lower rate of bleeding with asundexian compared with apixaban than patients who were OAC experienced. The mechanism of these findings is unknown and deserves further research.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT05643573

JAMA Cardiol. doi:10.1001/jamacardio.2025.0277
Published online March 26, 2025.

Supplemental content

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Oral anticoagulants (OACs) reduce the risk of stroke or systemic embolism in patients with atrial fibrillation (AF) who are at risk of stroke.[1] Retrospective analyses suggest that patients with little or no prior exposure to oral anticoagulation (ie, OAC naive) may be at higher risk for adverse outcomes (thromboembolic events and/or bleeding) than those who are OAC experienced.[2] An individual patient meta-analysis of clinical trials comparing direct OACs and warfarin identified the absence of prior OAC use as a predictor of a greater reduction in stroke or systemic embolism with direct OACs compared with warfarin.[1]

Asundexian, a novel factor XIa inhibitor, produces more than 90% inhibition of factor XIa activity at a dose of 50 mg daily and causes less bleeding than apixaban.[3] The phase 3 Oral Factor 11a Inhibitor Asundexian as Novel Antithrombotic-Atrial Fibrillation (OCEANIC-AF) study evaluated the efficacy and safety of asundexian compared with apixaban and was stopped early because asundexian 50 mg daily was less effective than apixaban at preventing stroke or systemic embolism in patients with AF at risk of stroke.[4] An enrichment criteria for enrollment into the OCEANIC-AF study was 6 or fewer consecutive weeks of prior treatment with an OAC at randomization. Patients enrolled in the OCEANIC-AF study who were already taking an OAC may respond differently to asundexian compared with apixaban than patients who are OAC naive. The objective of this prespecified exploratory subgroup analysis of the OCEANIC-AF study was to assess whether the effects of asundexian compared with apixaban were different in patients who were OAC naive compared with those who were OAC experienced.

Key Points

Question In patients with atrial fibrillation, will those without prior exposure to an oral anticoagulant (OAC) respond differently to a new OAC than patients with OAC exposure?

Findings In this secondary analysis of the Oral Factor 11a Inhibitor Asundexian as Novel Antithrombotic–Atrial Fibrillation (OCEANIC-AF) randomized clinical trial including 2493 participants who were OAC naive and 12 317 who were OAC experienced, compared with those who were OAC experienced, patients who were OAC naive had a smaller increase in stroke or systemic embolism and a similar lower rate of bleeding with asundexian compared with apixaban. Asundexian caused less bleeding than apixaban in both OAC-naive and OAC-experienced patients.

Meaning Results demonstrate that OAC-naive patients had a significantly smaller increase in stroke or systemic embolism with asundexian compared with apixaban than OAC-experienced patients; the mechanism behind these findings is unknown and deserves further research.

Methods

The methods and primary results of the OCEANIC-AF trial have been published (Supplement 1).[4] The OCEANIC-AF trial was an international, multicenter, double-blind, active-controlled, randomized clinical trial comparing the factor XIa inhibitor asundexian with the factor Xa inhibitor apixaban in patients with AF at risk of stroke. Ethics committee or institutional review board approval was obtained at all participating sites. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Patients were eligible for enrollment if they had electrocardiographically documented AF within the past 12 months with a CHA_2DS_2-VASc (indicates congestive heart failure, hypertension, age 75 years or older [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 years, and sex category [female]) score of 3 or greater if male or 4 or greater if female or had a CHA_2DS_2-VASc score of 2 if male or 3 if female with at least 1 of the following enrichment criteria: age 70 years or older; previous stroke, transient ischemic attack, or systemic embolism; kidney dysfunction with an estimated glomerular filtration rate (eGFR) of less than 50 mL/min/1.73 m^2; prior nontraumatic major bleeding; planned antiplatelet therapy for at least 6 months; or 6 or fewer consecutive weeks of prior treatment with an OAC (ie, OAC naive) at the time of randomization. This last criterion was intended to enrich the population for patients at risk for bleeding and is the focus of this analysis. Exclusion criteria included the presence of a mechanical heart valve, mitral stenosis, AF due to a reversible cause, successful AF ablation or left atrial appendage occlusion/exclusion, recent stroke, active bleeding, significant liver disease, severe kidney dysfunction with eGFR less than 25 mL/min/1.73 m^2, and recent major surgery. Race was self-reported by participants and included the following: Asian, Black, White, or other (ie, American Indian, Alaska Native, Native Hawaiian, Other Pacific Islander, and not reported). Race and ethnicity data were collected in the OCEANIC-AF trial because the reporting of race and ethnicity data is required by many national regulatory agencies and medical journals.

Written informed consent was obtained before randomization. After consent, eligible patients were randomly assigned in a 1:1 ratio to receive asundexian 50 mg daily or apixaban according to its label at 5 mg twice daily or 2.5 mg twice daily in patients with 2 or more dose reduction criteria (age ≥80 years, weight ≤60 kg, serum creatinine ≥1.5 mg/dL; to convert to micromoles per liter, multiply by 88.4). Patients previously taking a vitamin K antagonist (VKA) were required to stop their VKA for 10 days before randomization. They could be bridged with a direct OAC or low-molecular-weight heparin if considered indicated by the investigator. Patients previously taking a direct OAC continued their anticoagulant until randomization when they started the study drug (asundexian or apixaban).

The outcomes for this analysis largely paralleled those of the main trial analysis. The primary efficacy outcome was stroke or systemic embolism. The main safety outcome was International Society on Thrombosis and Haemostasis (ISTH) major bleeding. Other efficacy outcomes included ischemic stroke or systemic embolism, ischemic stroke, cardiovascular death, all-cause death, and the composite of cardiovascular death, myocardial infarction, or stroke. Other safety outcomes included ISTH major or clinically relevant nonmajor bleeding, hemorrhagic stroke, fatal bleeding, and any bleeding.

In this prespecified, subgroup analysis, we stratified patients based on whether or not they had 6 or fewer weeks of prior OAC use at the time of enrollment in the OCEANIC-AF

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trial. Patients with 6 or fewer weeks of prior OAC use were classified as OAC naive and those with more than 6 weeks of prior OAC use were classified as OAC experienced.

Statistical Analysis

The baseline characteristics of OAC-naive and OAC-experienced patients were compared. Continuous variables are reported as mean (SD) or median (IQR). Categorical variables are reported as counts (percentages). Differences in baseline characteristics between OAC-naive and OAC-experienced patients were evaluated univariately using a *t* test with Satterthwaite approximation for continuous variables or a χ^2 test for categorical variables and were not multiplicity controlled.

Efficacy outcomes were assessed in the full analysis dataset that included all randomized patients, excluding those from 1 site (n = 20) with Good Clinical Practice violations, and including all events through the end of follow-up irrespective of whether they occurred on study drug. Treatment arms were defined by intention to treat. Missing data were assumed to be missing at random. The effect of asundexian compared with apixaban on efficacy outcomes was assessed among OAC-naive and OAC-experienced patients. To compare the effect of asundexian vs apixaban on efficacy outcomes over time within the OAC-naive and OAC-experienced subgroups, cumulative incidence curves were estimated and hazard ratios (HRs) and 95% CIs reported. Proportional hazards assumptions were assessed. For each efficacy outcome, the interaction between asundexian or apixaban and OAC naive or experienced was tested by including asundexian or apixaban, OAC naive or experienced, and their interaction in a Cox proportional hazards model, and reporting the Wald interaction *P* value.

Safety outcomes were assessed in the as-treated population including all patients who received study drug and all events from the first intake of study drug through 2 days after discontinuation of study drug. The effect of asundexian compared with apixaban on safety outcomes was assessed among OAC-naive and OAC-experienced patients. To compare the effect of asundexian vs apixaban on safety outcomes over time among OAC-naive and OAC-experienced patients, cumulative incidence curves were estimated and HRs and 95% CIs reported. Proportional hazards assumptions were again assessed. For each safety outcome, the interaction between asundexian or apixaban and OAC naive or experienced was tested by including asundexian or apixaban, OAC naive or experienced, and their interaction in a Cox proportional hazards model, and reporting the Wald interaction *P* values. All *P* values were 2-sided, and $P < .05$ was considered statistically significant. All analyses were performed at the Duke Clinical Research Institute in Durham, North Carolina, from June to July 2024, using SAS, version 9.4 (SAS Institute).

Results

Population

Among the overall OCEANIC-AF population, 2493 (17%) were OAC naive (mean [SD] age, 72.6 [8.6] years; 1029 female [41%]; 1464 male [59%]) and 12 317 (83%) were OAC experienced (mean [SD] age, 74.2 [7.5] years; 4185 female [34%]; 8132 male [66%]) (**Table 1** and eFigure in Supplement 2). Among those who were OAC experienced, the most commonly used OAC in the 30 days before randomization was apixaban (5389 [44%]), followed by rivaroxaban (3727 [30%]), edoxaban (1609 [13%]), VKAs (1031 [8%]), and dabigatran (1002 [8%]). In the OAC-naive group, participants self-identified with the following races: 539 Asian (22%), 16 Black (1%), 1904 White (76%), and 34 other (1%). In the OAC-experienced group, participants self-identified with the following races: 3506 Asian (28%), 167 Black (1%), 8523 White (69%), and 121 other (1%).

Baseline characteristics of OAC-naive and OAC-experienced patients are shown in Table 1. Compared with patients who were OAC experienced, patients who were OAC naive tended to be younger, female, of White race, and enrolled in Western Europe, Australia, or Israel (962 [39%] vs 2979 [24%]). They also tended to have fewer comorbidities including less kidney dysfunction/chronic kidney disease (293 [12%] vs 2463 [20%]), heart failure (944 [38%] vs 5985 [49%]), diabetes (814 [33%] vs 4656 [38%]), obstructive sleep apnea (151 [6%] vs 1379 [11%]), and anemia (408 [17%] vs 2370 [20%]) and have more first-diagnosed (193 [8%] vs 59 [1%]) or paroxysmal (1223 [49%] vs 4178 [34%]) AF and less long-standing persistent (51 [2%] vs 813 [7%]) or permanent (371 [15%] vs 4340 [35%]) AF than patients who were OAC experienced. The mean (SD) CHA_2DS_2-VASc score was 4.1 (1.3) in patients who were OAC naive and 4.3 (1.3) in those who were OAC experienced. Within the OAC-naive and OAC-experienced cohorts, the characteristics of patients assigned to asundexian and apixaban were generally well balanced (eTable in Supplement 2). The median (IQR) duration of follow-up from randomization was 147 (84-204) days among OAC-naive patients and 155 (97-212) days among OAC-experienced patients.

Efficacy Outcomes

Efficacy outcomes among patients who were OAC naive and OAC experienced randomized to either asundexian or apixaban are shown in **Table 2**. In the asundexian arm, patients who were OAC naive had a stroke or systemic embolism rate of 0.8% (10 of 1238) compared with 1.4% (88 of 6177) in those who were OAC experienced. In the overall trial, there were more stroke or systemic embolic events with asundexian (1.3% [98 of 7415]) than with apixaban (0.4% [26 of 7395]; HR, 3.79; 95% CI, 2.46-5.83).[4] Among patients who were OAC naive, the rates of stroke or systemic embolism were 0.8% (10 of 1238) with asundexian compared with 0.6% (7 of 1255) with apixaban. Patients who were OAC experienced had a stroke or systemic embolism rate of 1.4% (88 of 6177) with asundexian compared with 0.3% (19 of 6140) with apixaban. Thus, the increase in risk of stroke or systemic embolism with asundexian compared with apixaban was less marked in patients who were OAC naive (HR, 1.42; 95% CI, 0.54-3.73) than in those who were OAC experienced (HR, 4.66; 95% CI, 2.84-7.65; *P* for interaction =.03). Particularly among patients who were OAC experienced, the increase in stroke or systemic embolic events with asundexian, compared with apixaban, appeared in the first few weeks after randomization (**Figure 1**). Although interaction tests were not statistically significant, a similar pattern of events,

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Table 1. Baseline Characteristics of OAC-Naive and OAC-Experienced Patients in the OCEANIC-AF Study

Characteristic	No. (%)		P value
	OAC naive (n = 2493)	OAC experienced (n = 12 317)	
Age, mean (SD), y	72.6 (8.6)	74.2 (7.5)	<.001
Age, y			
<65 y	369 (15)	1076 (9)	<.001
65-75 y	1135 (46)	5723 (46)	
>75 y	989 (40)	5518 (45)	
Sex			
Female	1029 (41)	4185 (34)	<.001
Male	1464 (59)	8132 (66)	
Race			
Asian	539 (22)	3506 (28)	<.001
Black	16 (1)	167 (1)	
White	1904 (76)	8523 (69)	
Other[a]	34 (1)	121 (1)	
Region			
Eastern Europe	523 (21)	2512 (20)	<.001
North America	316 (13)	2495 (20)	
South America	101 (4)	700 (6)	
Asia	591 (24)	3631 (29)	
Western Europe, Australia, and Israel	962 (39)	2979 (24)	
Single antiplatelet therapy >6 mo	320 (13)	1165 (10)	<.001
Moderate kidney dysfunction	329 (13)	2495 (20)	<.001
Major bleeding before randomization	14 (1)	138 (1)	.01
$CHAD_2DS_2$-VASc score, mean (SD)[b]	4.1 (1.3)	4.3 (1.3)	<.001
Type of AF			
First diagnosed	193 (8)	59 (1)	<.001
Paroxysmal	1223 (49)	4178 (34)	
Persistent	654 (26)	2924 (24)	
Long-standing persistent	51 (2)	813 (7)	
Permanent	371 (15)	4340 (35)	
Comorbidities			
Hypertension	2207 (89)	10 916 (89)	.89
Hyperlipidemia	1444 (58)	8020 (65)	<.001
Heart failure	944 (38)	5985 (49)	<.001
Coronary artery disease	782 (31)	4166 (34)	.02
Diabetes	814 (33)	4656 (38)	<.001
Chronic kidney disease	293 (12)	2463 (20)	<.001
Myocardial infarction	292 (12)	1556 (13)	.21
Obstructive sleep apnea	151 (6)	1379 (11)	<.001
Peripheral artery disease	142 (6)	713 (6)	.86
Deep venous thrombosis	944 (38)	5985 (49)	<.001
Gastrointestinal bleed	55 (2)	435 (4)	.001
Osteoarthritis	288 (12)	1647 (13)	.01
Gastroesophageal reflux disease	214 (9)	1327 (11)	.001
Anemia	408 (17)	2370 (20)	.002
Stroke or TIA	429 (17)	2265 (18)	.16

Abbreviations: AF, atrial fibrillation; OAC, oral anticoagulant; OCEANIC-AF, Oral Factor 11a Inhibitor Asundexian as Novel Antithrombotic–Atrial Fibrillation; TIA, transient ischemic attack.

[a] Other race includes American Indian, Alaska Native, Native Hawaiian, Other Pacific Islander, and not reported.

[b] $CHAD_2DS_2$-VASc indicates congestive heart failure, hypertension, age 75 years or older (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 years, and sex category (female).

with a smaller difference between asundexian and apixaban among patients who were OAC naive than patients who were OAC experienced, was seen for other efficacy outcomes.

Bleeding Outcomes

Bleeding outcomes among patients who were OAC naive and OAC experienced taking asundexian and apixaban are shown

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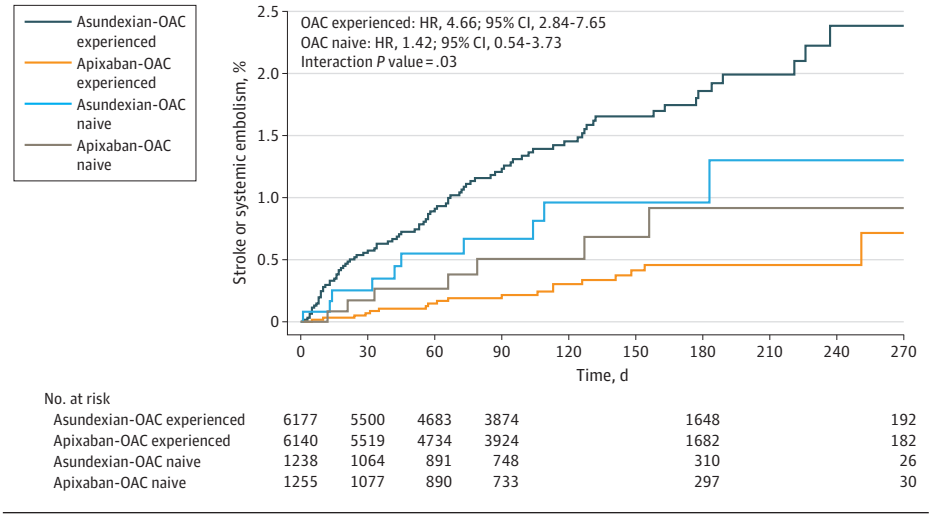
Table 2. Efficacy Outcomes by Treatment Group in Patients Who Were OAC Naive and OAC Experienced

	OAC naive (n = 2493)					OAC experienced (n = 12 317)					
	Asundexian (n = 1238)		Apixaban (n = 1255)			Asundexian (n = 6177)		Apixaban (n = 6140)			
Outcome	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	*P* value for interaction
Primary efficacy outcome (stroke or systemic embolism)	10/1238 (0.8)	2.45 (1.18-4.19)	7/1255 (0.6)	1.73 (0.70-3.23)	1.42 (0.54-3.73)	88/6177 (1.4)	4.12 (3.31-5.03)	19/6140 (0.3)	0.88 (0.53-1.32)	4.66 (2.84-7.65)	.03
Ischemic stroke or systemic embolism	10/1238 (0.8)	2.45 (1.18-4.19)	5/1255 (0.4)	1.24 (0.40-2.53)	2.00 (0.68-5.85)	86/6177 (1.4)	4.03 (3.22-4.92)	17/6140 (0.3)	0.79 (0.46-1.21)	5.09 (3.02-8.56)	.12
Ischemic stroke	9/1238 (0.7)	2.21 (1.01-3.86)	5/1255 (0.4)	1.24 (0.40-2.53)	1.80 (0.60-5.39)	76/6177 (1.2)	3.55 (2.80-4.40)	16/6140 (0.3)	0.74 (0.43-1.15)	4.77 (2.78-8.18)	.12
CV death	8/1238 (0.6)	1.95 (0.84-3.52)	11/1255 (0.9)	2.71 (1.35-4.53)	0.77 (0.31-1.92)	40/6177 (0.6)	1.86 (1.33-2.47)	33/6140 (0.5)	1.53 (1.05-2.10)	1.21 (0.76-1.92)	.33
CV death, MI, or stroke	25/1238 (2.0)	6.17 (3.99-8.81)	20/1255 (1.6)	4.95 (3.02-7.34)	1.31 (0.72-2.35)	130/6177 (2.1)	6.10 (5.09-7.19)	57/6140 (0.9)	2.65 (2.01-3.38)	2.29 (1.68-3.13)	.08
All-cause death	9/1238 (0.7)	2.19 (1.00-3.84)	17/1255 (1.4)	4.19 (2.44-6.40)	0.56 (0.25-1.26)	51/6177 (0.8)	2.37 (1.76-3.06)	54/6140 (0.9)	2.51 (1.88-3.22)	0.94 (0.64-1.38)	.22

Abbreviations: CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; OAC, oral anticoagulant.

Figure 1. Cumulative Event Rates for the Primary Efficacy End Point, Stroke or Systemic Embolism



Cumulative event rates for the primary efficacy end point, stroke or systemic embolism, among patients who were oral anticoagulant (OAC) naive or OAC experienced assigned to asundexian or apixaban. Interaction *P* value from Cox proportional hazards model. HR indicates hazard ratio.

in **Table 3**. In the overall trial, patients taking asundexian had less bleeding (0.2% [2 of 1228]) than those taking apixaban (0.7% [40 of 6115]; HR, 0.32; 95% CI, 0.18-0.55).[4] Bleeding rates were lower among both OAC naive patients (0.2% [2 of 1228]) and experienced patients (0.2% [15 of 6145]) assigned asundexian than among OAC naive patients (1.0% [13 of 1249]) and experienced patients (0.7% [40 of 6115]) assigned apixaban. A similar pattern of events was seen for other bleeding outcomes. The difference in major bleeding between asundexian and apixaban appeared gradually over the duration of study drug administration in both OAC-naive and OAC-experienced patients (**Figure 2**).

Discussion

In this prespecified, exploratory subgroup analysis of the OCEANIC-AF trial, we found clinically important differences in the effects of asundexian compared with apixaban in the 17% of patients who were OAC naive compared with the 83% of patients who were OAC experienced. With relatively short-term follow-up, rates of stroke or systemic embolism, other cardiovascular events, and bleeding were low overall and, despite OAC-naive patients having a lower baseline risk profile, roughly similar in patients who were OAC naive and OAC

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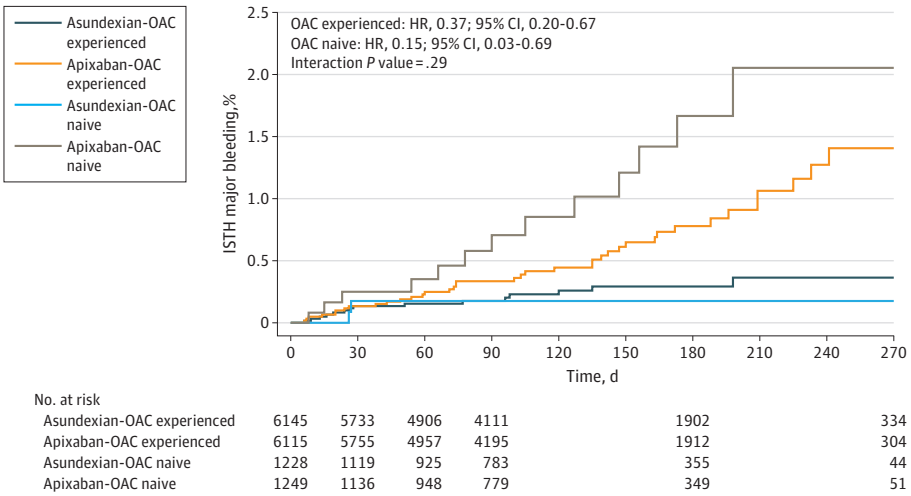
Table 3. Bleeding Outcomes by Treatment Group in Patients Who Were OAC Naive and OAC Experienced

	OAC naive (N = 2477)					OAC experienced (N = 12 260)					
	Asundexian (n = 1228)		Apixaban (n = 1249)			Asundexian (n = 6145)		Apixaban (n = 6115)			
Outcome	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	No. (%)	Events/100 patient-years (95% CI)	No. (%)	Events/100 patient-years (95% CI)	HR (95% CI)	*P* value for interaction
ISTH major bleeding	2/1228 (0.2)	0.46 (0.06-1.28)	13/1249 (1.0)	2.98 (1.59-4.80)	0.15 (0.03-0.69)	15/6145 (0.2)	0.66 (0.37-1.03)	40/6115 (0.7)	1.73 (1.24-2.31)	0.37 (0.20-0.67)	.29
ISTH major or CRNM bleeding	12/1228 (1.0)	2.77 (1.43-4.54)	41/1249 (3.3)	9.52 (6.83-12.64)	0.29 (0.15-0.56)	71/6145 (1.2)	3.12 (2.44-3.89)	147/6115 (2.4)	6.43 (5.43-7.51)	0.48 (0.36-0.64)	.17
Hemorrhagic stroke	0/1228 (0)	NA	2/1249 (0.2)	0.46 (0.06-1.27)	NA	1/6145 (<0.1)	0.04 (0-0.16)	4/6115 (0.1)	0.17 (0.05-0.38)	0.25 (0.03-2.28)	>.99
Fatal bleeding	0/1228 (0)	NA	1/1249 (0.1)	0.23 (0.01-0.84)	NA	0/6145 (0)	NA	3/6115 (<0.1)	0.13 (0.03-0.31)	NA	NA
Any (ISTH major, CRNM, or minor) bleeding	37/1228 (3.0)	8.66 (6.10-11.67)	90/1249 (7.2)	21.55 (17.33-26.22)	0.40 (0.28-0.59)	226/6145 (3.7)	10.12 (8.85-11.48)	400/6115 (6.5)	18.07 (16.34-19.88)	0.56 (0.47-0.66)	.14

Abbreviations: CRNM, clinically relevant non-major; HR, hazard ratio; ISTH, International Society on Thrombosis and Hemostasis; NA, not applicable; OAC, oral anticoagulant.

Figure 2. Cumulative Event Rates for the Primary Safety End Point, Major Bleeding



Cumulative event rates for the primary safety end point, major bleeding, among patients who were oral anticoagulant (OAC) naive or OAC experienced assigned to asundexian or apixaban. Interaction *P* value from Cox proportional hazards model. HR indicates hazard ratio; ISTH, International Society on Thrombosis and Hemostasis.

experienced. There was a quantitative interaction with a smaller increase in stroke or systemic embolism with asundexian compared with apixaban in patients who were OAC naive than in those who were OAC experienced. Compared with apixaban, asundexian caused less bleeding among both OAC-naive and OAC-experienced patients. These results suggest that patients with limited prior exposure to OACs may provide an important population for the evaluation of factor XI/XIa inhibitors as a new class of anticoagulants.

The OCEANIC-AF trial was designed to enroll a broad population of patients with AF at high risk for both stroke or systemic embolism and bleeding. In a population with a mean CHA_2DS_2-VASc score of 4.3, however, the observed event rates among patients assigned to apixaban were 1.02 per 100 patient-years for stroke or systemic embolism and 1.93 per 100 patient-years for major bleeding.[4] These rates for stroke or systemic embolism and bleeding, observed in both OAC-naive and OAC-experienced patients, are both lower than those observed with apixaban in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial overall (stroke or systemic embolism 1.27 per 100 patient-years and major bleeding 2.13 per 100 patient-years) and in the subgroup of patients with a baseline CHA_2DS_2-VASc score of 3 or greater (stroke or systemic embolism 1.48 per 100 patient-years and major bleeding 2.60 per 100 patient-years).[5,6]

The OCEANIC-AF trial population was enriched with patients who were OAC naive as they were anticipated to have higher rates of bleeding and perhaps benefit more from a factor XI inhibitor. OAC-naive patients in the OCEANIC-AF trial tended to be younger with fewer comorbidities and less nonparoxysmal AF than patients who were OAC experienced. As

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OAC-naive status was one of several enrichment factors, it is not surprising that the OAC-experienced patients enrolled in the OCEANIC-AF trial had more other risk factors. These differences in the baseline characteristics between OAC-naive and OAC-experienced patients confound unadjusted comparisons of absolute stroke or systemic embolism and bleeding event rates.

We observed an increase in stroke or systemic embolism with asundexian compared with apixaban that was more evident among patients who were OAC experienced than OAC naive. This finding could be the result of chance; however, there are at least 2 other plausible explanations for this finding. First, OAC-naive or OAC-experienced status, as defined in the OCEANIC-AF trial, may be a marker of patient characteristics that influence stroke or systemic embolism risk and the effects of OACs on stroke. Patients who are OAC experienced and already doing well while taking an OAC may have better outcomes, including both stroke prevention and bleeding, particularly if they are continuing with a similar anticoagulant. Based on their baseline characteristics, OAC-naive and OAC-experienced patients enrolled in the OCEANIC-AF trial are clearly different from each other. In addition, OAC use involves a complex interaction between the patient, practitioner, and health system. OAC use may not be a static characteristic and has likely changed from years ago when VKAs were the dominant OAC to today when direct OACs are widely available. Additional research is needed into the characteristics of OAC-naive and OAC-experienced patients that drive stroke risk and, perhaps, the lack of benefit from asundexian.

Second, there may be an effect of transitioning from a factor Xa to a factor XIa inhibitor, which inhibits coagulation further upstream and only via the intrinsic pathway. This effect could also potentially be exacerbated by a factor XIa inhibitor dose that provides incomplete factor XI inhibition. The observed large increase in stroke risk with asundexian compared with apixaban among OAC-experienced patients suggest that asundexian could be having prothrombotic effect in this population. In the OCEANIC-AF trial, the majority of OAC-experienced patients were taking a factor Xa inhibitor before enrollment and the excess in stroke was most evident early after transition to asundexian. Switching anticoagulants poses unique challenges. In the pivotal trials comparing factor Xa inhibitors with warfarin, an increase in thromboembolic events was observed at the end of the trial during the transition from factor Xa inhibitor to warfarin.[7,8] This observation has been attributed to a gap in adequate anticoagulation that was ameliorated with bridging with a factor Xa inhibitor.[9] A recent clinical trial documented an increase in bleeding and no reduction in thromboembolic events when switching from a VKA to apixaban and, in an observational analysis, higher rates of both bleeding and thromboembolic events among patients switching from one factor Xa inhibitor to another.[10,11] Understanding the potential risks and best approaches to switching anticoagulants is also an area in need of further study.

Differential effects of oral anticoagulation among OAC-naive and OAC-experienced groups of patients with AF have been investigated. In the majority of these prior analyses, however, OAC experienced meant VKA experienced. In 2 of these studies, greater OAC benefits were seen among patients who were OAC naive. In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE-W) trial, the advantages of a VKA over clopidogrel plus aspirin were more evident in patients who were VKA naive at enrollment.[12] In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, edoxaban had greater efficacy, compared with warfarin, in patients who were VKA naive than VKA experienced.[13] In contrast, in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial where 50% of the population was VKA naive by design, the effects of dabigatran did not differ according to prior VKA experience.[14] Similarly, in the ARISTOTLE trial, the effect of apixaban vs VKA was similar among patients with and without prior VKA experience, except that VKA-experienced patients had a larger reduction in intracranial hemorrhage with apixaban compared with VKA than those who were VKA naive.[15] Finally, in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, there were similar effects of rivaroxaban and VKA on stroke or systemic embolism but less bleeding after the first 7 days with rivaroxaban than VKA in patients who were VKA naive but not in those who were VKA experienced.[16] An individual patient meta-analysis of all of these trials identified the absence of prior VKA use as a factor associated with a greater reduction in stroke or systemic embolism with a direct OAC compared with warfarin.[1]

Limitations

Although prespecified, this was a secondary subgroup analysis and should be considered exploratory and hypothesis generating. The number of patients and events, particularly in the OAC-naive subgroup, was modest and lacked statistical power to detect clinically meaningful differences. The observed differential effect of asundexian compared with apixaban among patients who are OAC naive and OAC experienced could have been due to chance. There was no correction of *P* values, including interaction *P* values, for multiple comparisons. Comparisons between OAC-naive and OAC-experienced patients should not be considered causal as the primary analysis of the overall trial was not significant. Though prespecified, the definitions of OAC naive (≤6 weeks of OAC use) and OAC experienced (>6 weeks of OAC use) were arbitrary and other definitions could have been used. Thus, the OAC-naive group included both patients not taking an OAC and patients that had been taking an OAC for 6 or fewer weeks. We did not collect the reasons that OACs were not used in OAC-naive patients nor the details of previous OAC use (agent, duration, timing) in either the OAC-naive or OAC-experienced patients precluding additional analyses into the mechanisms that underlie our observations. Finally, the OCEANIC-AF trial was stopped early because asundexian was less effective than apixaban; thus, the results of the overall trial and this analysis may be more extreme than if the trial went to conclusion.

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Conclusions

In the OCEANIC-AF randomized clinical trial, asundexian caused less bleeding than apixaban in both patients who were OAC naive and experienced; however, patients who were OAC naive had a smaller increase in stroke or systemic embolism with asundexian compared with apixaban than patients who were OAC experienced. The mechanism behind these findings is unknown and deserves further research.

ARTICLE INFORMATION

Accepted for Publication: January 31, 2025.

Published Online: March 26, 2025. doi:10.1001/jamacardio.2025.0277

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Author Contributions: Drs Alexander and Lydon had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Drafting of the manuscript: Alexander, Halvorsen, Rockhold.
Critical review of the manuscript for important intellectual content: All authors.
Statistical analysis: Lydon, Rockhold.
Obtained funding: Mundl, Goudev, Vinereanu, Patel.
Administrative, technical, or material support: Goodman, Grove, Vinereanu, Coppolecchia, Patel.
Supervision: Viethen, Steffel, Mundl, Benczur, Gomez-Doblas, Vinereanu, Rockhold, Caso, Patel.

Conflict of Interest Disclosures: Dr Alexander reported receiving grants from Bayer Pharmaceuticals, Artivion, Bristol Myers Squibb, CSL Behring, Ferring, Humacyte and data safety monitoring board fees/consulting fees/honoraria from AbbVie, Artivion, AtriCure, Bayer, Bristol Myers Squibb, Curis, Eli Lilly, Ferring, GlaxoSmithKline, Janssen, Novostia, Pfizer, Portola, Theravance, and Veralox outside the submitted work. Dr Piccini reported receiving grants from Bayer, Abbott, Boston Scientific, the American Heart Association (AHA), Philips, iRhythm and personal fees from Sanofi, SymKardia, Milestone, and Kardium outside the submitted work. Dr Viethen reported being a full-time employee of Bayer AG at the time the data for this article were accrued. Dr Oldgren reported receiving fees to institution from Bayer, Amgen, AstraZeneca, Novartis, Pfizer, and Roche Diagnostics outside the submitted work. Dr Goodman reported receiving grants from Bayer to the Canadian Vigour Centre (for which he is codirector) for the Canadian site management in the OCEANIC-AF trial; steering committee/personal fees from Bayer, Alnylam, Amgen, Anthos Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, CYTE Ltd, Daiichi Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, HLS Therapeutics, Idorsia, JAMP Pharma, Merck, Novartis, Novo Nordisk A/C, Pendopharm/Pharmascience, Pfizer, Regeneron, Roche, Sanofi, Servier, Tolmar Pharmaceuticals, Valeo Pharma Research; and salary support and/or honoraria from the Canadian Heart Failure Society, Canadian Heart Research Centre and MD Primer, Canadian Vigour Centre, Cleveland Clinic Coordinating Centre for Clinical Research, Duke Clinical Research Institute, Jewish General Hospital\CIUSSS Centre-Ouest-de-l'Ile-de-Montreal, New York University Clinical Coordinating Centre, PERFUSE Research Institute, Peter Munk Cardiac Centre Clinical Trials and Translation Unit, Ted Rogers Centre for Heart Research, and TIMI Study Group (Brigham Health). Dr Steffel reported receiving consulting/speaker/personal fees from Bayer, BMS, Abbott, Berlin Chemie, Biosense Webster, Biotronik, Boehringer Ingelheim, Boston Scientific, Daiichi Sankyo, Medscape, Medtronic, Menarini, Pfizer, Saja, and WebMD outside the submitted work. Dr Russo reported receiving grants and personal (consulting/committee) fees from Bayer; personal fees/consulting fees/research funding from Sanofi-Aventis, Bristol Myers Squibb, Boston Scientific, Medtronic, Abbott, Biotronik, Atricure, Biosense Webster; and grants from Boston Scientific, Medtronic, and Abbott outside the submitted work. Dr Van Gelder reported receiving personal/consulting fees from Bayer, Boehringer Ingelheim, Sandoz, Pfizer/BMS, Boston Scientific; grants from Netherlands Cardiovascular Research Initiative, Embrace: Electro-Molecular Basis and the Therapeutic Management of Atrial Cardiomyopathy, Fibrillation, and Associated Outcomes, European Union's Horizon 2020, Dutch Heart Foundation, Roche, and Medtronic outside the submitted work. Dr Ferdinand reported receiving personal/consultant fees from Boehringer Ingelheim, Novartis, Medtronic, Janssen, Eli Lilly, and Amgen. Dr Lopes reported receiving grants from Amgen, Bristol Myers Squibb, Medtronic, Glaxo Smith Kline, Pfizer, Sanofi; consulting/personal/educational activities/lecture fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Novo Nordisk, and Pfizer outside the submitted work. Dr Mundl reported receiving personal fees (salary) and being an employee of Bayer AG during the conduct of the study. Dr Goudev reported receiving personal/consulting/lecture fees and/or honoraria from Bayer, Novartis, AstraZeneca, and Novo Nordisk outside the submitted work. Dr Grove reported receiving personal fees from Bayer OCEANIC-AF as national coordinating investigator and member of steering committee; grants from Boehringer Ingelheim; investigator/consultant/lecture/monitoring board fees from AstraZeneca, Idorsia, Bayer, Bristol Myers Squibb, Pfizer, Lundbeck Pharma, Novo Nordisk, and Pfizer outside the submitted work. Dr Halvorsen reported receiving steering committee/speaker fees from Bayer and Pfizer outside the submitted work. Dr Kiviniemi reported receiving funding from Bayer to perform the trial during the conduct of the study. Dr Martin reported receiving personal fees and nonfinancial support from Bayer; personal/lecture/consulting fees from Alliance BMS-Pfizer, Abbott, Carmat, Sanofi, and Novartis outside the submitted work. Dr Sandhu reported receiving personal/steering committee fees from Bayer during the conduct of the study. Dr Vinereanu reported receiving grants from Bayer and Boehringer Ingelheim and personal fees from Pfizer and Janssen outside the submitted work. Dr Rockhold reported receiving grants from Bayer Pharmaceuticals, Pfizer, BMS, Eidos, American Regent and personal/consulting/monitoring board fees and/or stock options from AstraZeneca, BMS, Eli Lilly, Biogen, Novartis, Merck, UCB, Amgen, Gilead, AskBio, Reunion, BridgeBio, Interceot, Clover, Inventprise, and GSK outside the submitted work. Dr Caso reported funding support from Bayer, Boehringer Ingelheim, Daiichi Sankyo,

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and Pfizer during the conduct of the study. Dr Coppolecchia reported being employed at Bayer. Dr Patel reported receiving grants and personal advisory fees from Bayer; grants/advisory board/consulting fees from Janssen; grants from Novartis, Idorsia, and National Heart, Lung, and Blood Institute; and consulting fees from Esperion outside the submitted work. No other disclosures were reported.

Funding/Support: This work was supported by Bayer AG, Leverkusen, Germany.

Role of the Funder/Sponsor: Bayer AG was involved in the design and conduct of the study; collection and management of the data; and review of the manuscript before submission, but had no role in the preparation or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: We thank Elizabeth E.S. Cook, BA (Duke Clinical Research Institute, Durham, North Carolina), who provided editorial assistance. Beyond usual salary, no one received financial compensation for their contribution.

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