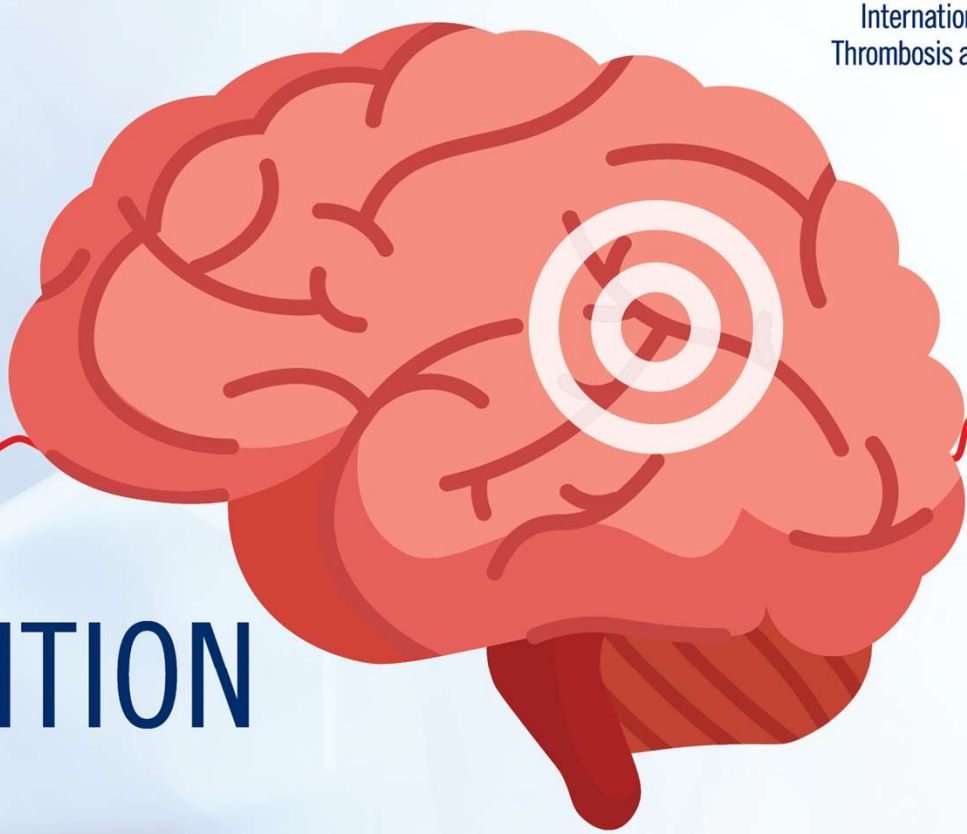
Rethinking SECONDARY STROKE PREVENTION:

The Emerging Role of FACTOR XI INHIBITION



ISTH
International Society on Thrombosis and Haemostasis

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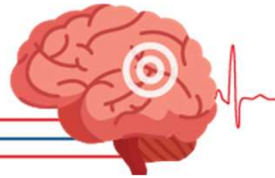
Today's Agenda:

1. Welcome and Framing the Unmet Need
2. Mechanisms of Thrombosis, Hemostasis, and Factor XI
3. Clinical Evidence for FXIa Inhibitors
4. Clinical Scenarios and Application to Practice
5. Audience Q&A, and Key Takeaways

Learning Objectives

- Differentiate the role of factor XI (FXI) in thrombosis versus hemostasis and its implications for addressing current unmet needs for secondary stroke prevention
- Evaluate recent clinical trial data to determine potential practice implications of FXIa inhibitors in secondary stroke prevention
- Analyze clinical scenarios to identify how FXIa inhibitors may address residual stroke risk while minimizing bleeding concerns

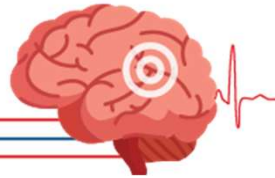
Knowledge Check!
Look for a light bulb symbol in the top right corner of the screen to find the answers to the "What Do You Know?" questions



Knowledge Check #1

In the context of secondary stroke prevention, how does FXI inhibition impact thrombotic risk?

A. Dissolves pre-existing arterial clots
B. Attenuates thrombin amplification and pathologic clot propagation
C. Directly blocks platelet adhesion
D. Directly interacts with fibrin to reduce cross-linking



Knowledge Check #2

JC1

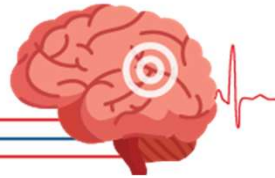
In the OCEANIC-STROKE trial, how did the primary efficacy outcome vary across prespecified subgroups?

A. The treatment benefit was observed only in patients with large-vessel atherosclerotic stroke

B. The treatment benefit was observed only in patients with prior transient ischemic attack

C. The treatment benefit was observed only in patients receiving dual antiplatelet therapy

D. The treatment benefit was consistent across all prespecified subgroups



Slide 6

JC1 Might be easy because option is an all and deviates from other answer options.

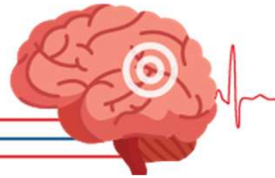
Slide light bulb take away says "Efficacy was not impacted by age, sex, stroke severity, or index event".

Melissa, Thoughts on adding the same language after " and was consistent across all prespecified groups"?
Jas Chahal, 2026-04-13T12:56:35.500

Knowledge Check #3

Which patient phenotype most closely aligns with the target population for FXIa inhibitors in secondary stroke prevention?

A. The patient with a cardioembolic stroke
B. The patient with recurrent ischemic events and prior major bleeding
C. The patient with atrial fibrillation who is intolerant to warfarin
D. The patient with a stroke due to intracranial atherosclerosis



Polling Question

How familiar are you with the mechanism of action of the FXI/XIa inhibitors in clinical trials for secondary stroke prevention?

1. Not at all familiar
2. A little familiar
3. Somewhat familiar
4. Very familiar
5. Extremely familiar

Unmet Needs in Stroke

Clinical Case Discussion #1: Walter

Clinical Dilemma: How do we reduce recurrent stroke risk without precipitating bleeding?

Case Summary

- Walter is a 77-year-old man
- 48 hours ago, had a lacunar ischemic stroke
- Second ischemic event in 6 months
- History of GI bleeding on DAPT
- Chronic kidney disease (eGFR ~35 mL/min)
- Difficulty with speaking
- Currently on SAPT with clopidogrel

Limitations of Current Therapies

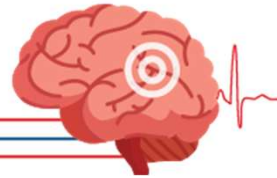
- DAPT → unacceptable bleeding risk
- DOACs → limited indication, renal considerations

DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulant; eGFR = estimated glomerular filtration rate; GI =gastrointestinal; SAPT = single antiplatelet therapy

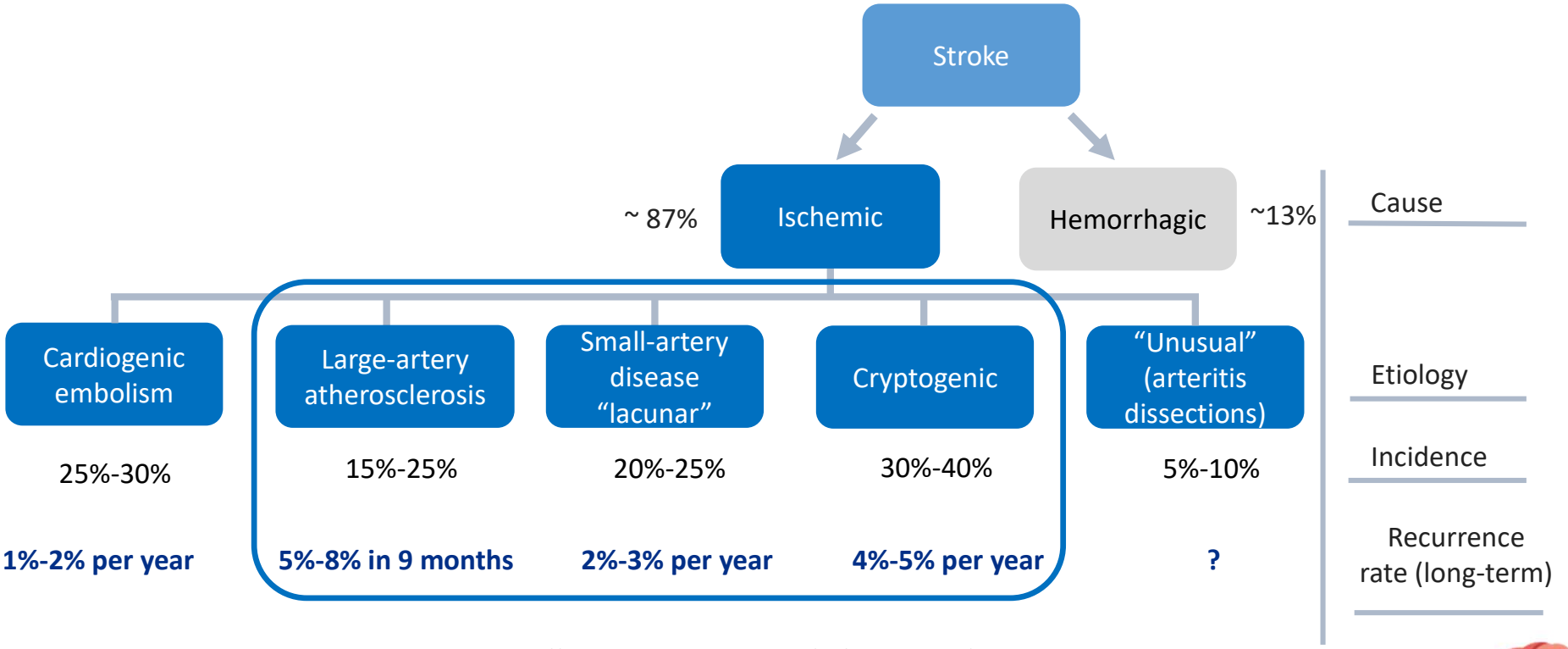
Vascular and Thromboembolic Diseases Remain Leading Causes of Death and Disability Worldwide

Ischemic stroke	**70** million people affected	**70** million years lost to death and disability	**3.6** million deaths	**Second-most common cause of death**
Atrial fibrillation (AF)	**52.6** million people affected	**8.4 million** years lost to death and disability	**339,000** deaths	**Incidence increases sharply with age**

Feigin VL, et al. *Int J Stroke*. 2025 Feb;20(2):132-144; Cheng S, et al. *Europace*. 2024;26(7):euae195; Liang P, et al. *Front Public Health*. 2025;13:1569179.



Current Landscape for Stroke Subtypes



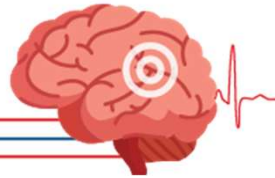
American Stroke Association. Accessed October 3, 2024. https://www.strokeassociation.org/en/about-stroke/types-of-stroke; Kolominsky-Rabas PL, et al. *Stroke*. 2001;32(12):2735-2740; Ekker MS, et al. *Neurology*. 2019;92(21):e2444-e2454; Tian D, et al. *Sci Rep*. 2018;8(1):5037; Toi S, et al. *J Atheroscler Thromb*. 2022;29(3):393-402; Zhang Y, et al. *Sci Rep*. 2019;9(1):2834.

Key Unmet Needs for Secondary Stroke Prevention

- Burden of treatment/issues with adherence
- Some high-risk groups are underrepresented in clinical trials, so risk-benefit analyses are not clearly defined
- Management of breakthrough bleeding events
  - Intracranial bleeding is a major concern

Factor XI/XIa inhibitors are being investigated to provide **antithrombotic efficacy** with **less intracranial and major bleeding**, which could address the unmet need in non-cardioembolic stroke and fragile AF populations

Botto G, et al. *Adv Ther*. 2021;38(6):2891-2907; Wańkowicz P, et al. *Arch Med Sci*. 2019;15(5):1217-1222; Caso V, et al. *Eur Stroke J*. 2026;11(1):aakaf012.



Polling Question

Which of the following challenges currently represents the greatest burden in your clinic?

A. Recurrent ischemic stroke
B. AF-related events
C. Bleeding on intensified therapy
D. Not applicable/Not currently practicing

Clinical Guidelines

American Heart Association/ American Stroke Association Recommendation

For participants with recent minor (**NIHSS score ≤ 3**) non-cardioembolic ischemic stroke or high-risk TIA ($ABCD^2$ score ≥ 4), DAPT (**ASA + clopidogrel**) should be initiated early (ideally within 12-24 hours of symptom onset and at least within 7 days of onset) and continued for **21 to 90 days**, followed by SAPT, to reduce the risk of recurrent ischemic stroke (Level 1A).

For participants with recent (< 24 hours) minor-to-moderate stroke (**NIHSS score ≤ 5**), high-risk TIA ($ABCD^2$ score ≥ 6), or symptomatic intracranial or extracranial ≥ 30% stenosis of an artery that could account for the event, DAPT with **ticagrelor + ASA for 30 days** may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including intracranial hemorrhage (Level 2B).

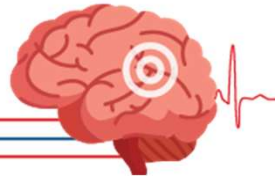
European Stroke Organisation Recommendation

In people with non-cardioembolic minor ischemic stroke (**NIHSS score ≤ 3**) or high-risk TIA ($ABCD^2$ score ≥ 4) in the past 24 hours, we recommend **21 days of DAPT with ASA and clopidogrel**, followed by antiplatelet monotherapy thereafter.

In people with non-cardioembolic mild-to-moderate ischemic stroke (**NIHSS score ≤ 5**) or high-risk TIA ($ABCD^2$ score ≥ 6 or other high-risk features*) in the past 24 hours, we suggest **30 days of DAPT with ASA and ticagrelor**, followed by antiplatelet monotherapy thereafter.

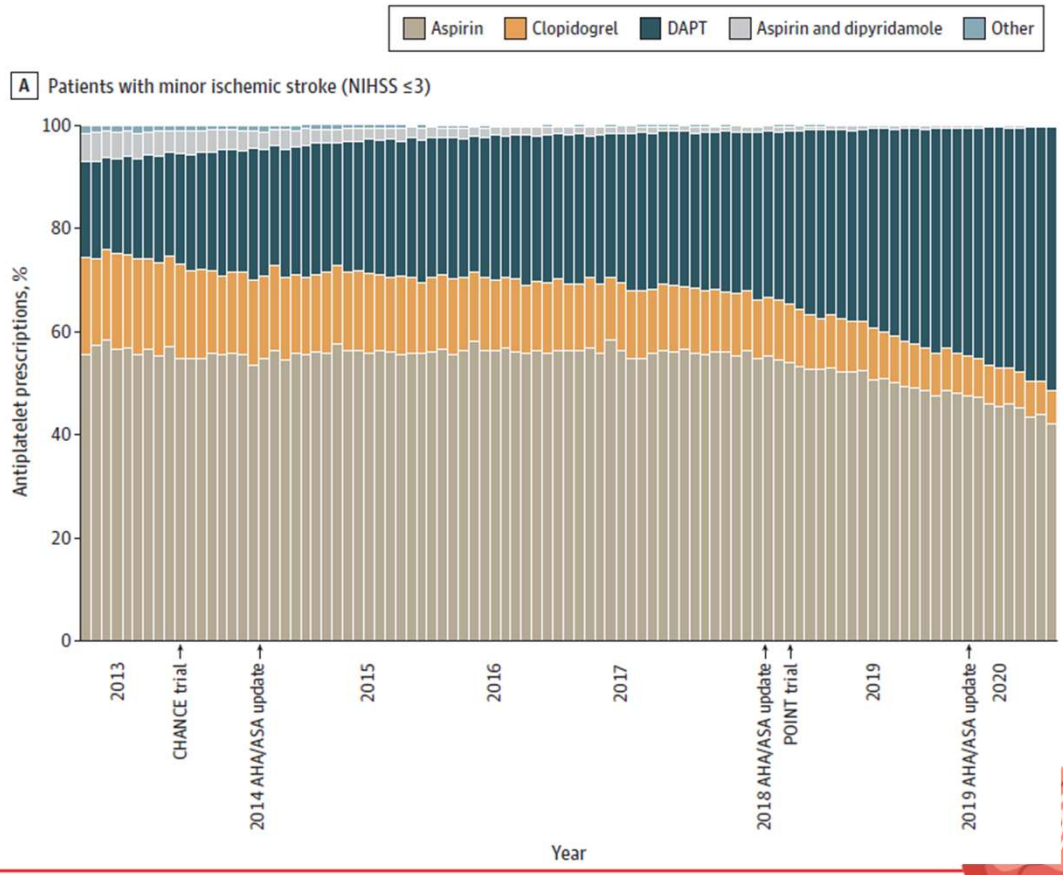
$ABCD^2$ = age, blood pressure, clinical features of TIA, duration, diabetes; ASA = aspirin; NIHSS = National Institutes of Health Stroke Scale; *Defined as either intracranial atherosclerotic disease or ≥ 50% stenosis in an internal carotid artery that could account for the presentation.

Kleindorfer DO, et al. *Stroke.* 2021;52(7):e364-e467; Dawson J, et al. *Eur Stroke J*. 2021;6(2):CLXXXVII-CXCI.



Patterns in Antiplatelet Prescriptions at Hospital Discharge in the US

A total of 1,281,034 patients hospitalized for acute ischemic stroke were prescribed antiplatelet therapy at discharge from 2,228 hospitals participating in the Get With the Guidelines Stroke Registry between October 1, 2012, and June 30, 2020



Xian Y, et al. *JAMA Intern Med*. 2022;182(5):559-564.

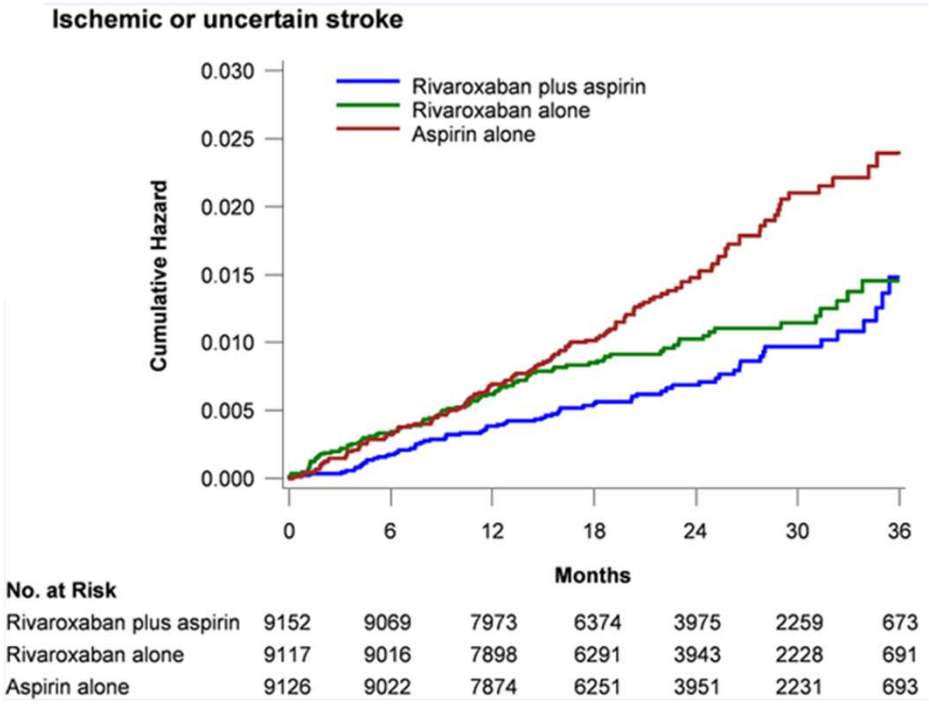
Impacts of Long-Term Anticoagulation After Stroke in Clinical Trials

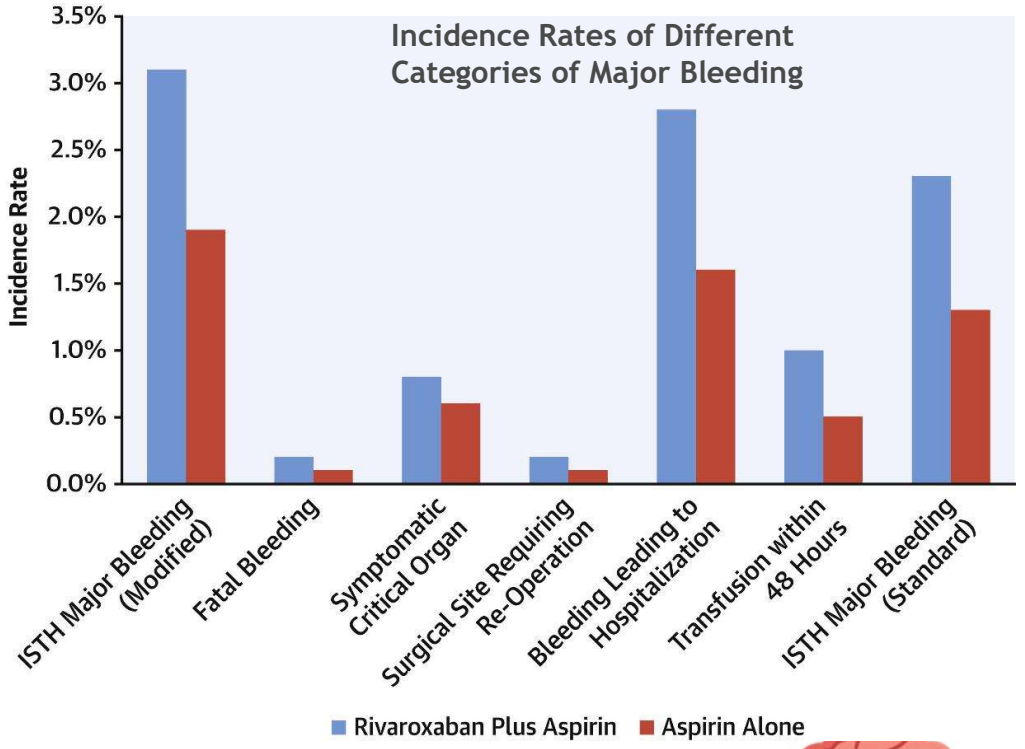
Study	Target population	N	Study intervention	Comparator	Bleeding criteria	Safety outcome rates	Duration
IST	Acute ischemic stroke ≤ 48h onset	19,435	sc UFH (5k/12.5k IU BID) ± ASA 300mg	ASA alone/heparin alone/both/neither	Major extracranial bleed; hemorrhagic stroke	Recurrence ↓ 2.2% offset by bleeds ↑ 2.0%	14 days (6mo f/u)
WARSS	Noncardioembolic stroke < 30d	2,206	Warfarin (INR 1.4-2.8)	ASA 325mg	ISTH major/minor	Stroke/death equivalent (17%); ↑ minor bleeds w/warfarin	Mean 2 years
WASID	Symptomatic ICAD 50-99%; recent TIA/stroke	569	Warfarin (INR 2.0-3.0)	ASA 1300mg	GUSTO severe/moderate	↑ Death (9.7% vs 5.8%); major ICH 8.3% annualized w/warfarin	Mean 1.8 years

BID = twice daily; GUSTO = global use of strategies to open occluded coronary arteries; ICAD = intracranial atherosclerotic disease; INR = international normalized ratio; ISTH = International Society for Thrombosis and Haemostsis; mo = month; sc = subcutaneous; UFH = unfractionated heparin

International Stroke Trial Collaborative Group. *Lancet*. 1997;349(9065):1569-1581; Mohr JP, et al. *N Engl J Med*. 2001;345(20):1444-1451; Chimowitz MI, et al. *N Engl J Med*. 2005;352(13):1305-1316.

COMPASS Study: Previous Experience of Anticoagulation on Top of Aspirin





Sharma M, et al. *Circulation.* 2019;139:1134-1145; Eikelboom J, et al. *J Am Coll Cardiol.* 2019;74 (12) 1519–1528.

Additional Learnings From the COMPASS Trial

Low-dose rivaroxaban + aspirin may be an efficacious antithrombotic therapy for primary and especially secondary prevention of stroke in patients with atherosclerosis

Major bleeding occurred more frequently with rivaroxaban plus aspirin compared to aspirin alone

Rivaroxaban alone (5 mg twice daily) did not improve cardiovascular outcomes over aspirin alone

Excluded patients with recent stroke, so treatment impact, early post-stroke was not examined

Steffel J, et al. *Circulation*. 2020;142(1):40-48; Eikelboom JW, et al. *N Engl J Med*. 2017;377(14):1319-1330.

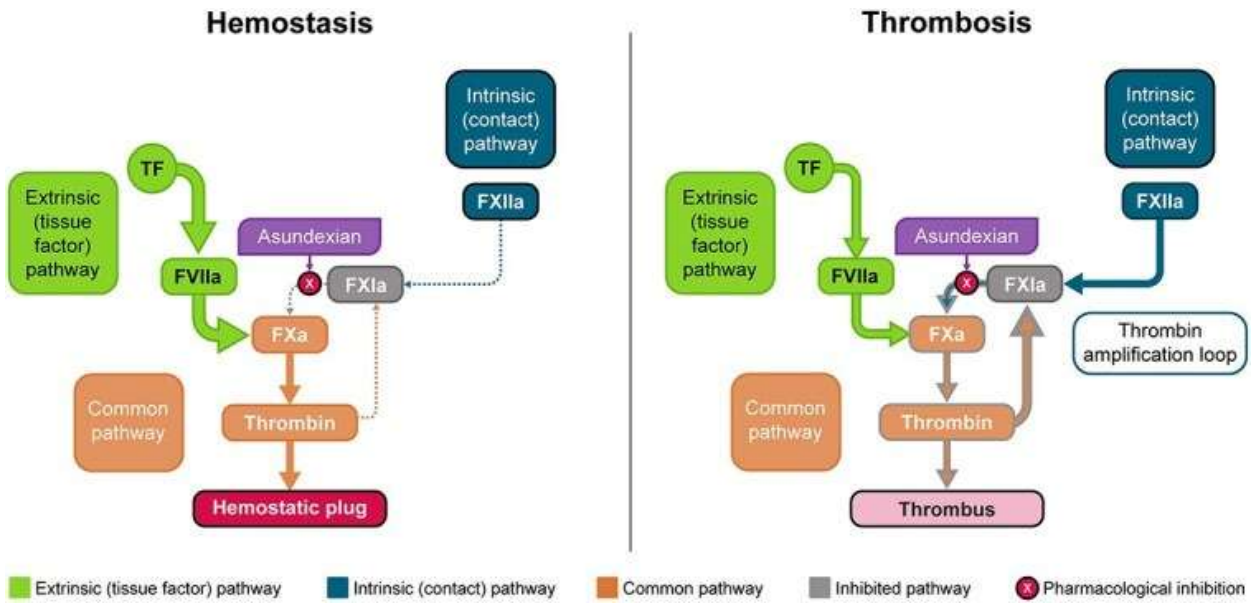
Section Takeaways

- Patients experience recurrent ischemic stroke despite therapeutic anticoagulation
- Fear of intracranial hemorrhage and major bleeding often leads to dose reduction, discontinuation, or avoidance of anticoagulation in high-risk patients

The Role of FXI/XIa in Hemostasis and Thrombosis

The Role of FXI/XIa in Hemostasis and Thrombosis

Inhibition of FXI/XIa attenuates thrombin amplification and pathologic clot propagation



Sharma M, et al. *Eur Stroke J*. 2026;11(1):aakaf017.

Evidence Supporting FXI/XIa as a Target

Human genetic deficiency

Subjects with severe congenital FXI deficiency (1 in 450 Ashkenazi Jews) have a reduced risk of thrombosis and rarely experience spontaneous bleeding

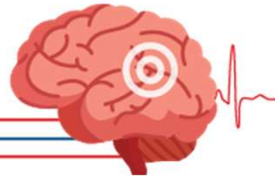
Genetic epidemiology

In large cohort studies, the risk of thrombosis was two-fold higher in subjects with high FXI levels compared with those with normal levels, and 40%-90% lower in those with reduced FXI levels

Animal studies

FXI inhibition attenuates thrombosis in mouse, rabbit, monkey, and baboon models with no increase in bleeding

Asselta R, et al. *Blood*. 2017;130(4):e1-e6; Meijers J, et al. *N Engl J Med.* 2000;9;342(10):696-701; Preis M, et al. *Blood.* 2017;129(9):1210-1215; Gailani D, et al. *Arterioscler Thromb Vasc Biol.* 2016;36(7):1316-22.

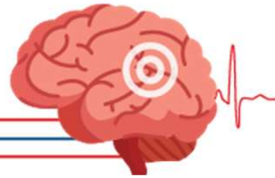


Features of FXIa Inhibitors and Current Therapeutic Options

Feature	Antiplatelet Therapy	DOACs	FXIa Inhibitors
Mechanistic rationale	Prevent platelet-rich arterial thrombi	Prevent fibrin-rich clots	Uncouple thrombosis from hemostasis
Impact on hemostasis	Moderate (↑ with dual therapy)	High	Low/none
Stroke prevention efficacy	Modest (single); moderate (dual)	High (especially cardioembolic)	26% reduction in OCEANIC-STROKE
Major bleeding risk	↑ with dual therapy	Clinically significant (GI, ICH)	No increased bleeding

ICH = intracranial hemorrhage

Brown DL, et al. *Stroke*. 2021;52(7):e468-e479; Coyle M, Lynch A, Higgins M, et al. *JAMA Netw Open*. 2024;7(12):e2449017; Sharma M, et al. *Lancet Neurol*. 2024;23(1):46-59; Shoamanesh A, et al. *Lancet*. 2022;400(10357):997-1007.



Oral FXIa Inhibitors in Clinical Trials for Stroke

Asundexian

- Small-molecule inhibitor
- Blocks active site of FXIa
- **Orally** administered OD

Phase 2 studies > 4,000 participants showed:

- > 90% inhibition of FXIa at peak and trough
- No significant increase in major bleeding over placebo with or without antiplatelets

Milvexian

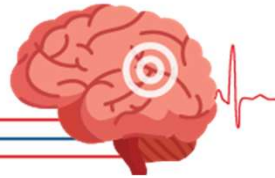
- Small-molecule inhibitor
- Blocks active site of FXIa
- Orally administered BID

Phase 2 studies > 2,300 participants showed:

- No significant increase in major bleeding over placebo with or without antiplatelets

BID, twice daily; OD, once daily

Sharma M, et al. *Lancet Neurol*. 2024;23(1):46-59; Shoamanesh A, et al. *Lancet*. 2022;400(10357):997-1007.



Section Takeaways

- FXI enhances thrombin generation and reinforces clot formation after the initial trigger
  - Inhibition of FXI/XIa attenuates thrombin amplification and pathologic clot propagation
- Lower FXI levels are associated with reduced risk of venous thromboembolism and ischemic stroke, supporting its pathologic role in thrombosis
- FXI/XIa inhibition aims to uncouple thrombosis from hemostasis

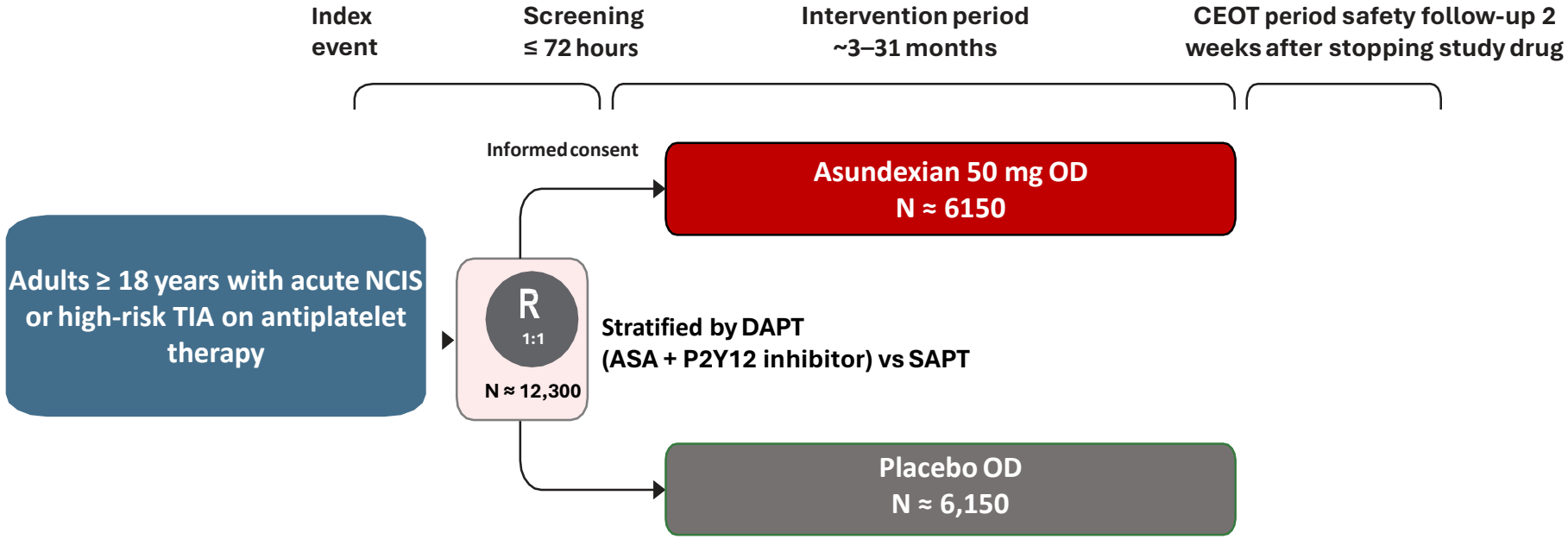
Asundexian Phase 3 Trial Data

Polling Question

How familiar are you with the current ongoing clinical trials of the FXI/XIa inhibitors for secondary stroke prevention?

1. Not at all familiar
2. A little familiar
3. Somewhat familiar
4. Very familiar
5. Extremely familiar

Asundexian for Preventing Recurrent Ischemic Stroke in Patients With Non-cardioembolic Ischemic Stroke or High-Risk TIA: OCEANIC-STROKE



NCIS = non-cardioembolic ischemic stroke; CEOT = common end of treatment

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA.

OCEANIC-STROKE: Key Inclusion and Exclusion Criteria

Key inclusion:

- Participants aged ≥ 18 years, within 72 hours of symptom onset:
  - **Non-cardioembolic ischemic stroke** (NIHSS ≤15) **or** high-risk TIA (ABCD^2 6 or 7)
  - History of **atherosclerosis** **or** evidence of **plaque on imaging** **or** **non-lacunar stroke** on imaging
  - Plan for antiplatelet therapy, single or dual

Key exclusion:

- History of AF or other cardioembolic source requiring anticoagulation
- Ischemic stroke within 7 days of index event
- Strokes following procedures (TAVI, CABG) or other specific cause (e.g. vasculitis)
- End-stage renal disease requiring dialysis
- Active non-trivial bleeding (e.g. PH1 or PH2); asymptomatic HT and CMB permitted
- History of non-traumatic ICH; significant GI bleeding within 6 months

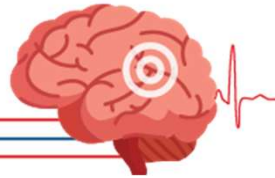
ABCD^2, age, blood pressure, clinical features, duration of symptoms, and diabetes; CABG, coronary artery bypass grafting;
CMB, cerebral microbleed; GI, gastrointestinal; HT, hemorrhagic transformation; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; TAVI, transcatheter aortic valve implantation.

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA.

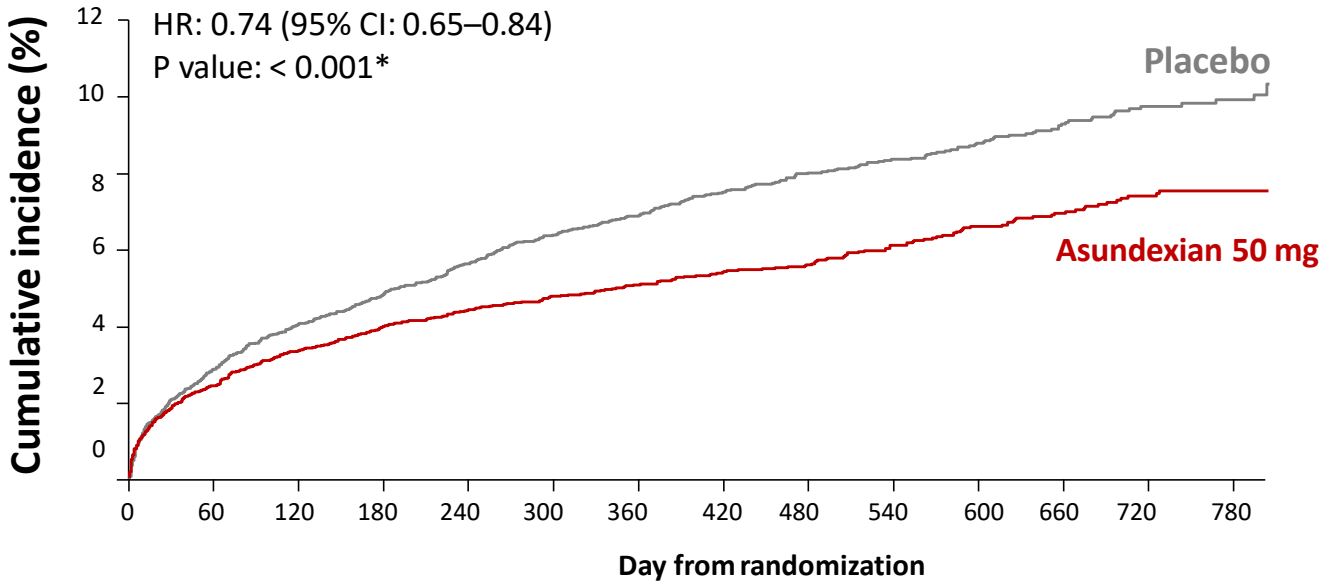
Asundexian for Preventing a Stroke Caused by a Clot in Participants After an Acute Ischemic Stroke or After a High-risk TIA: OCEANIC-STROKE

Endpoints (time to first occurrence)	
Primary efficacy	**Primary safety**
Ischemic stroke	ISTH major bleeding
Secondary efficacy	**Secondary safety**
• All strokes (ischemic and hemorrhagic) • Composite of CV death, MI or stroke • Composite of all-cause mortality, MI or stroke • Ischemic stroke in the first 90 days • Disabling stroke (mRS ≥ 3 at 90 days)	• Composite of ISTH major or CRNM bleeding • ISTH CRNM bleeding • Symptomatic intracranial hemorrhage • Hemorrhagic stroke • Fatal bleeding • Minor bleeding

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA.



OCEANIC-STROKE: Cumulative Incidence of Ischemic Stroke



No. at risk

Placebo	6,165	5,949	5,853	5,754	5,370	4,840	4,406	3,990	3,497	3,070	2,564	1,961	1,410	792
Asundexian 50 mg	6,162	5,958	5,859	5,763	5,384	4,876	4,463	4,033	3,543	3,101	2,588	2,004	1,428	810

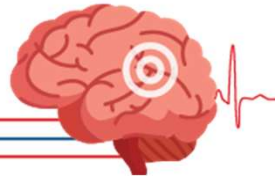
Efficacy was not impacted by age, sex, stroke severity, or index event

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA.

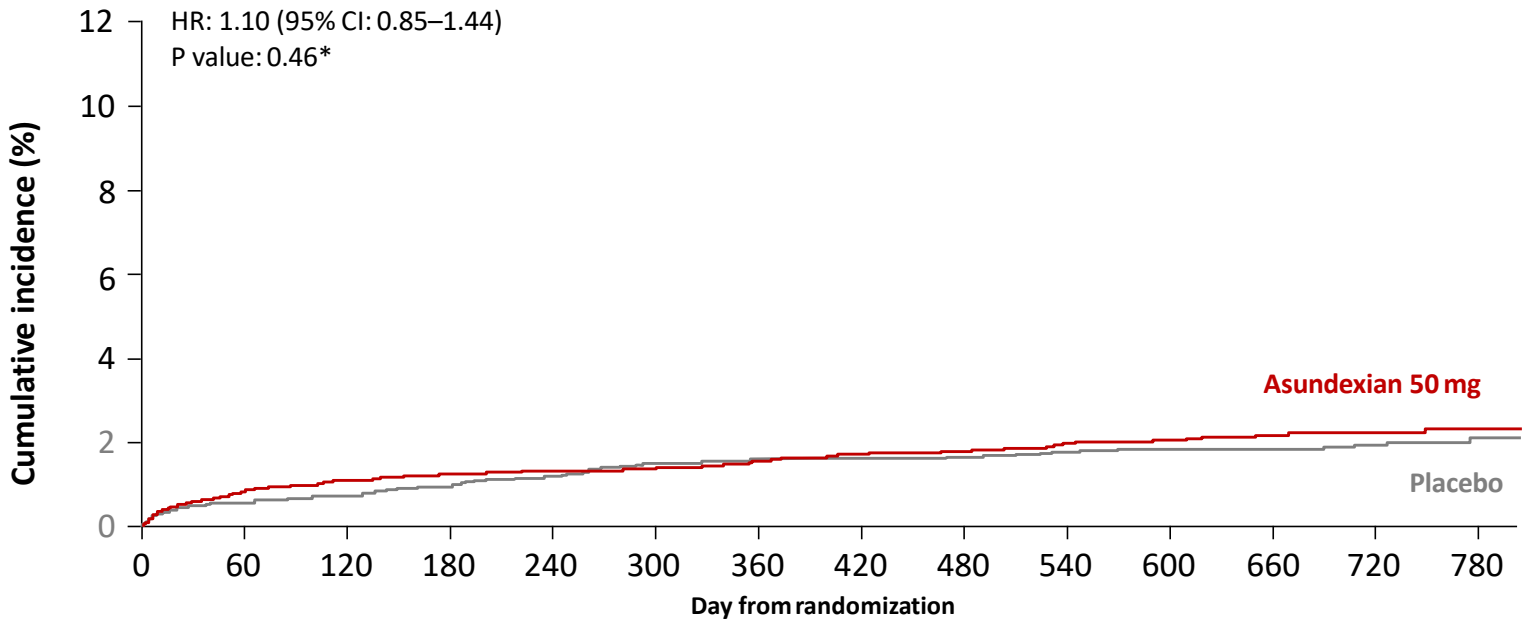
Efficacy of OCEANIC STROKE

Outcome	Asundexian 50 mg (N = 6,162) n (%)	Placebo (N = 6,165) n (%)	csHR (95% CI)†	P value‡
Primary efficacy event				
Ischemic stroke	384 (6.2)	518 (8.4)	0.74 (0.65–0.84)	< 0.001
Secondary efficacy events				
All strokes (ischemic, hemorrhagic)	404 (6.6)	545 (8.8)	0.74 (0.65–0.84)	< 0.001
CV death, MI or stroke	568 (9.2)	685 (11.1)	0.83 (0.74–0.92)	< 0.001
All-cause mortality, MI, or stroke	649 (10.5)	757 (12.3)	0.85 (0.77–0.95)	0.003
Ischemic stroke in the first 90 days	183 (3.0)	218 (3.5)	0.84 (0.69–1.02)	0.08
Disabling/fatal stroke¶	128 (2.1)	185 (3.0)	0.69 (0.55–0.87)	Not applicable

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA.



OCEANIC-STROKE: Cumulative Incidence of ISTH Major Bleeding



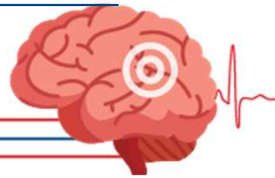
No. at risk

Placebo	6,130	5,391	5,021	4,833	4,415	3,944	3,572	3,165	2,775	2,441	2,026	1,549	1,121	618
Asundexian 50 mg	6,124	5,354	4,968	4,807	4,366	3,900	3,547	3,104	2,699	2,374	1,943	1,508	1,082	613

Safety Outcomes of OCEANIC STROKE

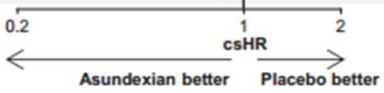
Outcome	Asundexian 50 mg (N = 6,162) n (%)	Placebo (N = 6,165) n (%)	csHR (95% CI)†
Primary safety event			
ISTH major bleeding	117 (1.9)	107 (1.7)	1.10 (0.85–1.44)
Secondary safety events			
ISTH major or clinically relevant non-major bleed	339 (5.5)	307 (5.0)	1.12 (0.96–1.30)
Clinically relevant non-major bleeding	231 (3.8)	210 (3.4)	1.11 (0.92–1.34)
Symptomatic intracranial hemorrhage (includes intracerebral hemorrhage)	41 (0.7)	36 (0.6)	1.15 (0.74–1.80)
Hemorrhagic stroke	13 (0.2)	20 (0.3)	0.66 (0.33–1.32)
Fatal bleeding	14 (0.2)	8 (0.1)	1.77 (0.74–4.23)
Minor bleeding	479 (7.8)	512 (8.4)	0.94 (0.83–1.07)

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA.



Subgroup Analyses for Ischemic Stroke

	Asundexian 50 mg n/N (%)	Placebo n/N (%)	csHR (95% CI)
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)
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)
Western Europe, Australia, and Israel	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 prior to 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 prior to 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 prior to 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)



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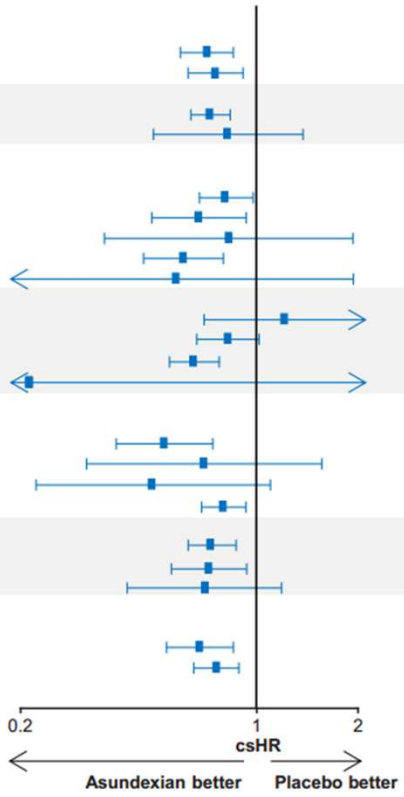
Subgroup Analyses for Ischemic Stroke

	Asundexian 50 mg n/N (%)	Placebo n/N (%)	csHR (95% CI)
Brain imaging demonstrating an acute non-lacunar infarct			
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 (TOAST) classification*			
Large-artery atherosclerosis	203/2512 (8.1%)	247/2484 (9.9%)	0.82 (0.68–0.98)
Small-vessel occlusion (lacune)	59/1290 (4.6%)	90/1349 (6.7%)	0.68 (0.49–0.94)
Stroke of other determined etiology	9/161 (5.6%)	13/188 (6.9%)	0.84 (0.36–1.96)
Stroke of undetermined etiology	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 hours	27/335 (8.1%)	24/356 (6.7%)	1.22 (0.70–2.11)
>24–48 hours	152/2190 (6.9%)	181/2150 (8.4%)	0.83 (0.67–1.03)
>48–72 hours	204/3592 (5.7%)	310/3630 (8.5%)	0.66 (0.55–0.78)
>72 hours	1/45 (2.2%)	3/29 (10.3%)	0.22 (0.02–2.08)
Intravenous thrombolysis and/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 of 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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Milvexian Ongoing Phase 3 Trials

Milvexian in Participants After an Acute Ischemic Stroke or High-Risk Transient Ischemic Attack: LIBREXIA-STROKE

Inclusion Criteria (max 48 hours after one of the following):

- **Ischemic stroke:** Acute brain infarction with NIHSS ≤ 7 plus ≥ 1 of the following: persistent symptoms at randomization, imaging-confirmed acute ischemic lesion, or treatment with thrombolysis/thrombectomy
- **TIA:** Transient focal neurological deficit due to brain ischemia with complete symptom resolution, no infarction on CT/MRI, and ABCD2 score ≥ 6

Patients were excluded if the index stroke or TIA was considered to have another known cause, not related to athero-thrombotic sources

Phase 3 Clinical Trial

R

- Milvexian 25 mg BID + SAPT or DAPT
- Placebo + SAPT or DAPT

Milvexian in Participants After an Acute Ischemic Stroke or High-Risk Transient Ischemic Attack: LIBREXIA-STROKE

1

Primary Outcome Measure:

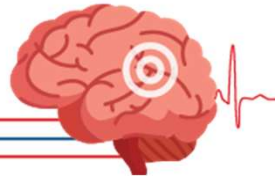
- Time to first occurrence of ischemic stroke

2

Secondary Outcome Measures:

- Time to first occurrence of:
  - Any component of the composite of CVD, MI, or ischemic stroke
  - Ischemic stroke in the first 90 days
  - Any component of major adverse vascular events

CT, computed tomography; MI, myocardial infarction; MRI, magnetic resonance imaging



LIBREXIA-AF

Phase 3 Clinical Trial

Inclusion Criteria

- Age ≥ 18 years
- AF or atrial flutter
- Eligible for anticoagulation
- One or both categories of risk:
  - — One or more of the following:
    - ➢ Age > 75 years
    - ➢ History of stroke
  - — Two or more of the following:
    - ➢ Age 65-74 years
    - ➢ Hypertension
    - ➢ Diabetes
    - ➢ Vascular disease
    - ➢ Congestive heart failure

R 1:1

- Milvexian 100 mg BID
- Apixaban 5 mg BID (or 2.5 mg per label indications)

OLE*

Primary Efficacy Objective

- Non-inferiority of milvexian for the prevention of stroke and systemic embolism

Primary Safety Objective

- Superiority in reducing ISTH major bleeding

*Minimum of 13 weeks with study drug after the last patient is randomized

Takeaways from Clinical Trials

- Asundexian reduced the occurrence of ischemic stroke by 26% in OCEANIC-STROKE
  - Efficacy was not impacted by age, sex, stroke severity, or index event
- No increase in ISTH major bleeding between the placebo and treated groups
  - Shows evidence that it is possible to uncouple hemostasis and thrombosis
- Efficacy and safety data of milvexian from LIBREXIA-STROKE and LIBREXIA-AF are eagerly anticipated

Clinical Scenarios for FXI/XIa Inhibition

Practical and Implementation Considerations

- Which stroke subtypes stand to benefit the most?
- FXI/XIa inhibitors as add-on or replacement for current therapies? Optimal combination?
- Duration of treatment with FXI/XIa inhibitors?
- How should patients taking FXI/XIa inhibitors be monitored? Can procedures be done on this treatment?

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA.

Practical and Implementation Considerations

→ OCEANIC-STROKE showed that efficacy was not impacted by stroke severity, subtype, and patient age, sex, or index event

→Current evidence **ONLY supports FXIa inhibitors** as **add-on therapy** for SSP. Clinical trials ONLY examined FXI/XIa when added to anti-platelet therapy, and not independently.

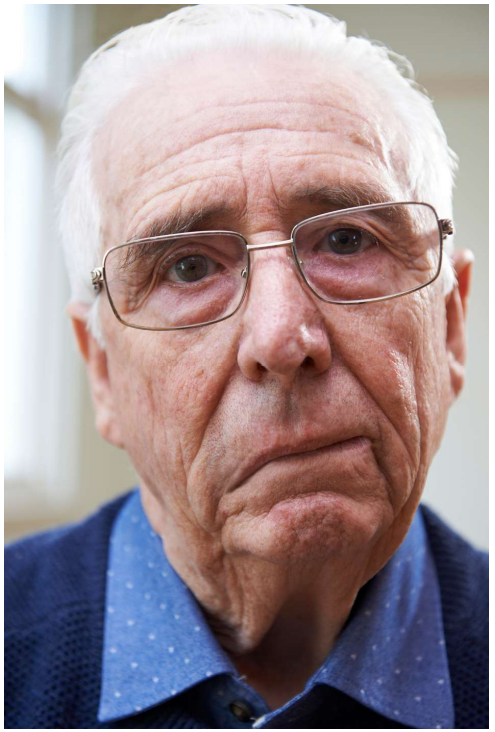
→ So far there has been **no loss of efficacy or safety** up to over **780 days**

→ Monitoring schedule might be comparable to DOACs and reversal strategies are unlikely to be needed. Likely to be safe for procedures based on evidence in other clinical trials for other clinical indications.

Sharma M, et al. Presented at the International Stroke Conference. February 4, 2026. New Orleans, LA; Sharma M, et al. *Lancet Neurol*. 2024;23(1):46-59; Shoamanesh A, et al. *Lancet*. 2022;400(10357):997-1007.

Clinical Case Discussion #1: Return to Walter

- Walter read about the results of OCEANIC-STROKE in the news and wonders if he might be a candidate for FXI/XIa inhibitors
- **How would you talk to Walter about the implications of this study?**
- Potential for FXIa Inhibitors
  - Efficacy across many stroke-subtypes
  - No increase in bleeding
  - Low renal clearance



Sharma M, et al. *Lancet Neurol*. 2024;23(1):46-59; Shoamanesh A, et al. *Lancet*. 2022;400(10357):997-1007.

Clinical Case Discussion #2: Dolores

Case Summary

- 74-year-old woman, recent (72 hours) non-cardioembolic ischemic stroke due to intracranial atherosclerosis
  - NIHSS = 13
- Currently on SAPT
- Hypertension and diabetes; moderate intracranial atherosclerosis

Limitations of Current Therapies

- DAPT → unacceptable bleeding risk
- DOACs → limited indication
- Residual thrombotic risk remains

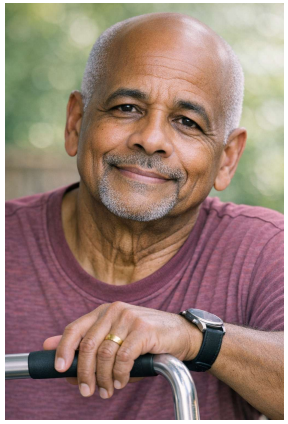
Potential for FXIa Inhibitors

- Reduce thrombus propagation without markedly affecting primary hemostasis
- Could provide additive stroke prevention without increasing bleeding

Clinical Case Discussion #3: Peter

Case Summary

- 72-year-old man with recent (24 hours) non-cardioembolic ischemic stroke
- NIHSS 4 (mild–moderate severity)
- MRI-confirmed right MCA territory infarct
- 50–60% intracranial M1 stenosis
- No indication for therapeutic anticoagulation
- Initiated on DAPT



Limitations of Current Therapies

- DAPT reduces risk but residual recurrence remains
- DAPT increases bleeding risk with limited long-term use
- No role for DOACs in non-cardioembolic stroke
- Atherosclerotic thrombotic risk persists

Potential for FXIa Inhibitors

- Upstream thrombus modulation
- Non-platelet, non-FXa strategy
- Potential to reduce recurrence without excess bleeding

Key Takeaways

- Current therapies to reduce risk of stroke after non-cardioembolic ischemic stroke or TIA are limited
- FXIa inhibition has the potential to block the thrombosis that leads to stroke without impacting hemorrhage risk
  - FXI/XIa inhibitors attenuates thrombin amplification and pathologic clot propagation
- Asundexian is now proven as an adjunct to antiplatelet therapy for secondary stroke prevention
  - Trials were in patients with recent no on-cardioembolic ischemic stroke with a history of atherosclerosis or evidence of plaque on imaging or non-lacunar stroke on imaging
  - Efficacy was not impacted by age, sex, stroke severity, or index event
  - The LIBREXIA-STROKE trial is testing milvexian in a similar population
- Other indications for FXI/FXIa inhibition are under study