

# OCEANIC-AF: Asundexian vs. Apixaban in Patients with Atrial Fibrillation

ESC Late-Breaking Trial Presentation  
September 1st, 2024

Manesh R. Patel, MD on behalf of the OCEANIC-AF Executive Committee, Steering Committee, and Investigators



# Disclosures



**Research Grants:** Bayer, Novartis, Janssen, Idorsia, NHLBI

**Advisory Board/Consultancy:** Bayer, Janssen, Esperion



# Background: The Need for a Better Antithrombotic Therapy for Atrial Fibrillation



- DOACs now accepted as first-line therapy over warfarin, with lower rates of stroke, mortality, and ICH
- Patients on DOACs still face a bleeding risk of 2.7–3.5%/year
- Bleeding and fear of bleeding remain a major challenge for DOAC therapy and adherence to treatment, resulting in:



## Undertreatment

< 66% of patients with atrial fibrillation and  $CHA_2DS_2-VASc \geq 2$  are prescribed an OAC at all



## Underdosing

Up to 25% of patients on DOACs are underdosed, which might result in higher rates of thromboembolic events



## Poor treatment compliance

1 in 3 patients adhere to their DOAC < 80% of the time and the nonadherence is associated with poor clinical outcomes



January et al. JACC 2019;74:104–132.

Carnicelli et al. Circulation 2022;145:242–255.

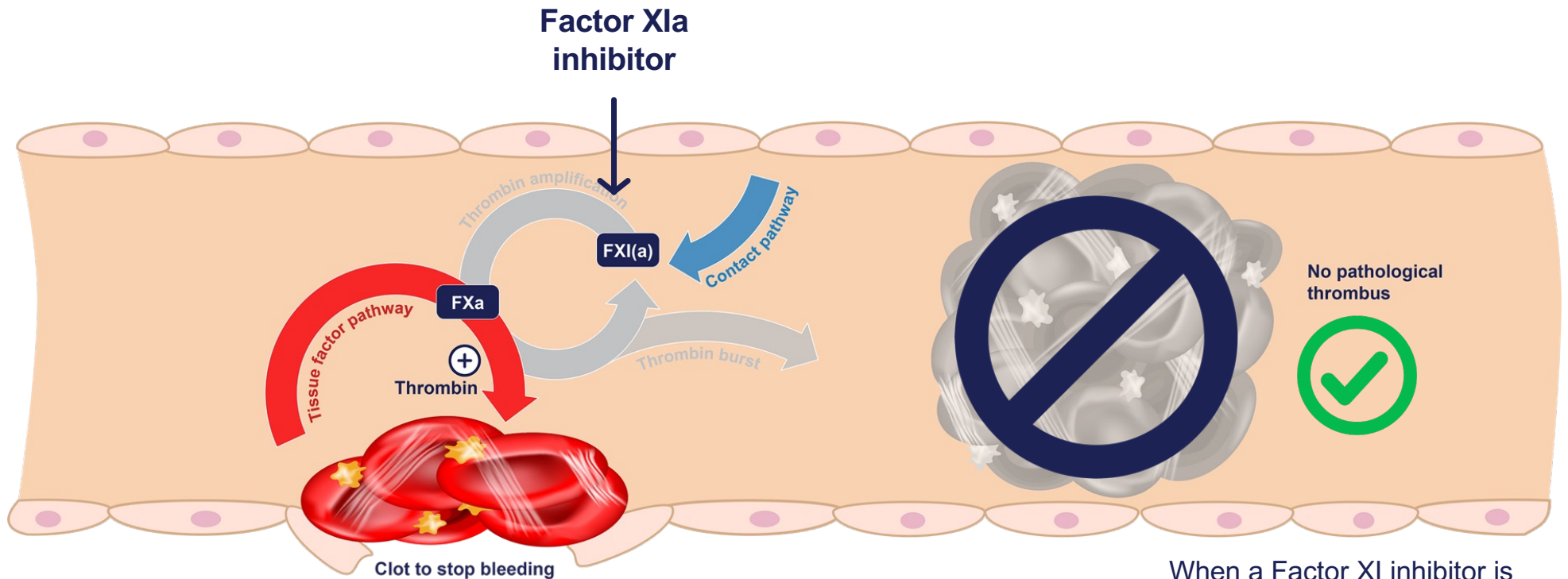
Oldgren et al. Circulation 2014;129:1568–1576.

Camm et al. JACC 2020; 76:1425–1436.

Kakkar et al. PLoS One 2013;8:e63479.

# With a Factor XIa Inhibitor

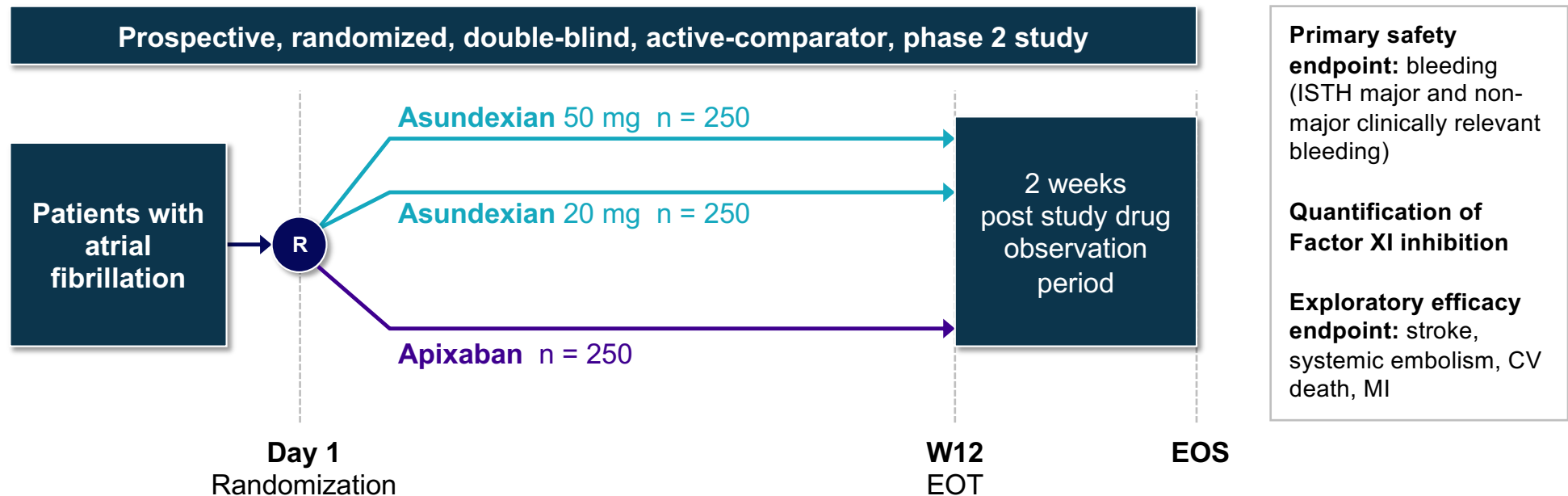
## Hypothesis: Uncoupling Hemostasis from Thrombosis



AND the tissue factor pathway still produces thrombin, which allows beneficial blood clots to form.

When a Factor XI inhibitor is used, thrombin amplification is inhibited, which prevents pathological thrombi—

# Randomized, Active Comparator-Controlled, Double-Blind, Double-Dummy, Parallel-Group, Dose-Finding Phase 2 Study to Compare the Safety of the Oral FXIa Inhibitor Asundexian with Apixaban in Patients with Atrial Fibrillation (PACIFIC-AF)



**Primary Objective:** to evaluate that the oral FXIa inhibitor Asundexian when compared with Apixaban leads to a **lower incidence of bleeding** in participants with atrial fibrillation



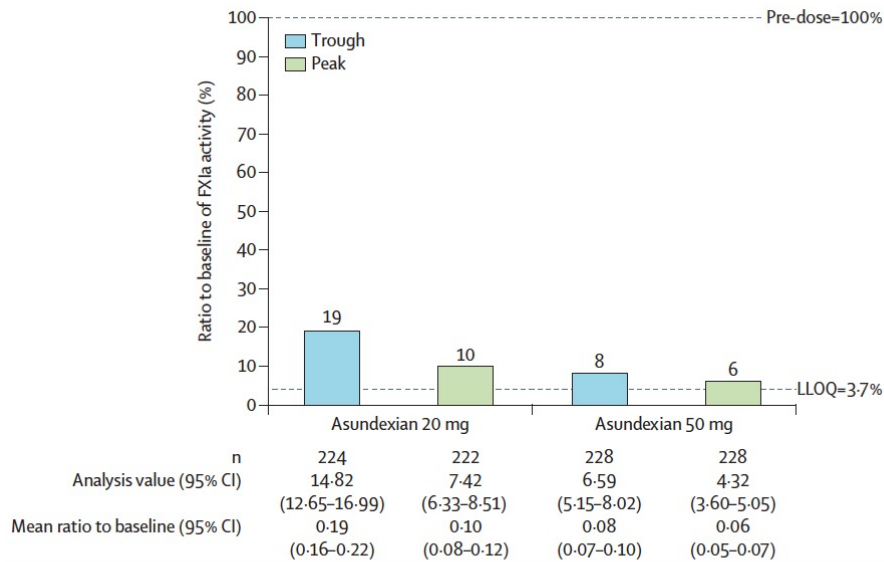
# PACIFIC-AF: Phase 2 Study in Patients with Atrial Fibrillation

Safety of the oral factor XIa inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study

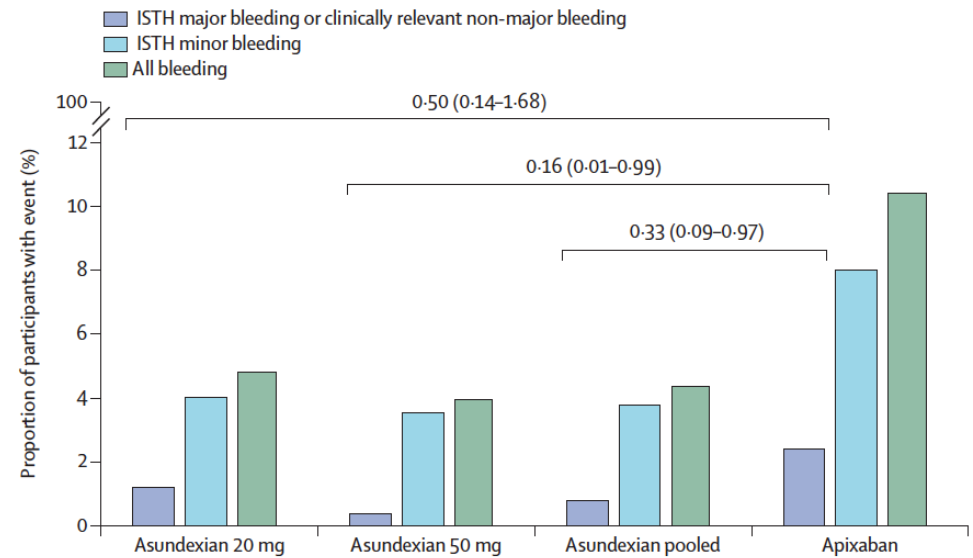


Jonathan P Piccini, Valeria Caso, Stuart J Connolly, Keith A A Fox, Jonas Oldgren, W Schuyler Jones, Diana A Gorog, Václav Durdil, Thomas Viethen, Christoph Neumann, Hardi Mundl, Manesh R Patel, on behalf of the PACIFIC-AF Investigators\*

## FXIa Activity — Inhibition Data



## Primary Safety Outcome (ISTH bleeding classification)



# Hypothesis



# Hypothesis

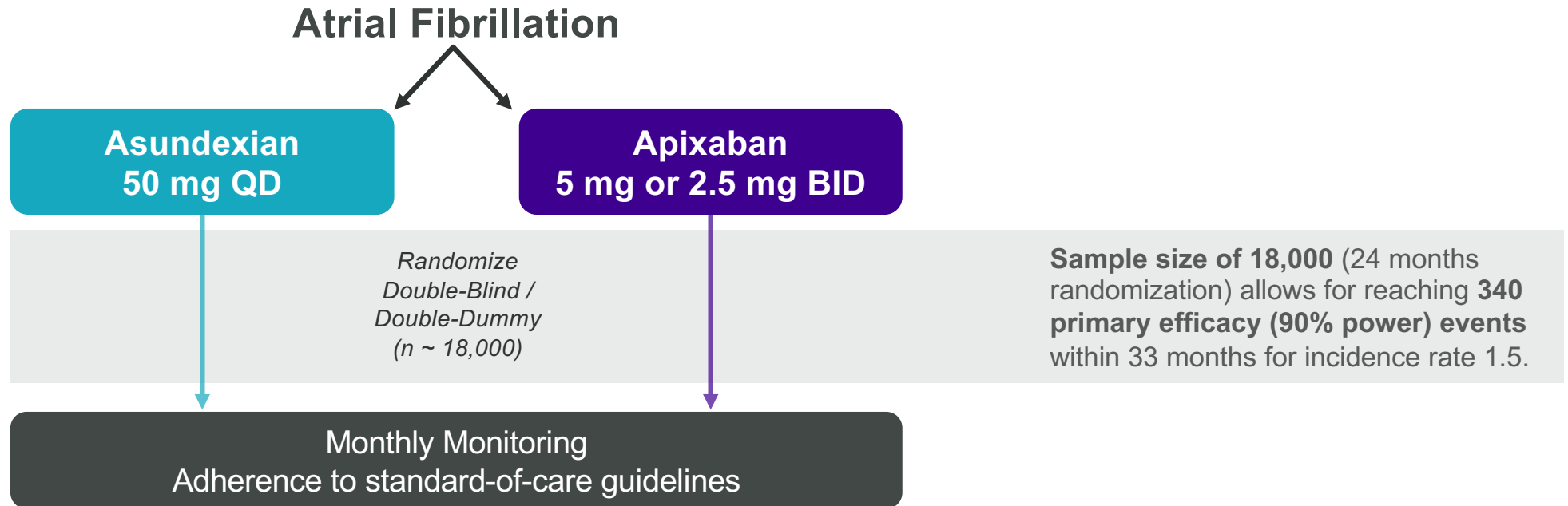


Asundexian at 50 mg daily will be at least **non-inferior** to Apixaban for the prevention of stroke or systemic embolism in patients with atrial fibrillation at risk for stroke.

Also powered to determine if Asundexian is **superior** to Apixaban for reduction in ISTH major bleeding and net clinical benefit combining stroke, systemic embolism, and ISTH major bleeding.



# OCEANIC-AF Study Design



**Primary Efficacy Endpoint:** Stroke or Systemic Embolism

**Primary Safety Endpoint:** ISTH Major Bleeding

**Primary Net Clinical Benefit Endpoint:** Stroke or Systemic Embolism and ISTH Major Bleeding

# Inclusion Criteria



**Patients will be eligible for the study if they have:**

- Atrial fibrillation\* with indication for indefinite treatment with an anticoagulant
- A CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 3$  if male or  $\geq 4$  if female

**OR**

- A CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 if male or 3 if female **AND at least 1 of the following:**
  - age  $\geq 70$  years
  - previous stroke, transient ischemic attack, or systemic embolism
  - renal dysfunction with CKD-EPI eGFR  $< 50$  mL/min/1.73m<sup>2</sup> within 14 days prior to randomization
  - prior episode of non-traumatic major bleeding
  - current single agent antiplatelet therapy planned for at least the next 6 months
  - $\leq 6$  consecutive weeks of treatment with oral anticoagulant prior to randomization (OAC Naïve)

*\* Documented on 6 (or more) lead EKG or as  $\geq 30$  seconds on continuous rhythm strip in last 12 months*

# Key Exclusion Criteria



## Patients will be not eligible for the study:

- Mechanical heart valve prosthesis (not including transcatheter aortic valve replacement)
- Moderate-to-severe mitral stenosis at the time of inclusion into the study
- Atrial fibrillation only due to reversible cause (e.g., thyrotoxicosis, endocarditis, pneumonia, pulmonary embolism)
- Participants after successful ablation therapy without documented recurrent atrial fibrillation or participants after left atrial appendage (LAA) occlusion / exclusion or plan for ablation or LAA occlusion / exclusion within the next 6 months starting from randomization
- Recent ischemic stroke (within 7 days prior to randomization)
- eGFR < 25 mL/min/1.73m<sup>2</sup> within 14 days prior to randomization or on dialysis or expected to be started on dialysis within the next 12 months starting from randomization
- Requirement for chronic anticoagulation for a different indication than atrial fibrillation, e.g., mechanical heart valve or left ventricular cardiac thrombus (atrial thrombus is allowed), or dual antiplatelet therapy (single agent therapy is allowed)

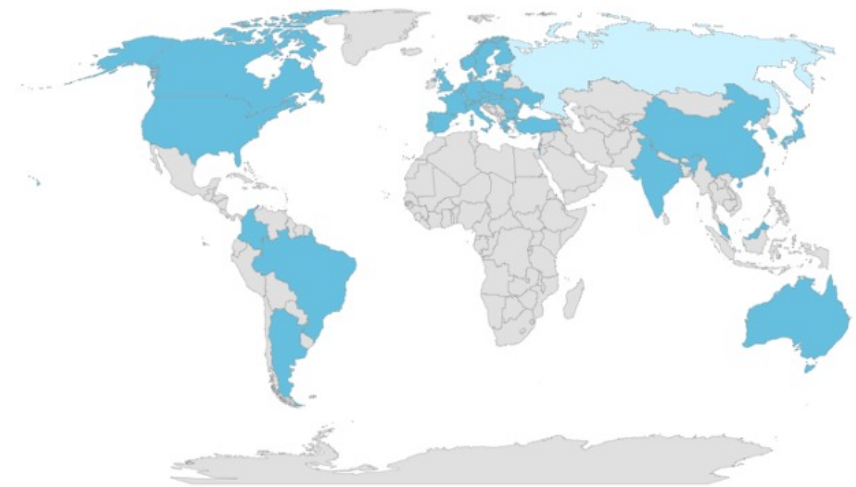
# Study Results



# IDMC Recommends Stopping OCEANIC-AF



- From December 2022 to November 2023, 14,830 of the planned 18,000 patients had been randomized
- IDMC recommended stopping OCEANIC-AF to the EC and study team due to inferiority of Asundexian to Apixaban for the prevention of stroke and systemic embolism
- November 19th, 2023: Sites notified worldwide
  - // Patients transition to open-label therapy and close-out visits conducted across the world



# Patient Disposition



# Patient Demographics



	Asundexian 50 mg (N=7415)	Apixaban (N=7395)	Total (N=14,810)
<b>Age, mean (SD), yrs</b>	73.9 (7.7)	73.9 (7.7)	73.9 (7.7)
<b>Female</b>	2656 (35.8%)	2558 (34.6%)	5214 (35.2%)
<b>Race, White</b>	5216 (70%)	5211 (70%)	10,427 (70%)
<b>Region</b>			
Eastern Europe	1520 (20.5%)	1515 (20.5%)	3035 (20.5%)
North America	1405 (18.9%)	1406 (19.0%)	2811 (19.0%)
South America	400 (5.4%)	401 (5.4%)	801 (5.4%)
Asia	2114 (28.5%)	2108 (28.5%)	4222 (28.5%)
Western EU, Australia, Israel	1976 (26.6%)	1965 (26.6%)	3941 (26.6%)
<b>≤6 weeks of prior OAC use (DOAC or warfarin)</b>	1238 (16.7%)	1255 (17.0%)	2493 (16.8%)
<b>SAPT for &gt;6 months</b>	742 (10.0%)	743 (10.0%)	1485 (10.0%)
<b>CHA<sub>2</sub>DS<sub>2</sub>-VASc score mean (SD)</b>	4.3 (1.3)	4.3 (1.3)	4.3 (1.3)
<b>Type of AF</b>			
First detected	118 (1.6%)	134 (1.8%)	252 (1.7%)
Paroxysmal	2760 (37%)	2641 (36%)	5401 (36%)
Persistent	1773 (24%)	1805 (24%)	3578 (24%)
Long-standing persistent	436 (5.9%)	428 (5.8%)	864 (5.8%)
Permanent	2327 (31%)	2384 (32%)	4711 (32%)

# Patient Demographics



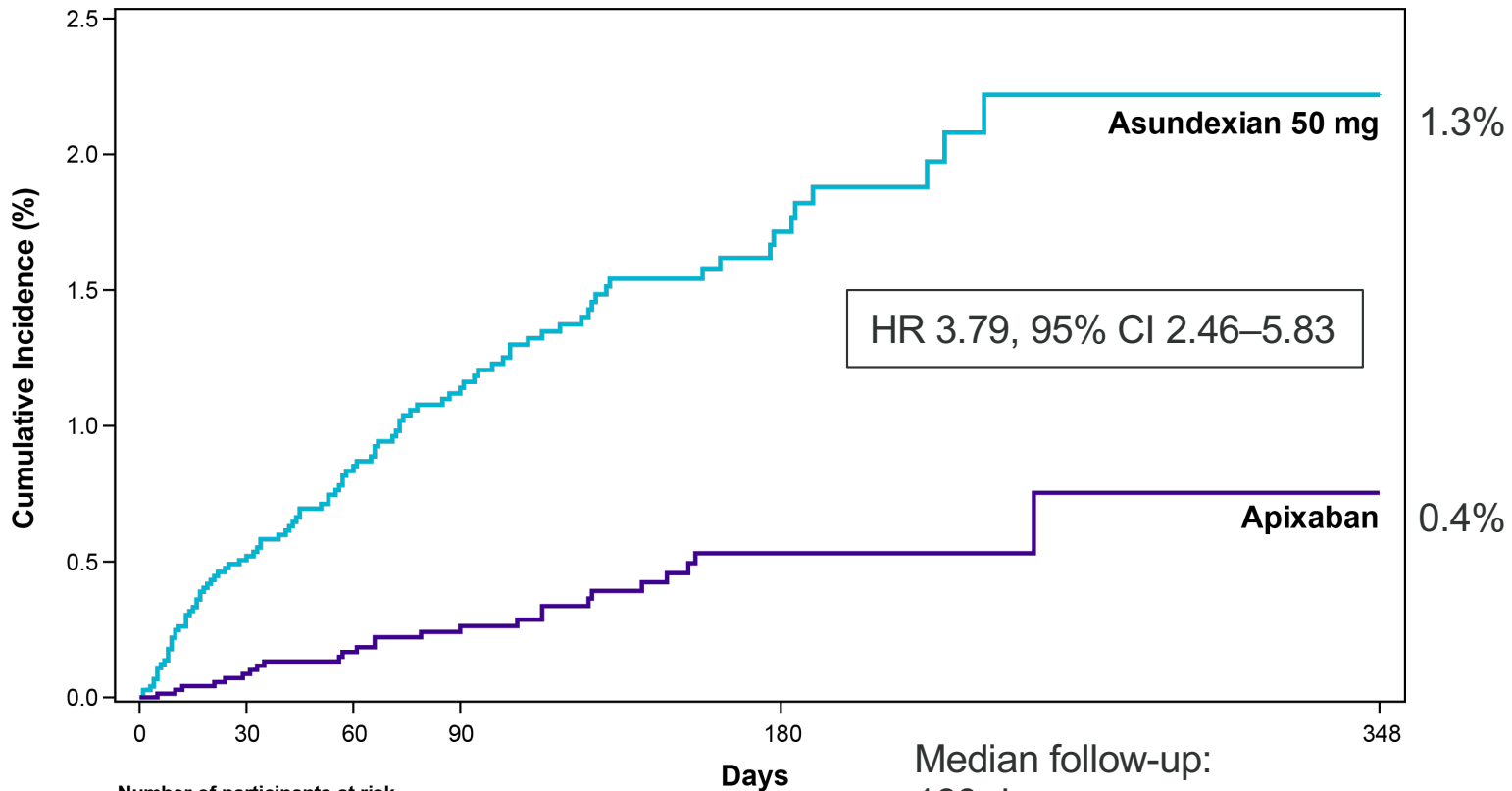
Comorbidities	Asundexian 50 mg (N=7415)	Apixaban (N=7395)	Total (N=14,810)
Hypertension	6558 (88.4%)	6565 (88.8%)	13123 (88.6%)
Hyperlipidemia	4747 (64.0%)	4719 (63.8%)	9466 (63.9%)
Heart failure	3456 (46.6%)	3473 (47.0%)	6929 (46.8%)
Coronary artery disease	2496 (33.7%)	2452 (33.2%)	4948 (33.4%)
Diabetes mellitus	2722 (36.7%)	2748 (37.2%)	5470 (36.9%)
Chronic kidney disease	1399 (18.9%)	1357 (18.4%)	2756 (18.6%)
Obstructive sleep apnea	786 (10.6%)	744 (10.1%)	1530 (10.3%)
Peripheral artery disease	442 (6.0%)	485 (6.6%)	927 (6.3%)
Deep venous thrombosis	170 (2.3%)	162 (2.2%)	332 (2.2%)
Gastrointestinal bleed	276 (3.7%)	214 (2.9%)	490 (3.3%)
Hyperuricemia	841 (11.3%)	763 (10.3%)	1604 (10.8%)
Osteoarthritis	951 (12.8%)	984 (13.3%)	1935 (13.1%)
Gastroesophageal reflux disease	775 (10.5%)	766 (10.4%)	1541 (10.4%)
Anemia	1432 (19.3%)	1346 (18.2%)	2778 (18.8%)
Stroke or TIA	1389 (18.7%)	1305 (17.6%)	2694 (18.2%)



# Primary Results



# Cumulative Event Rate for the Primary Efficacy Endpoint



	Number of participants at risk				Days
Asundexian 50 mg	7415	6564	5574	4622	1958
Apixaban	7395	6596	5624	4657	1979



# Efficacy Events



Efficacy Events According to ITT	Asundexian (N=7415)	Apixaban (N=7395)	Total (N=14,810)	csHR (95% CI)*
Stroke or SE	98 (1.3%)	26 (0.4%)	124 (0.8%)	3.79 (2.46–5.83)
Ischemic stroke or SE	96 (1.3%)	22 (0.3%)	118 (0.8%)	4.38 (2.76–6.96)
All-cause mortality	60 (0.8%)	71 (1.0%)	131 (0.9%)	0.84 (0.60–1.19)
Ischemic stroke	85 (1.1%)	21 (0.3%)	106 (0.7%)	4.06 (2.52–6.54)
CV death	48 (0.6%)	44 (0.6%)	92 (0.6%)	1.09 (0.72–1.64)
CV death, MI, or stroke	155 (2.1%)	77 (1.0%)	232 (1.6%)	2.02 (1.54–2.66)

\*Derived from a stratified cause-specific Cox proportional hazards regression model. Cumulative Incidence Rates provided  
 CI indicates confidence interval; csHR, cause-specific hazard ratio; CV, cardiovascular; ITT, intention to treat; MI, myocardial infarction; SE, systemic embolism.

# Safety Events



	Asundexian 50 mg (N=7373)	Apixaban (N=7364)	Total (N=14,737)	csHR (95% CI) <sup>†</sup>
<b>ISTH major bleeding</b>	17 (0.2%)	53 (0.7%)	70 (0.5%)	0.32 (0.18–0.55)
<b>ISTH major and CRNM bleeding</b>	83 (1.1%)	188 (2.6%)	271 (1.8%)	0.44 (0.34–0.57)
<b>ISTH CRNM bleeding</b>	67 (0.9%)	140 (1.9%)	207 (1.4%)	0.48 (0.36–0.64)
<b>Hemorrhagic stroke</b>	1 (<0.1%)	6 (0.1%)	7 (<0.1%)	0.17 (0.02–1.42)
<b>Symptomatic intracranial hemorrhage</b>	3 (<0.1%)	18 (0.2%)	21 (0.1%)	0.16 (0.05–0.55)
<b>Fatal bleeding</b>	0 (0%)	4 (0.1%)	4 (<0.1%)	Not calculated
<b>ISTH minor bleeding</b>	187 (2.5%)	317 (4.3%)	504 (3.4%)	0.59 (0.49–0.70)
<b>Stroke, SE, or ISTH major bleeding (net clinical benefit endpoint)</b>	120 (1.6%)	75 (1.0%)	195 (1.3%)	1.61 (1.21–2.15)

\*The primary safety estimand is the cause-specific hazard ratio of ISTH major bleeding when treatment with Asundexian is compared with treatment with Apixaban in adult patients with atrial fibrillation at risk for stroke who have taken at least one dose of Asundexian or Apixaban while alive and while exposed to Asundexian or Apixaban.

<sup>†</sup>Cause-specific hazard ratios and their associated 95% confidence intervals were derived from a stratified cause-specific Cox proportional hazards regression model.

CI indicates confidence interval; CRNM, clinically relevant non-major; csHR, cause-specific hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; SE, systemic embolism.

# Adverse Events



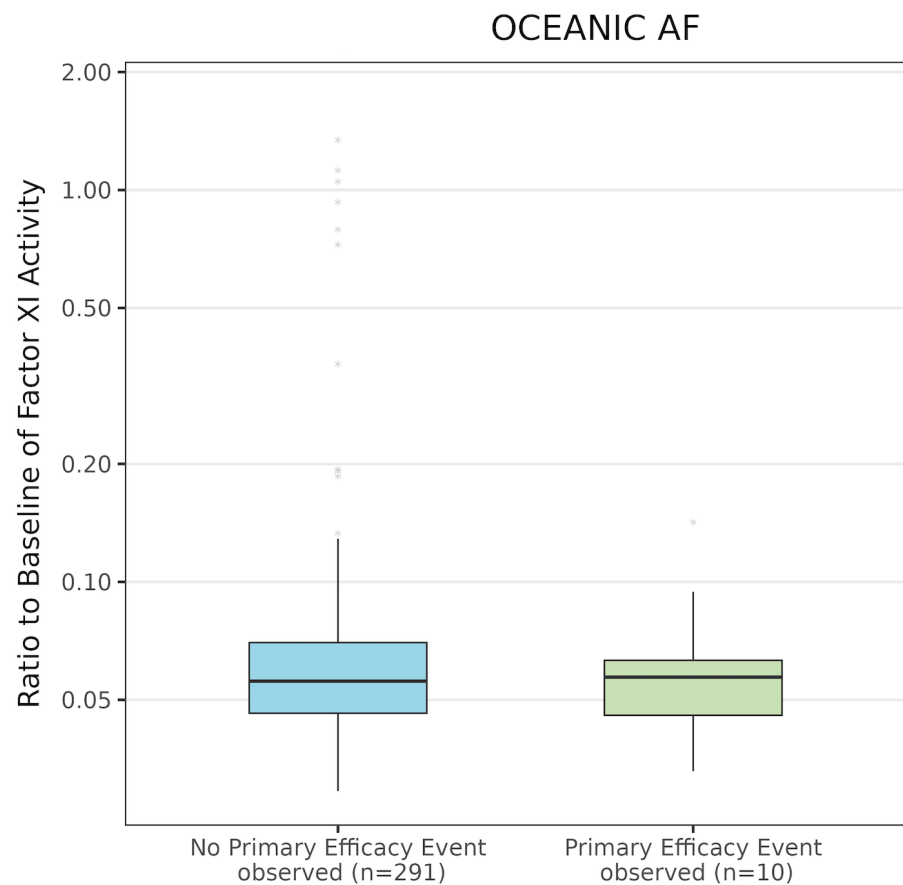
	Asundexian 50 mg (N=7373)	Apixaban (N=7364)	Total (N=14,737)
Any treatment-emergent adverse event (TEAE)	2573 (35%)	2569 (35%)	5142 (35%)
Any study intervention-related TEAE	385 (5.2%)	502 (6.8%)	887 (6.0%)
Any TEAE leading to discontinuation of study intervention	147 (2.0%)	118 (1.6%)	265 (1.8%)
Any serious TEAE	582 (7.9%)	599 (8.1%)	1181 (8.0%)
Any study intervention-related serious TEAE	27 (0.4%)	47 (0.6%)	74 (0.5%)
Any serious TEAE leading to discontinuation of study intervention	38 (0.5%)	35 (0.5%)	73 (0.5%)
TEAE with outcome death	29 (0.4%)	43 (0.6%)	72 (0.5%)

# Key Data and Subgroup Evaluation

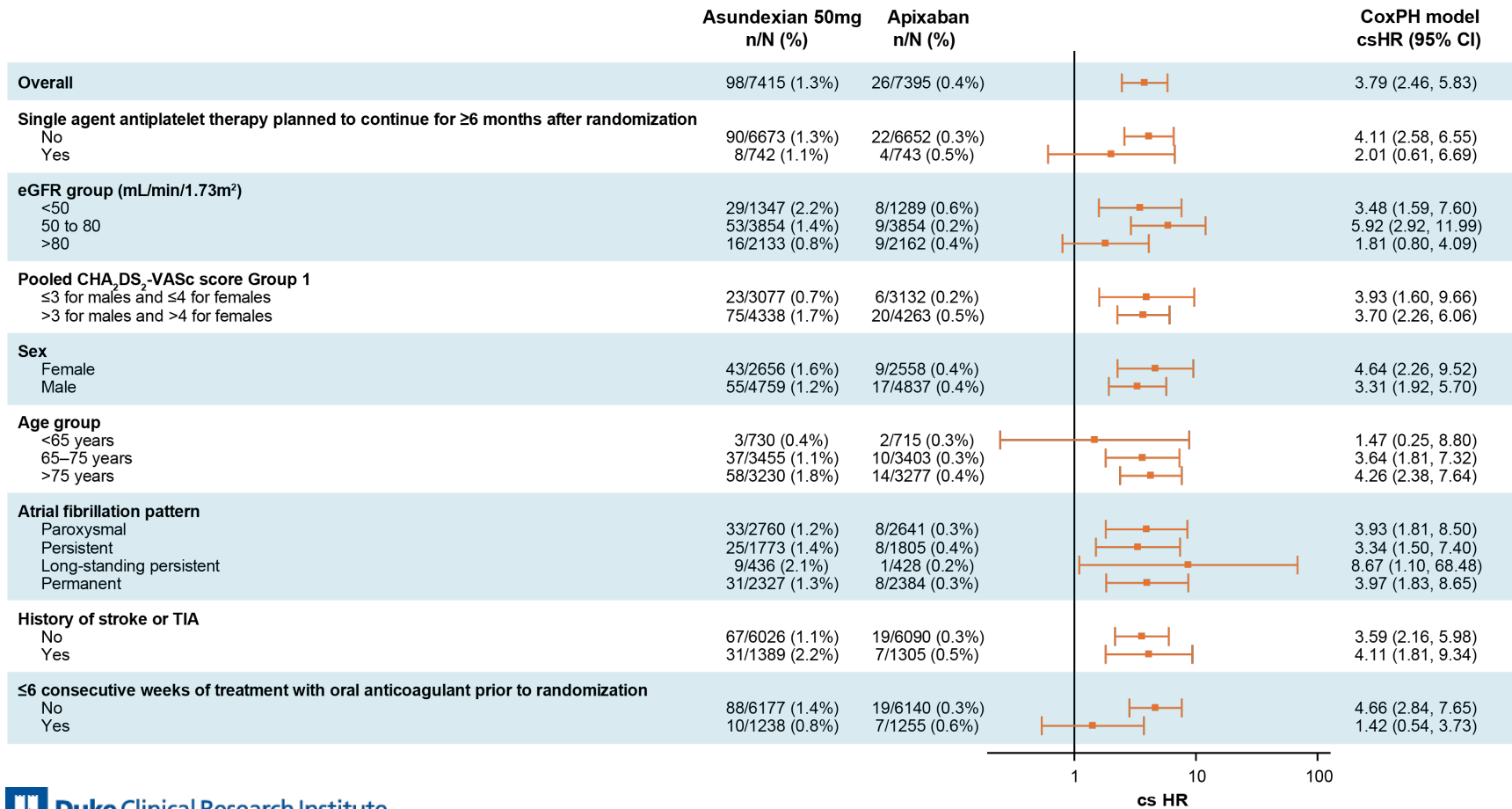


# Factor XI Activity

- Planned PK/PD substudy in OCEANIC-AF patients with evaluation at 4 weeks post-randomization
- PK (not shown) was similar between OCEANIC-AF and PACIFIC-AF
- Factor XI activity at trough was similar between OCEANIC-AF (8.1%) and PACIFIC-AF (8.0%)
- Limited number of patients with primary efficacy events but no observed differences in Factor XI activity



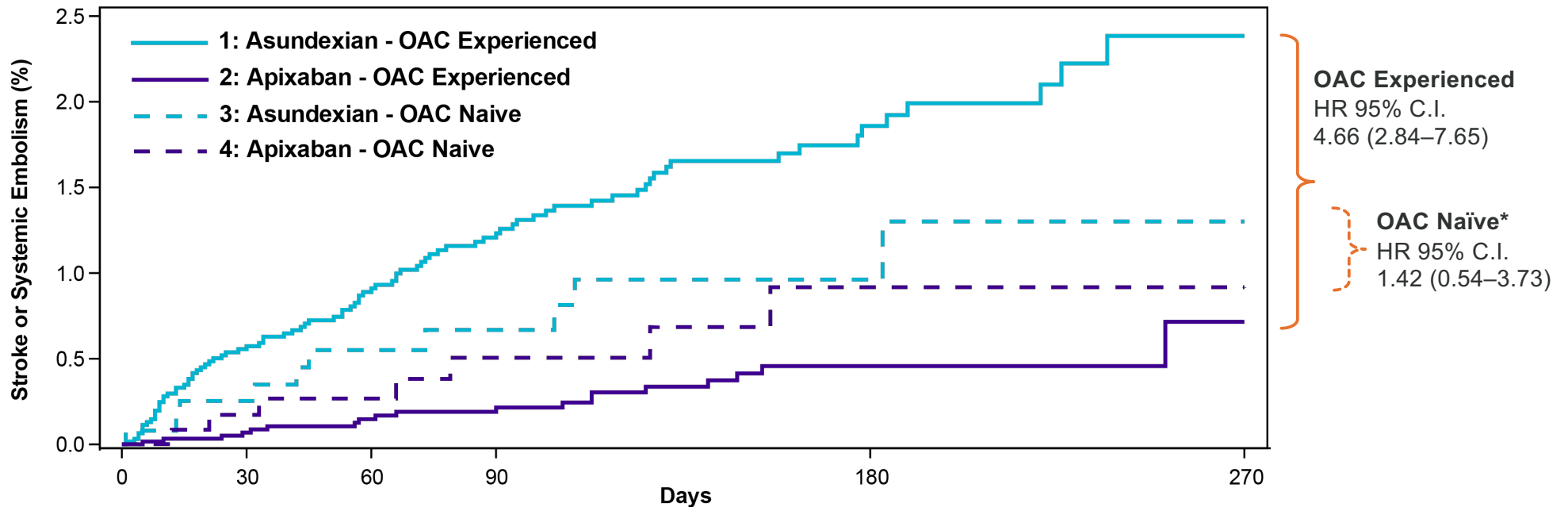
# Subgroup Evaluation



P < 0.05



# Pre-specified Post Hoc Hypothesis Generating: OAC Naïve or OAC Experienced Assigned to Asundexian or Apixaban



**OAC Experienced**  
HR 95% C.I.  
4.66 (2.84–7.65)

**OAC Naïve\***  
HR 95% C.I.  
1.42 (0.54–3.73)

Participants at risk						
	0	30	60	90	180	270
1	6177	5500	4683	3874	1648	192
2	6140	5519	4734	3924	1682	182
3	1238	1064	891	748	310	26
4	1255	1077	890	733	297	30



# OAC Naïve vs. OAC Experienced



	OAC Naïve* (N=2493)			OAC Experienced (N=12,317)			P value Interaction
	Asundexian (N=1238) n (%) Events/100 pt-yrs (95% CI)	Apixaban (N=1255) n (%) Events/100 pt-yrs (95% CI)	HR (95% CI)	Asundexian (N=6177) n (%) Events/100 pt-yrs (95% CI)	Apixaban (N=6140) n (%) Events/100 pt-yrs (95% CI)	HR (95% CI)	
<b>Stroke or systemic embolism</b>	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)	0.03
<b>Ischemic stroke or systemic embolism</b>	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)	0.12
<b>Ischemic stroke</b>	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)	0.12
<b>Cardiovascular death</b>	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)	0.33
<b>CV death, MI, or stroke</b>	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)	0.08
<b>All-cause death</b>	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)	0.22

# Conclusions and Implications



# Conclusions



- Over 14,810 patients with atrial fibrillation at risk for stroke were enrolled over 11 months worldwide.
- Asundexian 50 mg once daily was inferior for prevention of stroke and systemic embolism compared with Apixaban in patients with atrial fibrillation at high risk for stroke.
  - // The majority of patients (83%) had previously been treated with OAC.
  - // Observed rate of stroke and systemic embolism on Apixaban in this high-risk population was lower than previously observed.

# Implications



- More research is needed to determine the correct amount of FXIa inhibition for atrial fibrillation stroke prevention.
  - Ongoing patient risk adjusted analyses of PK/PD, FXI activity, and stroke rates.
  - Near total suppression of FXIa activity may be required for this indication.
- Prior use of oral anticoagulants without clinical issues and current medical therapy may lead to lower rates of stroke and systemic embolism and bleeding compared with historical data based on patient risk.
- Multiple ongoing studies with Factor XI inhibition in different indications are ongoing with IDMC oversight. These will be informative to the effect of targeting Factor XI on patient care.

# Thank You

## Executive Committee

Manesh Patel, Chair  
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United Kingdom	Diana Gorog
United States	Jon Piccini (DCRI PI)

We thank the patients who agreed to be involved in this study.

# Results Online



The NEW ENGLAND  
JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Asundexian versus Apixaban in Patients with Atrial Fibrillation

J.P. Piccini, M.R. Patel, J. Steffel, K. Ferdinand, I.C. Van Gelder, A.M. Russo,  
C.-S. Ma, S.G. Goodman, J. Oldgren, C. Hammett, R.D. Lopes, M. Akao,  
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for the OCEANIC-AF Steering Committee and Investigators\*

