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A NEW CHAPTER IN SECONDARY STROKE PREVENTION

Clinical Insights from Phase III FXIa Inhibitor Trials

Canadian Stroke Congress (CSC)

May 25, 2026 | 1:00pm-2:30pm MT

Banff, Alberta

Welcome and Introductions

Mike Sharma, MD, MSc

Professor of Medicine (Neurology), McMaster University
Vascular Neurologist, Hamilton Health Sciences
Michael G DeGroote Chair in Stroke Prevention
Population Health Research Institute, Hamilton, ON

Disclosure of Conflict of Interest

Mike Sharma, MD, MSc

The following financial relationships have been disclosed:

- **Bayer, Regeneron, Anthos, Novartis** - Consultant
- **Bayer, Regeneron, Novartis** - Advisory Board
- **Bayer** - Clinical trial funding (paid to institution)

Planning Committee

Chair

Dr. Mike Sharma
MD, MSc
Professor of Medicine (Neurology),
McMaster University
Population Health Research Institute,
Hamilton, ON

Speakers

Dr. Ashkan Shoamanesh
MD, FRCPC
Associate Professor of Medicine (Neurology),
McMaster University
Population Health Research Institute,
Hamilton, ON

Dr. Laura Gioia
MD, MSc
Stroke Neurologist, CHUM
Clinical Associate Professor of Neurosciences
University of Montreal,
Montreal, QC

Disclosure of Financial Support

This program has received financial support from **Bayer AG** in the form of an unrestricted educational grant.

Mitigating Potential Bias

Potential bias in this program has been mitigated as follows:

- All content has been developed and reviewed by an independent expert faculty
- Content is based on current evidence and clinical best practices
- All faculty have disclosed potential conflicts of interest, and these have been addressed
- The program has been designed to ensure balance, scientific rigor, and objectivity

Learning Objectives

At the end of this program, participants will be able to:

- **Describe limitations of current secondary stroke prevention strategies**, including the balance of ischemic risk reduction and bleeding, and efforts to improve the risk–benefit profile.
- **Evaluate the role of Factor XIa inhibition with antiplatelet therapy as a novel antithrombotic strategy** for secondary prevention of non-cardioembolic stroke/TIA.
- **Interpret efficacy and safety outcomes from recent late-phase trials of Factor XIa inhibitors**, including relevant subgroup analyses.
- **Apply emerging evidence to Canadian stroke care pathways** to optimize acute and early secondary prevention, while addressing implementation considerations.

Agenda

TIME	SESSIONS	SPEAKER
1:15 PM	**Welcome and Introductions**	Dr. Mike Sharma
1:20 PM	**The Evolution and Challenges of Secondary Stroke Prevention: Reducing Recurrent Risk While Preserving Safety**	Dr. Ashkan Shoamanesh
1:35 PM	**Evidence for FXIa Inhibition in Stroke Prevention**	Dr. Mike Sharma
1:50 PM	**Audience Q&A**	All Faculty Moderator: Ashkan Shoamanesh
2:00 PM	**Apply the Evidence to Canadian Models of Stroke Care**	Dr. Laura Gioia
2:20 PM	**Panel Discussion and Audience Q&A**	All Faculty Moderator: Dr. Mike Sharma

The Evolution and Challenges of Secondary Stroke Prevention: Reducing Recurrent Risk While Preserving Safety

Dr. Ashkan Shoamanesh, MD, FRCPC
Associate Professor of Medicine (Neurology),
McMaster University
Population Health Research Institute, Hamilton, ON

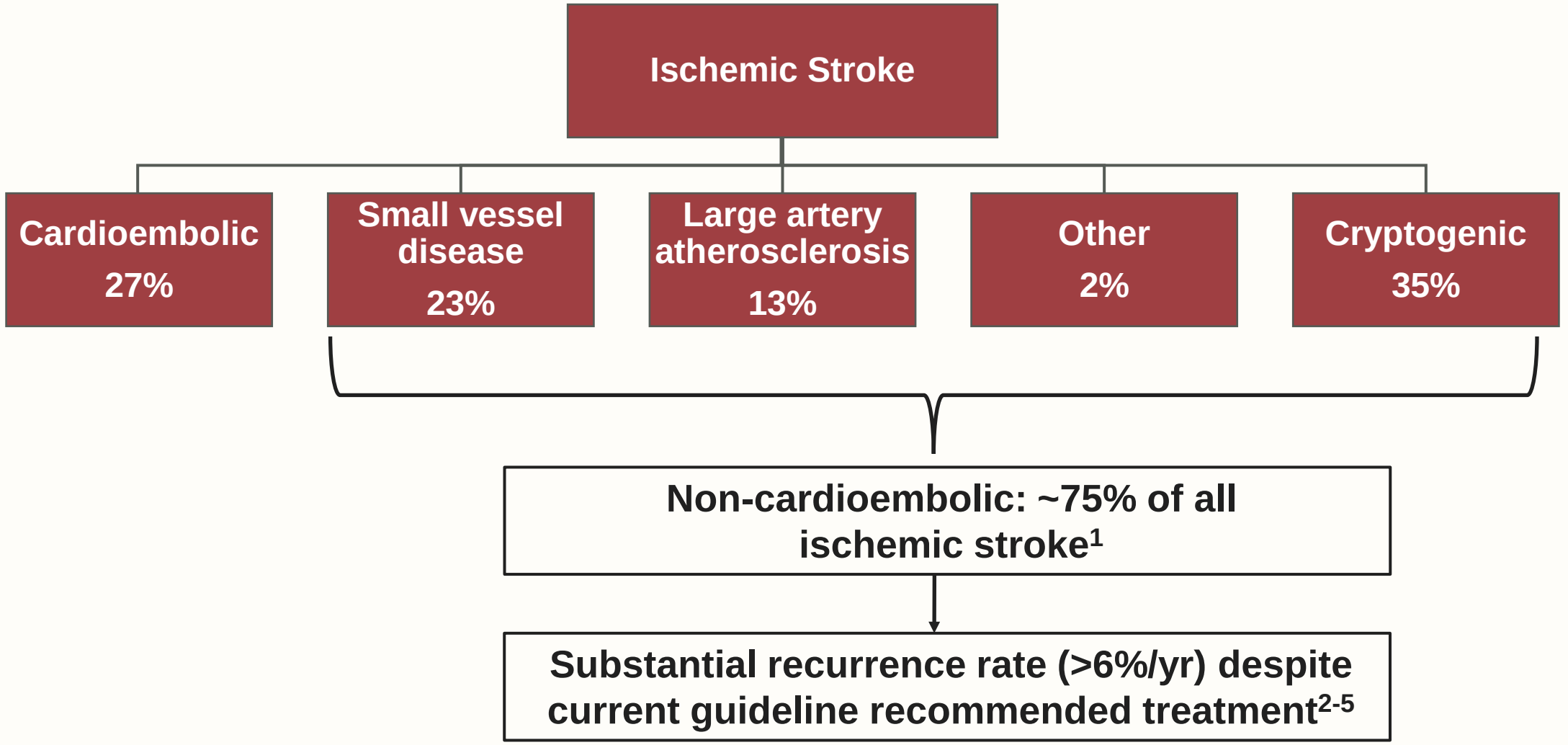
Disclosure of Conflict of Interest

Ashkan Shoamanesh, MD, FRCPC

The following financial relationships have been disclosed:

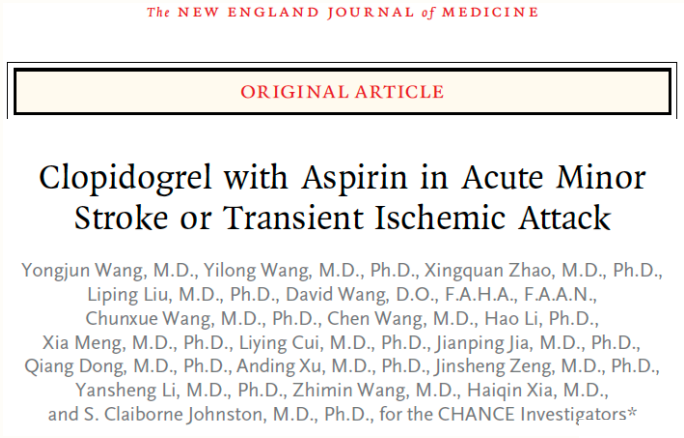
- **Bayer AG, Daiichi Sankyo, AstraZeneca, Javelin** - Funded grants / clinical trials
- **Bayer AG, Daiichi Sankyo, SilverCreek Pharmaceuticals, AstraZeneca** - Advisory Board / consulting
- **Asundexian, Andexanet alfa** - Patents / related interests

Non-Cardioembolic Ischemic Stroke



1. Kleindorfer, et al. *Stroke* 2021; 52: e364–467. **2**. Wang, et al. *NEJM* 2013; 369:11-9. **3**. Johnston, et al. *NEJM* 2018; 379:215-25.
4. Johnston, et al. *NEJM* 2020;383:207-17. **5**. Dawson J, et al. *Eur Stroke J*. 2022 Sep;7(3):I-II.

Acute Short Duration DAPT



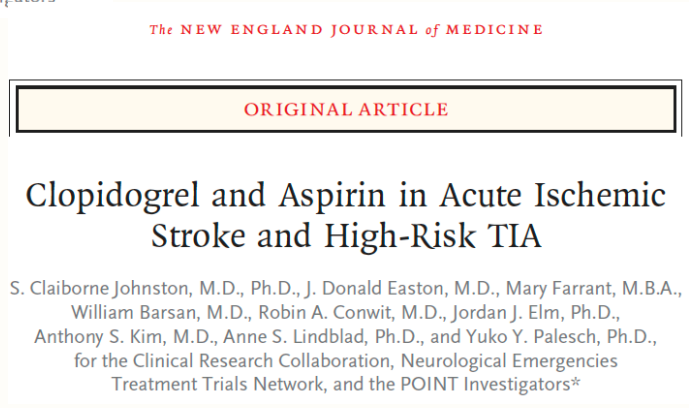
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

Yongjun Wang, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Liping Liu, M.D., Ph.D., David Wang, D.O., F.A.H.A., F.A.A.N., Chunxue Wang, M.D., Ph.D., Chen Wang, M.D., Hao Li, Ph.D., Xia Meng, M.D., Ph.D., Liying Cui, M.D., Ph.D., Jianping Jia, M.D., Ph.D., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jinsheng Zeng, M.D., Ph.D., Yansheng Li, M.D., Ph.D., Zhimin Wang, M.D., Haiqin Xia, M.D., and S. Claiborne Johnston, M.D., Ph.D., for the CHANCE Investigators*

CHANCE 2013[1]



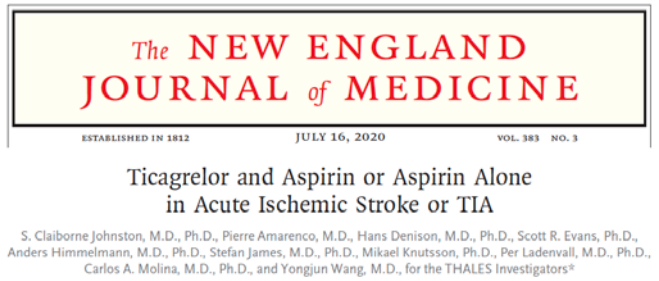
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA

S. Claiborne Johnston, M.D., Ph.D., J. Donald Easton, M.D., Mary Farrant, M.B.A., William Barsan, M.D., Robin A. Conwit, M.D., Jordan J. Elm, Ph.D., Anthony S. Kim, M.D., Anne S. Lindblad, Ph.D., and Yuko Y. Palesch, Ph.D., for the Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators*

POINT 2018[2]



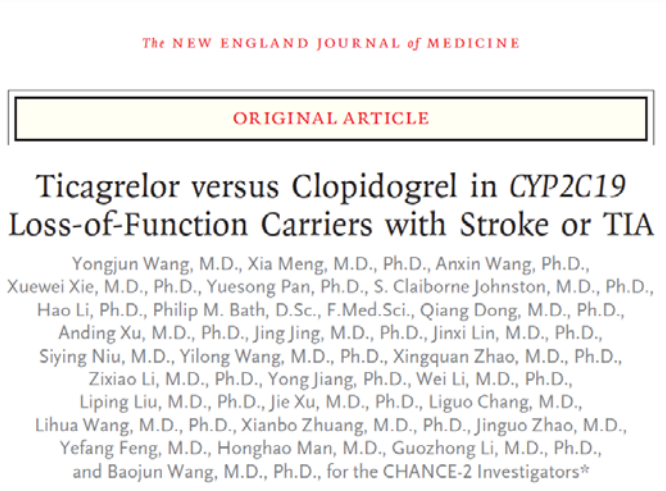
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 16, 2020 VOL. 383 NO. 3

Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA

S. Claiborne Johnston, M.D., Ph.D., Pierre Amarenco, M.D., Hans Denison, M.D., Ph.D., Scott R. Evans, Ph.D., Anders Himmelmann, M.D., Ph.D., Stefan James, M.D., Ph.D., Mikael Knutsson, Ph.D., Per Ladenvall, M.D., Ph.D., Carlos A. Molina, M.D., Ph.D., and Yongjun Wang, M.D., for the THALES Investigators*

THALES 2020[3]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

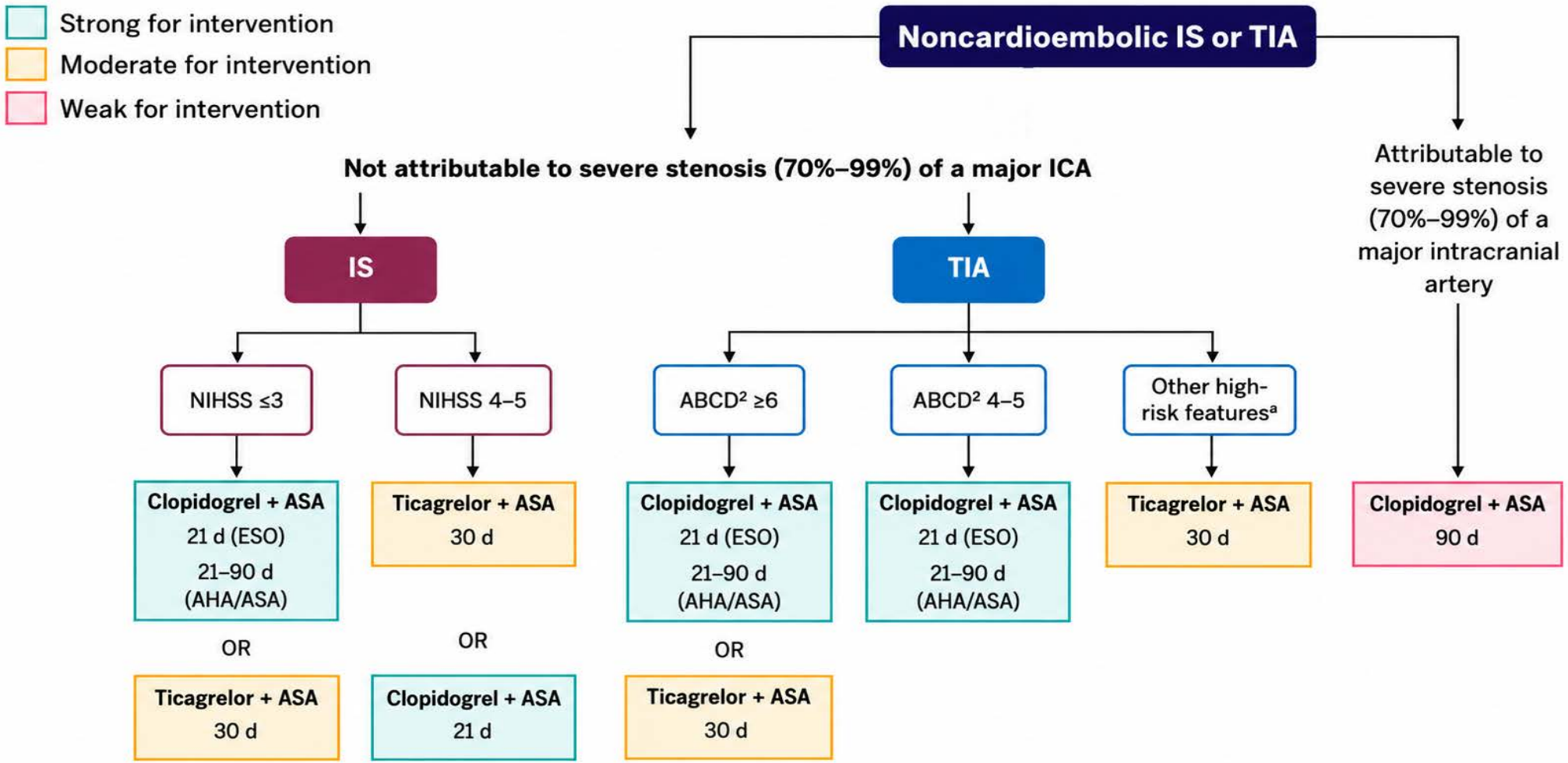
Ticagrelor versus Clopidogrel in *CYP2C19* Loss-of-Function Carriers with Stroke or TIA

Yongjun Wang, M.D., Xia Meng, M.D., Ph.D., Anxin Wang, Ph.D., Xuewei Xie, M.D., Ph.D., Yuesong Pan, Ph.D., S. Claiborne Johnston, M.D., Ph.D., Hao Li, Ph.D., Philip M. Bath, D.Sc., F.Med.Sci., Qiang Dong, M.D., Ph.D., Anding Xu, M.D., Ph.D., Jing Jing, M.D., Ph.D., Jinxi Lin, M.D., Ph.D., Siying Niu, M.D., Yilong Wang, M.D., Ph.D., Xingquan Zhao, M.D., Ph.D., Zixiao Li, M.D., Ph.D., Yong Jiang, Ph.D., Wei Li, M.D., Ph.D., Liping Liu, M.D., Ph.D., Jie Xu, M.D., Ph.D., Liguo Chang, M.D., Lihua Wang, M.D., Ph.D., Xianbo Zhuang, M.D., Ph.D., Jinguo Zhao, M.D., Yefang Feng, M.D., Honghao Man, M.D., Guozhong Li, M.D., Ph.D., and Baojun Wang, M.D., Ph.D., for the CHANCE-2 Investigators*

CHANCE-2 2021[4]

1. Wang Y, et al. *N Engl J Med*. 2013;369(1):11-9. **2**. Johnston SC, et al. *N Engl J Med*. 2018;379(3):215-225.
3. Johnston SC, et al. *N Engl J Med*. 2020;383(3):207-217. **4**. Wang Y, et al. *N Engl J Med*. 2021;385(27):2520-2530.

Short-Term DAPT for Non-Cardioembolic Ischemic Stroke or TIA[1–3]

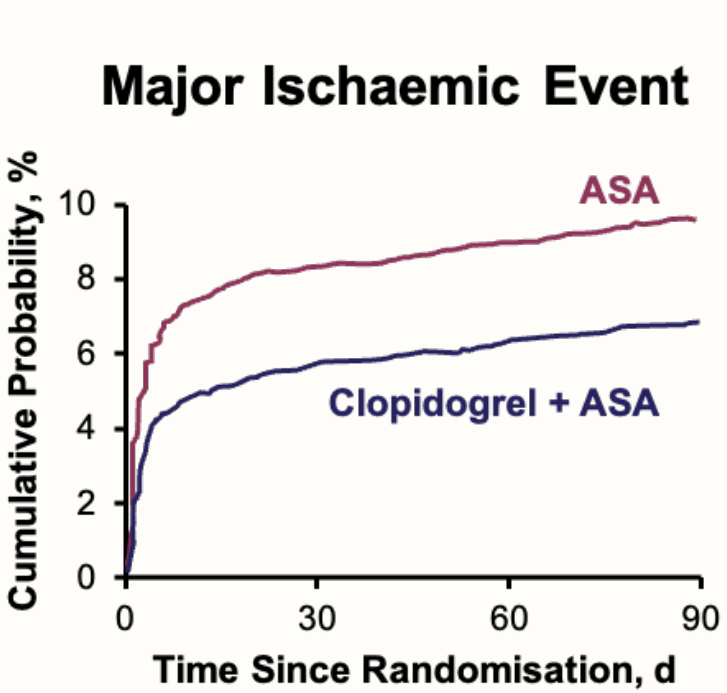


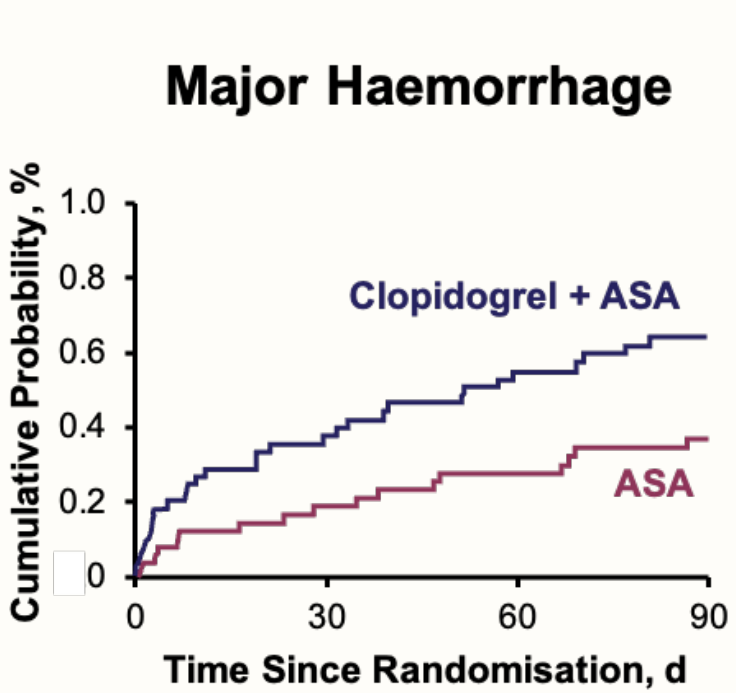
AHA/ASA, American Heart Association/American Stroke Association; ABCD², Age Blood Pressure Clinical Features Duration Diabetes score; ASA, acetylsalicylic acid (aspirin); DAPT, dual antiplatelet therapy; d, days; ESO, European Stroke Organization; h, hours; ICA, internal carotid artery; IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

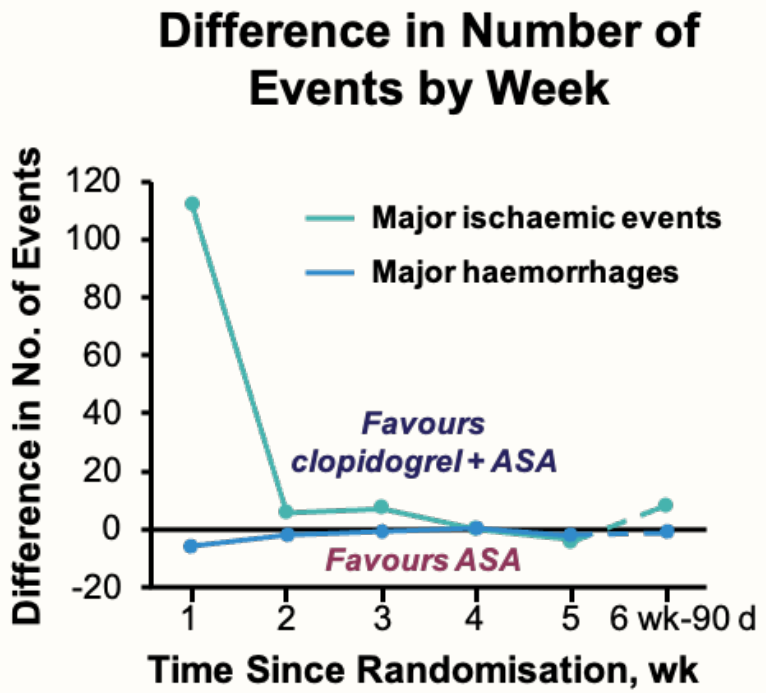
1. Dawson J et al. *Eur Stroke J.* 2021;6:CLXXXVII-CXCI. **2**. Mele F et al. *Neurol Sci*. 2023;44:37-43. **3**. Kleindorfer DO et al. *Stroke*. 2021;52:e364-e467.

Optimal Duration of DAPT After a Minor Stroke or High-Risk TIA

The main net clinical benefit of DAPT occurred within the first 21 d





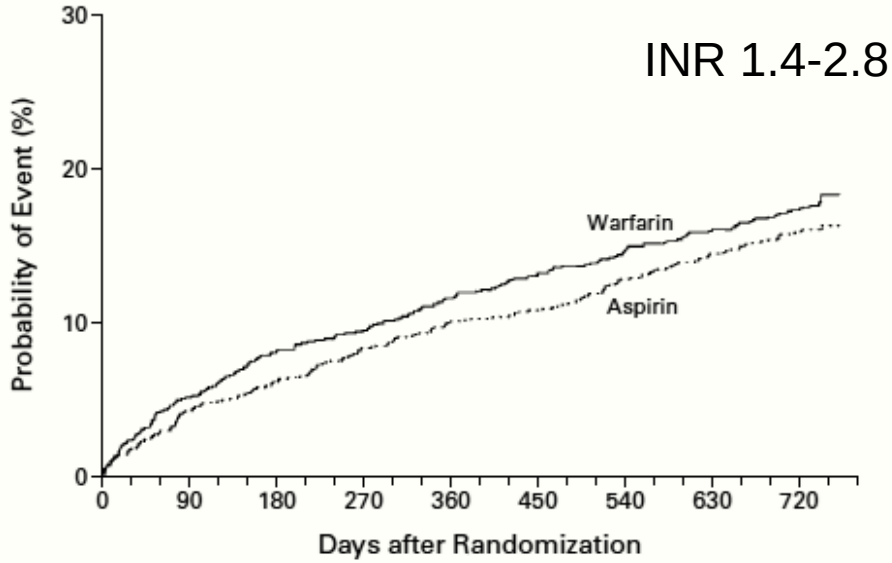


ASA, acetylsalicylic acid (aspirin); DAPT, dual antiplatelet therapy; d, days; TIA, transient ischemic attack; wk, week(s).
Pan Y et al. *JAMA Neurol*. 2019;76:1466-1473.

A COMPARISON OF WARFARIN AND ASPIRIN FOR THE PREVENTION OF RECURRENT ISCHEMIC STROKE

J.P. MOHR, M.D., J.L.P. THOMPSON, PH.D., R.M. LAZAR, PH.D., B. LEVIN, M.D., R.L. SACCO, M.D., K.L. FURIE, M.D., J.P. KISTLER, M.D., G.W. ALBERS, M.D., L.C. PETTIGREW, M.D., H.P. ADAMS, JR., M.D., C.M. JACKSON, M.D., AND P. PULLICINO, M.D., FOR THE WARFARIN–ASPIRIN RECURRENT STROKE STUDY GROUP*

INR 1.4-2.8



NO. AT RISK

Warfarin	1103	1047	1013	998	972	956	939	924	885
Aspirin	1103	1057	1032	1004	984	974	951	932	900

Figure 2. Kaplan–Meier Analyses of the Time to Recurrent Ischemic Stroke or Death According to Treatment Assignment.

TABLE 3. ADVERSE EVENTS ACCORDING TO TREATMENT ASSIGNMENT.*

EVENT	WARFARIN (N=1103)	ASPIRIN (N=1103)	ODDS RATIO (95% CI)	P VALUE†
	no. (%)			
Death	47 (4.3)	53 (4.8)	0.88 (0.58–1.32)	0.61
Related to hemorrhage	7 (0.6)	5 (0.4)	1.40 (0.42–5.13)	0.77
First hemorrhage‡				
Major	38 (3.4)	30 (2.7)	1.28 (0.78–2.10)	0.39
Minor	261 (23.7)	188 (17.0)	1.51 (1.22–1.87)	<0.001
			RATE RATIO (95% CI)	P VALUE§
	no. of events (rate/100 patient-yr)			
All hemorrhages¶				
Major	44 (2.2)	30 (1.5)	1.48 (0.93–2.44)	0.10
Minor	413 (20.8)	259 (12.9)	1.61 (1.38–1.89)	<0.001

INR, International Normalized Ratio.

Mohr JP, et al. *N Engl J Med*. 2001;345(20):1444-51.

Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind placebo-controlled trial

Hans-Cristoph Diener, Julien Bogousslavsky, Lawrence M Brass, Claudio Cimminiello, Laszlo Csiba, Markku Kaste, Didier Leys, Jordi Matias-Guiu,Hans-Jürgen Rupprecht, on behalf of the MATCH investigators*

Figure 2: Ka

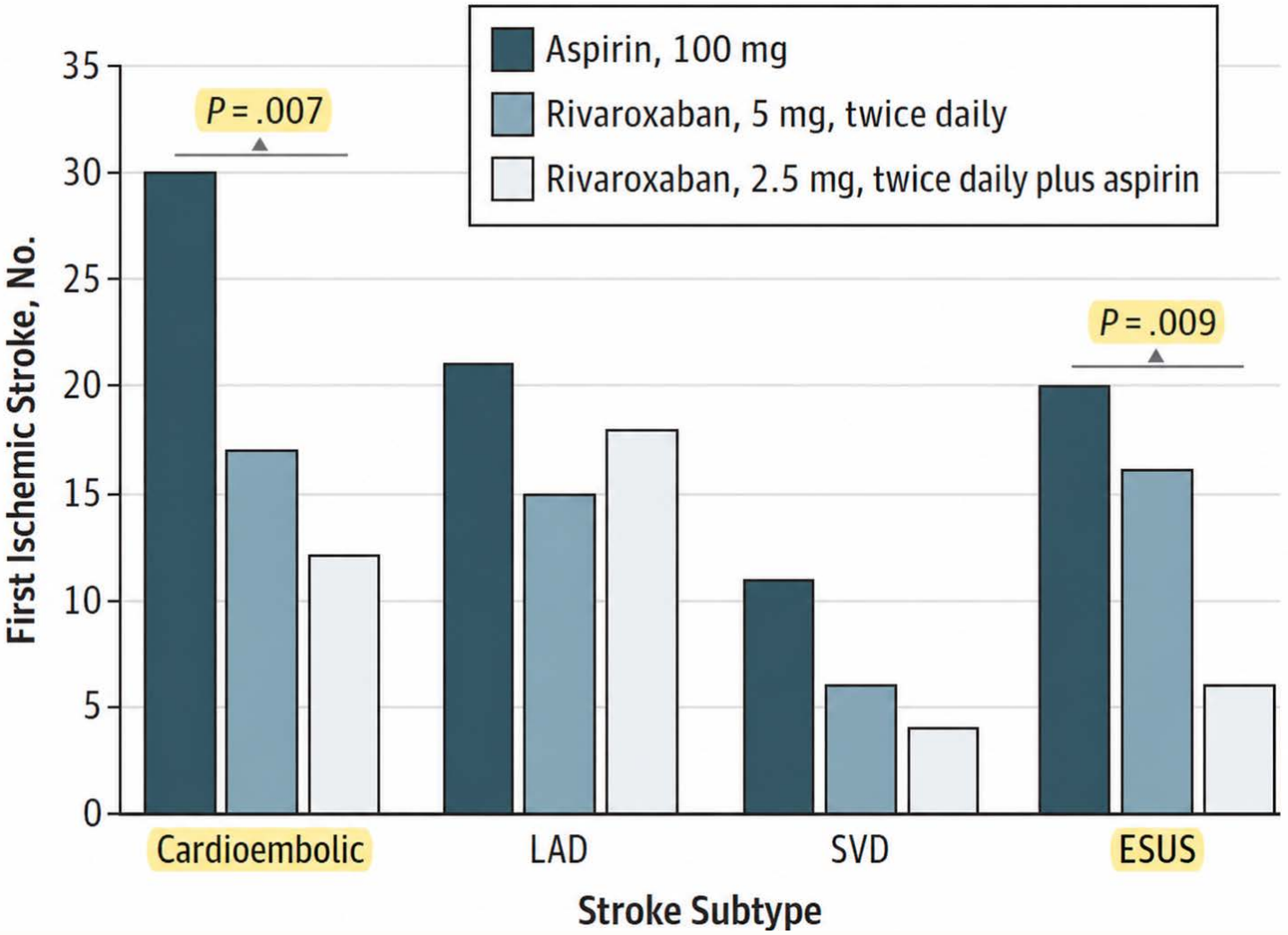
	Number (%) with event		Absolute risk reduction (95% CI)	Relative risk reduction (95% CI)	p*
	Aspirin and clopidogrel (n=3797)	Placebo and clopidogrel (n=3802)			
Primary outcome†	596 (16%)	636 (17%)	1·0% (−0·6 to 2·7)	6·4% (−4·6 to 16·3)	0·244
Myocardial infarction (fatal or not)	59 (2%)	62 (2%)	..	..	..
Ischaemic stroke (fatal or not)	299 (8%)	319 (8%)	..	..	..
Other vascular death	69 (2%)	74 (2%)	..	..	..
Rehospitalisation for acute ischaemic event	169 (4%)	181 (5%)	..	..	..

*Log-rank test. †Only the first event was counted. For every component of the primary endpoint, only the event regarded as first outcome from the composite was counted.

***Table 2:* Primary endpoint analysis**

ne to
zation: 27 days
ıp: 1.5 years

Diener HC, et al. *Lancet*. 2004;364(9431):331-7.



HR 0.30
(95% CI 0.12-0.74)

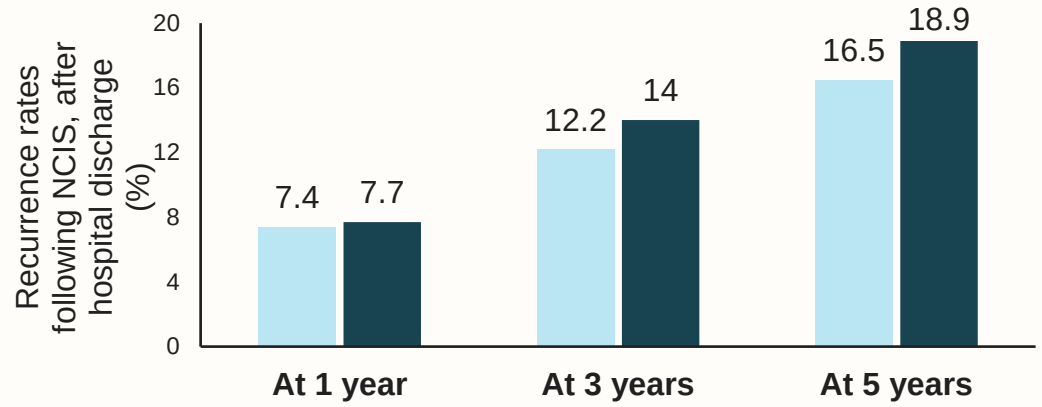
COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; ESUS, Embolic Stroke of Undetermined Source; LAD, Large Artery Disease; SVD, Small Vessel Disease.

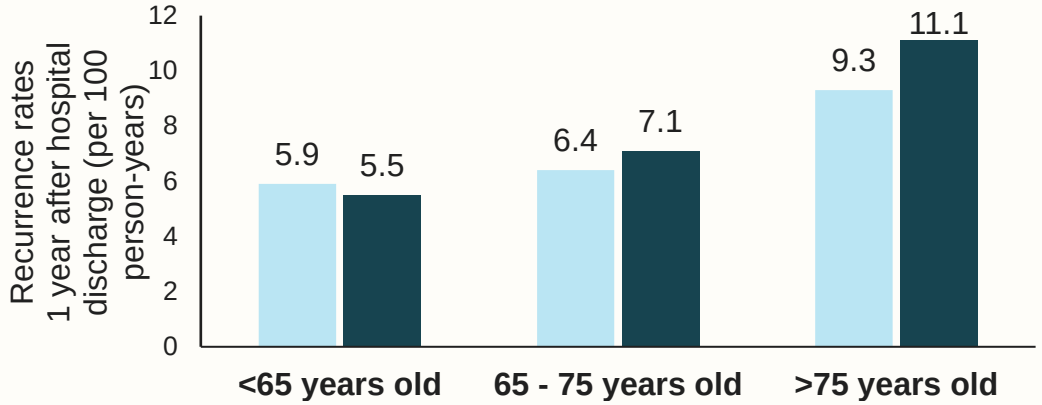
Perera KS, et al. *JAMA Neurol*. 2020;77:43-48.

Real-world Data Reveal a Higher Recurrence Rate of Ischemic Stroke Than Reported in Clinical Trials

ASTRIS studies aimed to estimate the recurrence rate of ischemic strokes in Japan, Denmark and the UK[1]

Note that the ASTRIS studies followed patients **after discharge** from hospital and therefore do not include stroke recurrences immediately after the index event, when recurrence rates are highest.[2]





Key:

RIVER CV ASTRIS UK

Study population:
52,419 patients who experienced a first ischemic stroke (mean age: 70.7 years; female: 46.8%)

RIVER CV ASTRIS DENMARK

Study population:
62,501 patients who experienced a first ischemic stroke (mean age: 70.0 years; female: 44.1%)

RIVER CV ASTRIS JAPAN

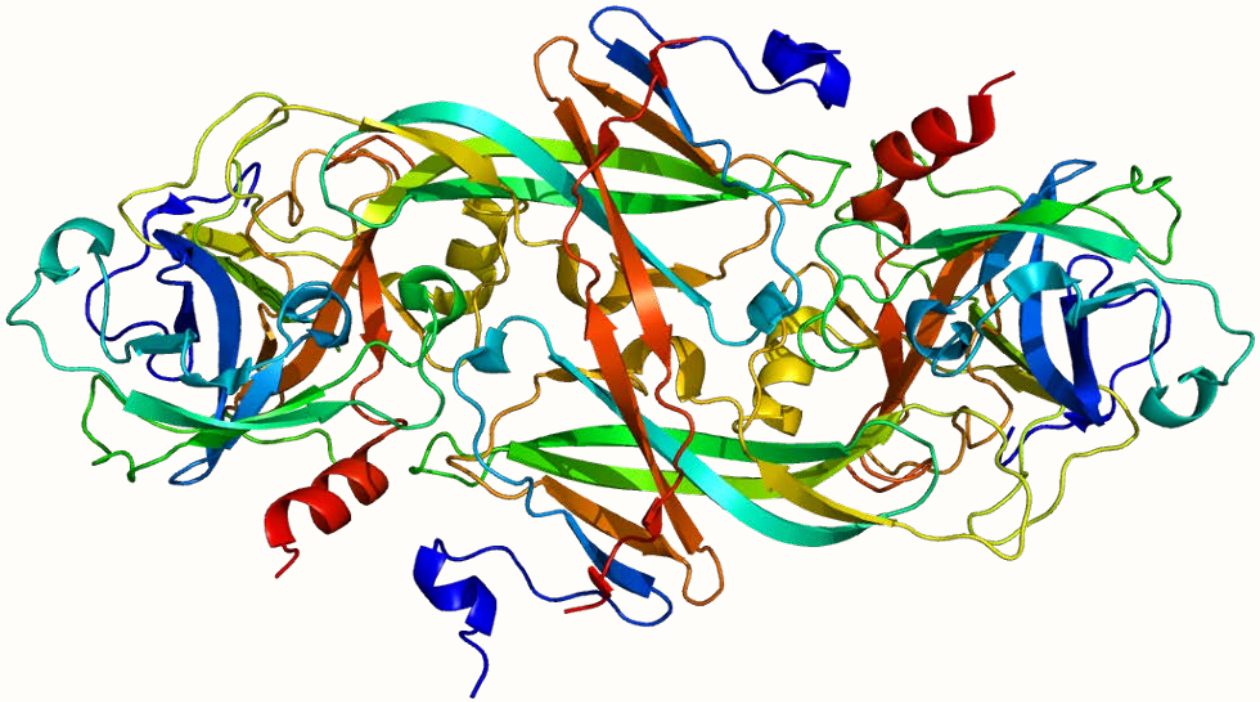
Recurrence rate after 2 years, following:	
NCIS	**TIA**
18.4%	8.2%

Study population:
18,719 patients hospitalized for NCIS or TIA (mean age: 74.6 years; female: 44.4%)

ASTRIS, Acute STroke Registry and analysis of Imaging Studies; NCIS, non-cardioembolic ischemic stroke; TIA, transient ischemic attack.

1. 11th European Stroke Organization Conference Abstracts - 21-23 May 2025, Helsinki, Finland. *Eur Stroke J*. 2025 Jun;10(2_suppl):3-789. **2**. Arsava EM, et al. *AMA Neurol*. 2016;73(4):396-401.

Factor XI[1-4] (Plasma Thromboplastin Antecedent)

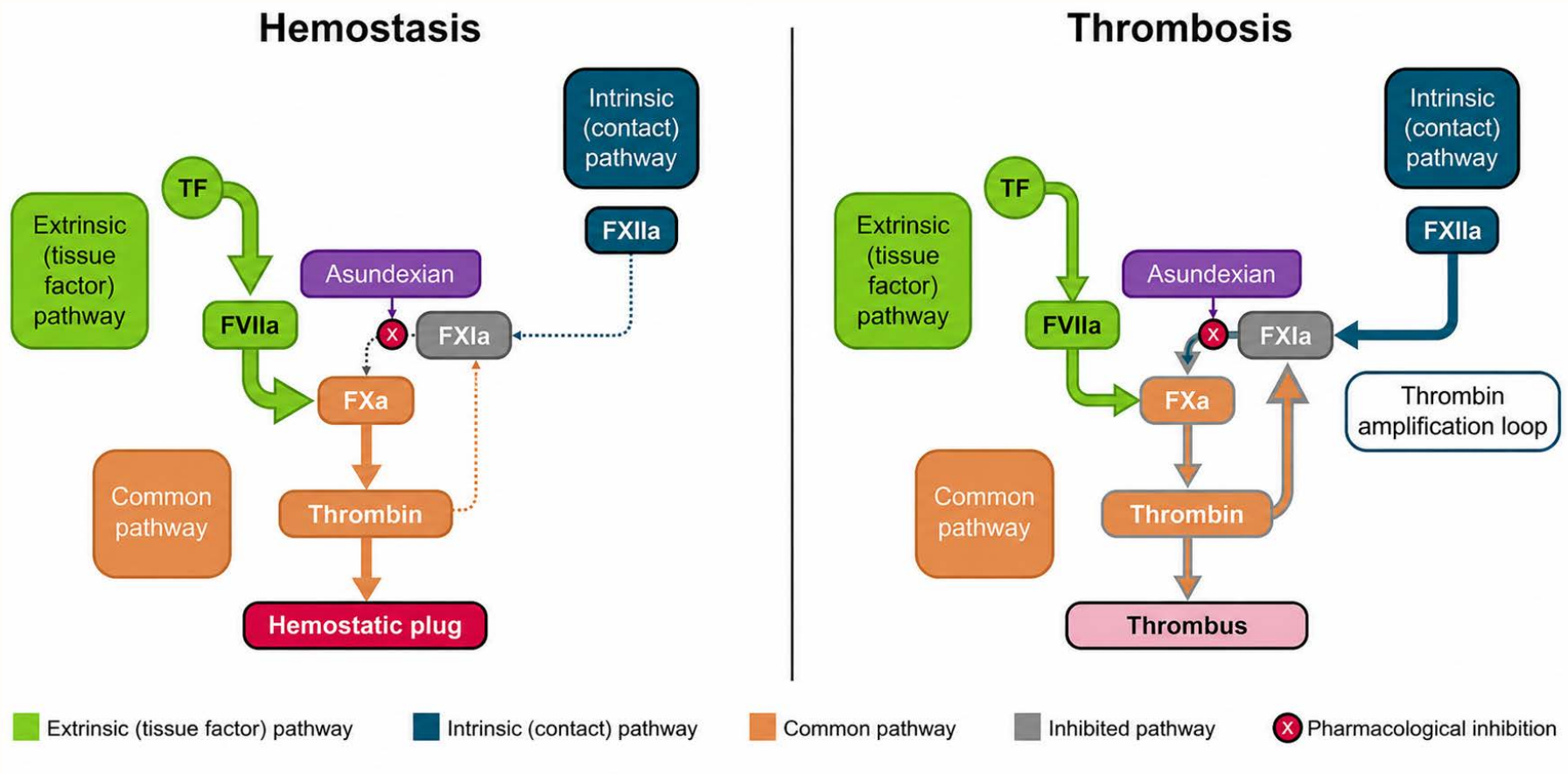


- Zymogen form of FXIa
- Produced in the liver
- Plasma half life: 52 hours
- Activated to FXIa by FXIIa and **thrombin**

1. Crystal Structure of the FXIa Catalytic Domain in Complex with EcotinM84R. Protein Data Bank. Available at: https://www.rcsb.org/structure/1XX9 **2**. Minnema MC, Meijers JCM. Factor XI, TAFI and DIC. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience; 2000-2013. Available from: https://www.ncbi.nlm.nih.gov/books/NBK6496/ **3**. Walsh PN. *Thromb Haemost*. 2001;86(1):75-82. **4**. Ali AE, Becker RC. *J Thromb Thrombolysis*. 2024;57(8):1283-1296.

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.

Inherited FXI deficiency (Hemophilia C)

- Autosomal recessive
- Prevalence (1 in 100K-1M)
  - Most prevalent in Ashkenazi Jews (1/450 severe deficiency; 0.22%)
- Spontaneous bleeding, including ICH rare
- Identified by elevated APTT, menorrhagia or excess bleeding at time of surgery (oral cavity, nose, tonsils, urinary tract), and sometimes following trauma
- Reduced rates of ischemic stroke and VTE

World Stroke Organization

World Stroke Academy

APTT, activated partial thromboplastin time; FXI, Factor XI; ICH, intracerebral hemorrhage; VTE, venous thromboembolism.

Seligsohn, U. *J Thromb Haemost*. 2009;1:84-7

McMaster University

Population Health Research Institute

HEALTH THROUGH KNOWLEDGE

Hemostasis, Thrombosis, and Vascular Biology

Reduced incidence of ischemic stroke in patients with severe factor XI deficiency

Ophira Salomon,[1] David M. Steinberg,[2] Nira Koren-Morag,[3] David Tanne,[4] and Uri Seligsohn[1]

[1]The Amalia Biron Research Institute of Thrombosis and Hemostasis, Sheba Medical Center, Tel Hashomer and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; [2]Department of Statistics and Operations Research, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv; [3]Division of Epidemiology and Preventive Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv; and [4]Stroke Unit, Department of Neurology, Sheba Medical Center, Tel Hashomer and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Incident ischemic stroke: Standardized incidence ratio (SIR): 0.12 (95%CI 0.03-0.69)

Prevalent ischemic stroke: SIR: 0.12 (95% 0.03-0.65)

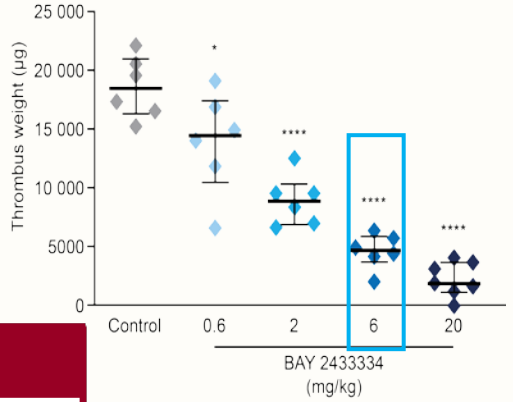
SIR, standardized incidence ratio.
Salomon O, et al. *Blood*. 2008;111(8):4113-7.

Evidence Supporting FXIa Inhibition as a Target

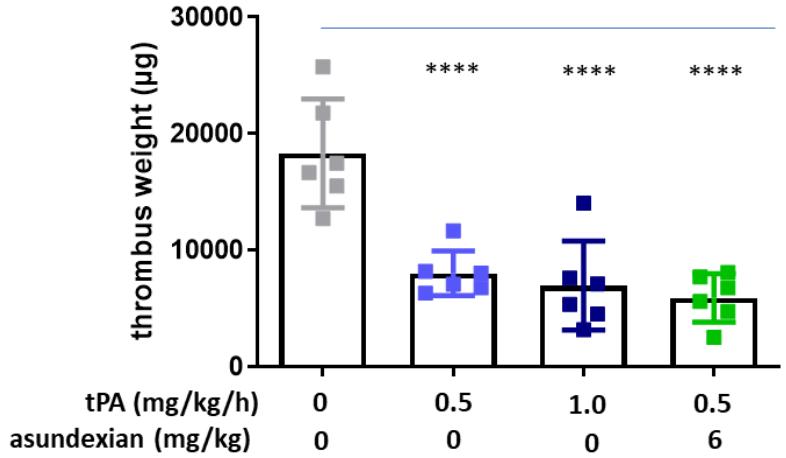
CONDITION	OBSERVATION
FXI-knockout mice[1]	• Homozygous FXI-knockout mice **are protected from thrombosis** • At the same time, they **do not show a bleeding phenotype** differing from wild-type mice
***In vivo* animal models**[2]	• Reducing/inhibiting FXI showed **strong antithrombotic** effects *in vivo* • **No increase in bleeding time** even at very high doses or on top of dual antiplatelet therapy

1. Schumacher WA, et al. *Arterioscler Thromb Vasc Biol.* 2010;30:388-92. **2**. Heitmeier S, et al. *JTH*. 2022;20:1400–1411.

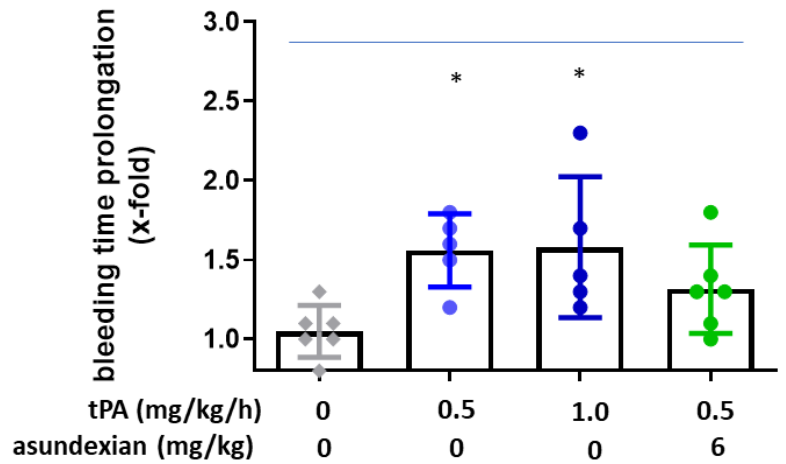
Impact of the Combination of Asundexian and tPA on Bleeding Times and Thrombosis in Rabbit Models



$FeCl_2$-induced thrombosis (A. carotis)



Gum bleeding time



Data are presented as means and SD; n = 5–7 animals per dose. Adjusted *p* values versus control: *$p < 0.05$, **p<0.01, ****$p < 0.0001$. Asundexian administered as i.v. bolus 30 min prior to thrombosis experiment, tPA as i.v. infusion starting 25 min prior to thrombosis experiment.

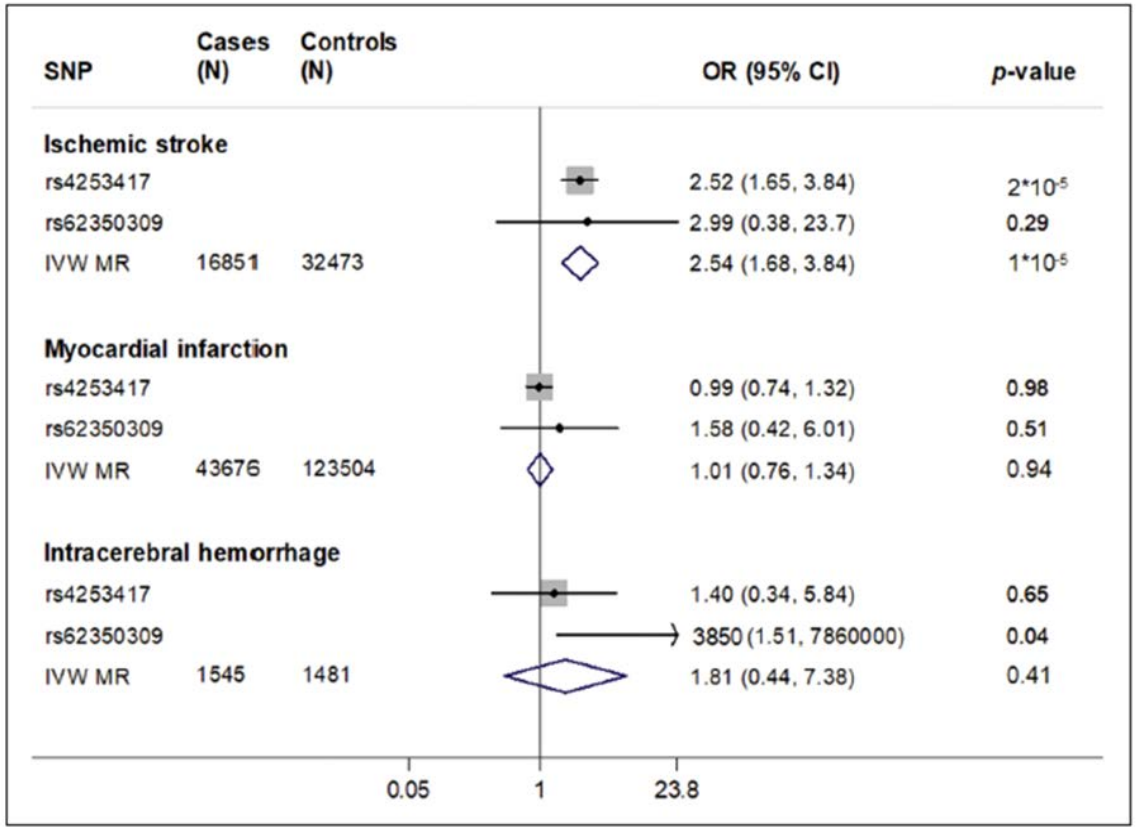
When given on top of tPA, administration of asundexian resulted in no increase in bleeding times vs. tPA alone

Asundexian is not approved for the treatment of stroke.
i.v., intravenous; tPA, tissue plasminogen activator.
Data on file

Brief Report

Genetically Determined FXI (Factor XI) Levels and Risk of Stroke

Dipender Gill, MD; Marios K. Georgakis, MD; Mike Laffan, MD, PhD; Maria Sabater-Lleal, PhD; Rainer Malik, PhD; Ioanna Tzoulaki, PhD; Roland Veltkamp, MD*; Abbas Dehghan, MD, PhD*

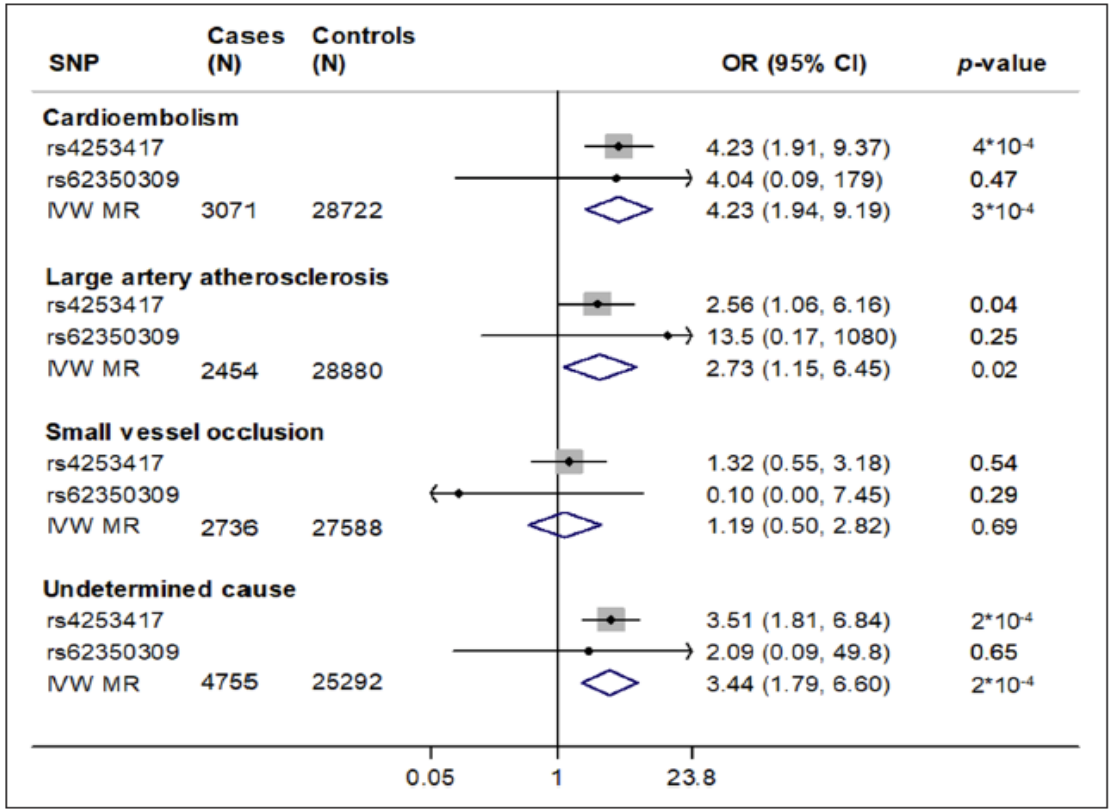


IVW MR, inverse-variance weighted mendelian randomization; SNP, single nucleotide polymorphism.
Gill D, et al. *Stroke*. 2018;49(11):2761-2763.

Brief Report

Genetically Determined FXI (Factor XI) Levels and Risk of Stroke

Dipender Gill, MD; Marios K. Georgakis, MD; Mike Laffan, MD, PhD; Maria Sabater-Lleal, PhD; Rainer Malik, PhD; Ioanna Tzoulaki, PhD; Roland Veltkamp, MD*; Abbas Dehghan, MD, PhD*



IVW MR, inverse-variance weighted mendelian randomization; SNP, single nucleotide polymorphism.
Gill D, et al. *Stroke*. 2018;49(11):2761-2763.

Circulation

ORIGINAL RESEARCH ARTICLE

Novel Drug Targets for Ischemic Stroke Identified Through Mendelian Randomization Analysis of the Blood Proteome

Michael Chong, MSc
Jennifer Sjaarda, PhD
Marie Pigeyre, MD, PhD
Pedrum Mohammad-Shemirani, BSc
Ricky Lali, MSc
Ashkan Shoamanesh, MD
Hertzel Chaim Gerstein, MD, MSc
Guillaume Paré, MD, MSc

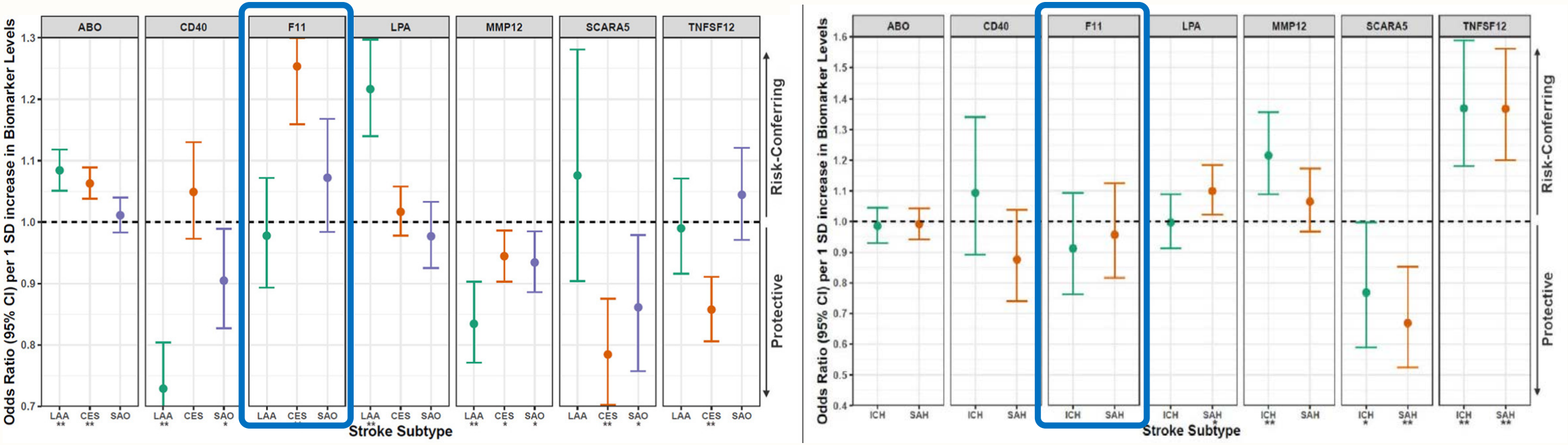
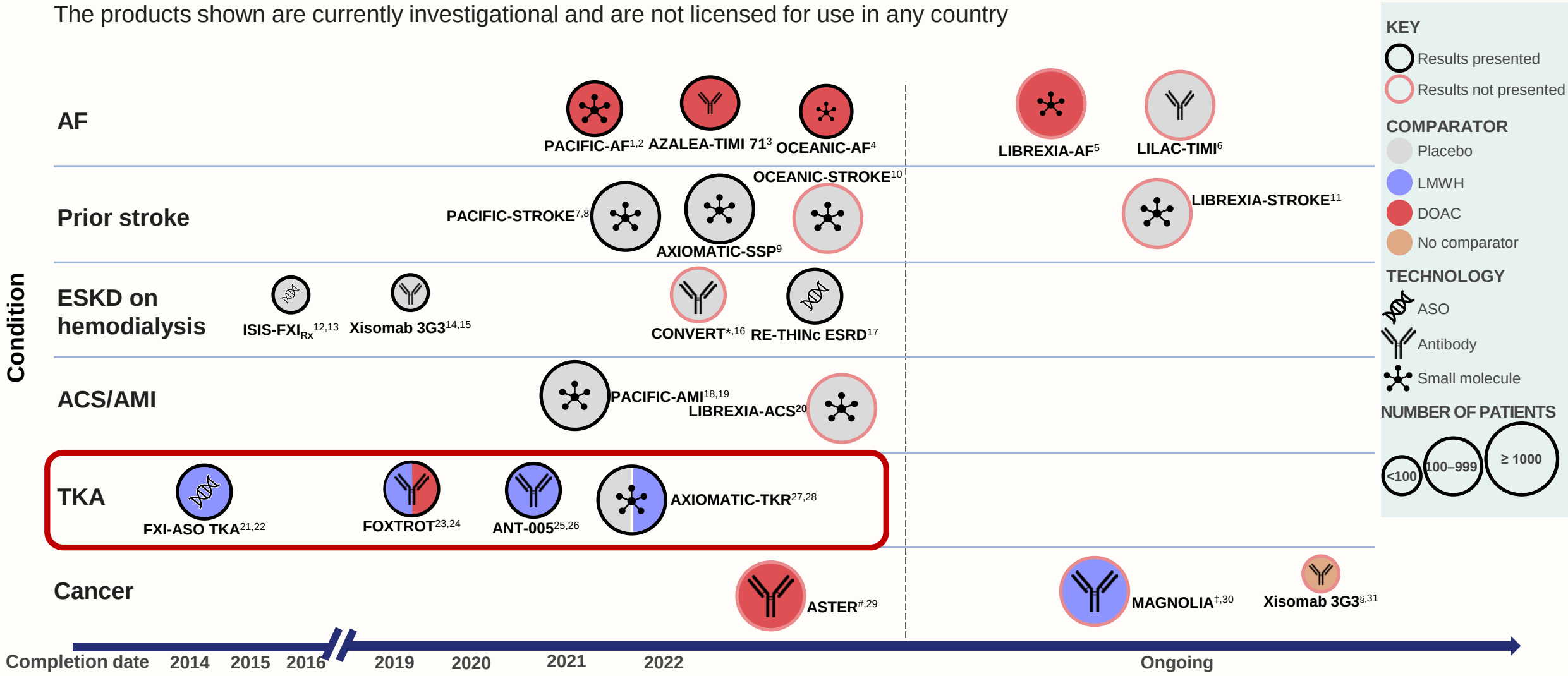


Figure 3. Association between identified biomarkers and risk for hemorrhagic stroke subtypes.

ABO, ABO blood group; CD40, cluster of differentiation 40; CES, cardioembolic stroke; F11, coagulation factor XI; ICH, intracerebral hemorrhage; LAA, large artery atherosclerosis; LPA, lipoprotein(a); MMP12, matrix metalloproteinase 12; SAH, subarachnoid hemorrhage; SAO, small artery occlusion; SCARA5, scavenger receptor class A member 5; TNFSF12, tumor necrosis factor superfamily member 12.
Chong M, et al. *Circulation*. 2019;140(10):819-830.

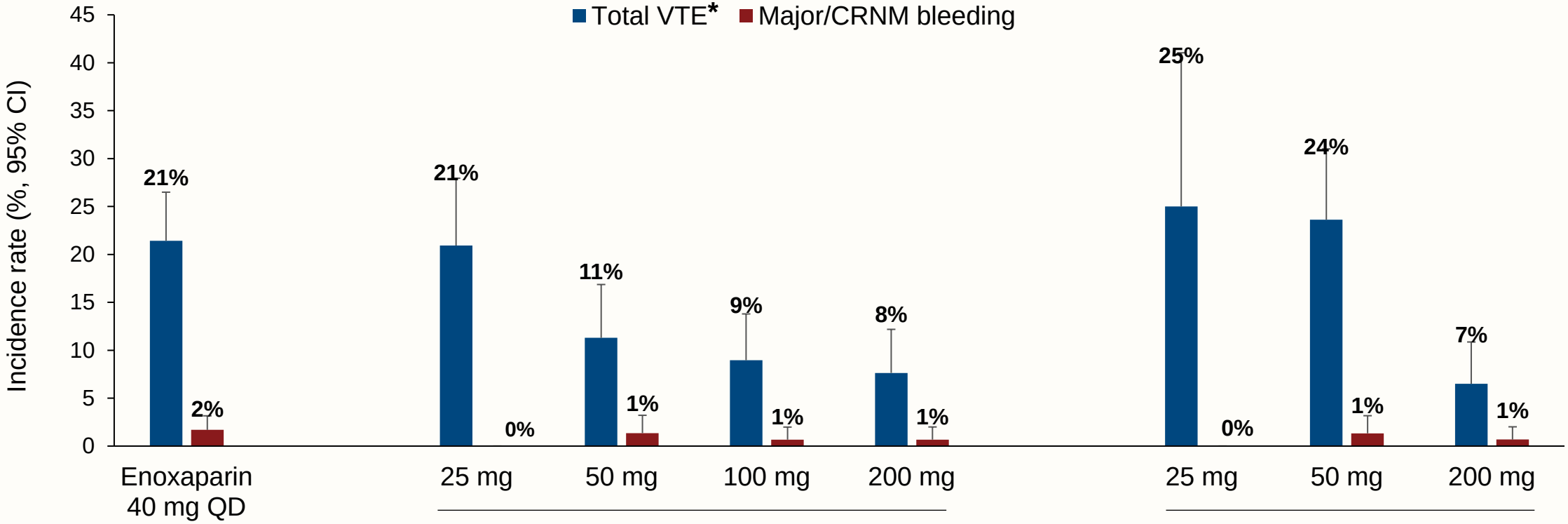
Overview of Clinical Trials Investigating FXI Inhibition

The products shown are currently investigational and are not licensed for use in any country



Reference details are in the speaker notes. *Osocimab. #Patients with CAT currently receiving or having received anticancer therapy in the last 6 months. ‡Patients with GI or GU cancer and CAT receiving LMWH for ≥6 months. §Patients with cancer receiving chemotherapy. ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ASO, antisense oligonucleotide; CAT, cancer-associated thrombosis; DOAC, direct oral anticoagulant; ESKD, end-stage kidney disease; FXI, Factor XI; GI, gastrointestinal; GU, genitourinary; LMWH, low molecular weight heparin; TKA, total knee arthroplasty.

Milvexian Phase 2 Total Knee Replacement Study



RR (95% CI) vs Enoxaparin	Enoxaparin 40 mg QD	Milvexian BID 25 mg	Milvexian BID 50 mg	Milvexian BID 100 mg	Milvexian BID 200 mg	Milvexian OD 25 mg	Milvexian OD 50 mg	Milvexian OD 200 mg
Total VTE*		0.97 (0.65, 1.45)	0.53 (0.31, 0.90)	0.42 (0.23, 0.76)	0.37 (0.19, 0.69)	1.00 (0.51, 1.97)	1.15 (0.78, 1.70)	0.30 (0.15 0.62)
Major/CRNM bleeding		0 (NA)	0.79 (0.16, 3.96)	0.39 (0.05, 3.30)	0.39 (0.05, 3.28)	0 (NA)	0.68 (0.14, 3.39)	0.40 (0.05, 3.34)

*Composite of asymptomatic deep-vein thrombosis, confirmed symptomatic venous thromboembolism, or death from any cause. CRNM, clinically relevant nonmajor; OD, once daily; BID, twice daily; NA, not applicable.

Weitz JI, et al. *N Engl J Med*. 2021;385(23):2162-2172.

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Dual Pathway Inhibition

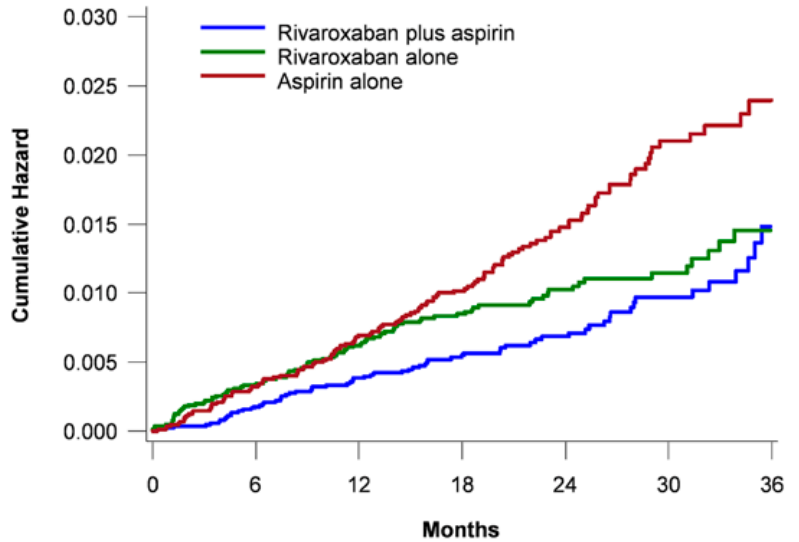
Circulation

ORIGINAL RESEARCH ARTICLE

Stroke Outcomes in the COMPASS Trial

Mukul Sharma, MD, MSc et al

A Ischemic or uncertain stroke



No. at Risk							
Rivaroxaban plus aspirin	9152	9069	7973	6374	3975	2259	673
Rivaroxaban alone	9117	9016	7898	6291	3943	2228	691
Aspirin alone	9126	9022	7874	6251	3951	2231	693

Research

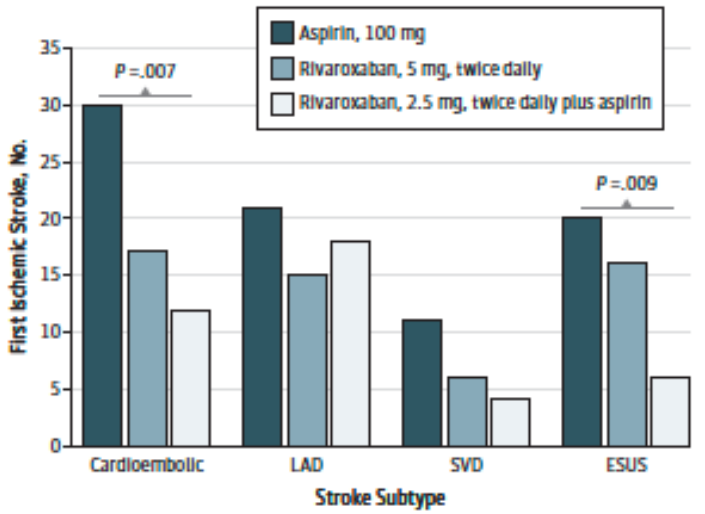
JAMA Neurology | Original Investigation

Association Between Low-Dose Rivaroxaban With or Without Aspirin and Ischemic Stroke Subtypes

A Secondary Analysis of the COMPASS Trial

Kanjana S. Perera, MBBS; Kelvin K. H. Ng, MBBS; Sumiti Nayar, MD; Luciana Catanese, MD; Leanne Dyal, MSc; Mukul Sharma, MD, MSc; Stuart J. Connolly, MD; Salim Yusuf, MBBS; Jackie Bosch, PhD; John W. Eikelboom, MD; Robert G. Hart, MD

Figure 2. Treatment Effect on Stroke Subtypes According to TOAST (Trial of Org 10172 in Acute Stroke Treatment) Criteria Among Participants With Ischemic or Unknown Stroke

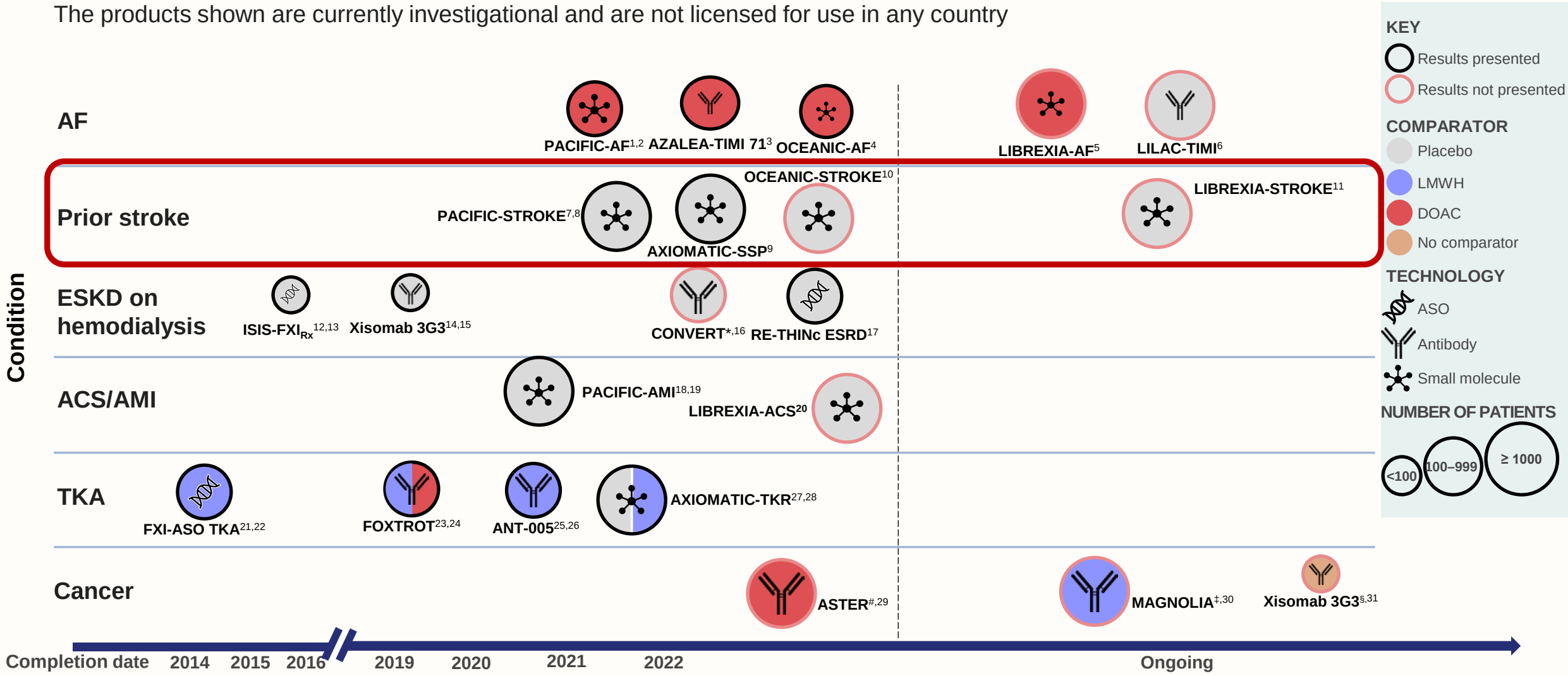


ESUS, embolic stroke of undetermined source; LAD, large artery disease; SVD, small vessel disease; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

1. Sharma M, et al. Stroke *Circulation*. 2019;139(9):1134-1145. **2**. Perera KS, et al. *JAMA Neurol*. 2020;77(1):43-48.

Overview of Clinical Trials Investigating FXI Inhibition

The products shown are currently investigational and are not licensed for use in any country



Reference details are in the speaker notes. *Osocimab. #Patients with CAT currently receiving or having received anticancer therapy in the last 6 months. ‡Patients with GI or GU cancer and CAT receiving LMWH for ≥6 months. §Patients with cancer receiving chemotherapy. ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial infarction; ASO, antisense oligonucleotide; CAT, cancer-associated thrombosis; DOAC, direct oral anticoagulant; ESKD, end-stage kidney disease; FXI, Factor XI; GI, gastrointestinal; GU, genitourinary; LMWH, low molecular weight heparin; TKA, total knee arthroplasty.

Conclusions

- Patients with non-cardioembolic ischemic stroke remain at high risk of stroke recurrence despite guideline recommended treatment.[1-5]
- FXI(a)’s distinct role within the thrombin amplification loop enables its inhibition to dissociate pathologic thrombus formation from physiologic hemostasis.[6]
- Multiple lines of evidence consistently demonstrate that FXI is associated with an increased risk of ischemic stroke, while showing little to no association with hemorrhagic stroke or major bleeding.[7]
- These characteristics position FXIa inhibition as a highly promising strategy for optimizing secondary stroke prevention, particularly when used in combination with antiplatelet therapy within a dual pathway inhibition approach.[8-9]

1. Kleindorfer, et al. *Stroke* 2021; 52: e364–467. **2**. Wang, et al. *NEJM* 2013; 369:11-9. 3. Johnston, et al. *NEJM* 2018; 379:215-25. **4.** Johnston, et al. *NEJM* 2020;383:207-17.
5. Dawson J, et al. *Eur Stroke J*. 2022;7(3):I-II. **6**. Sharma M, et al. *Eur Stroke J*. 2026;11(1):aakaf017. **7**. Gill D, et al. *Stroke*. 2018;49(11):2761-2763.
8. Sharma M, et al. *Stroke Circulation*. 2019;139(9):1134-1145. **9**. Perera KS, et al. *JAMA Neurol*. 2020;77(1):43-48.

Evidence for FXIa Inhibition in Stroke Prevention

Mike Sharma, MD, MSc
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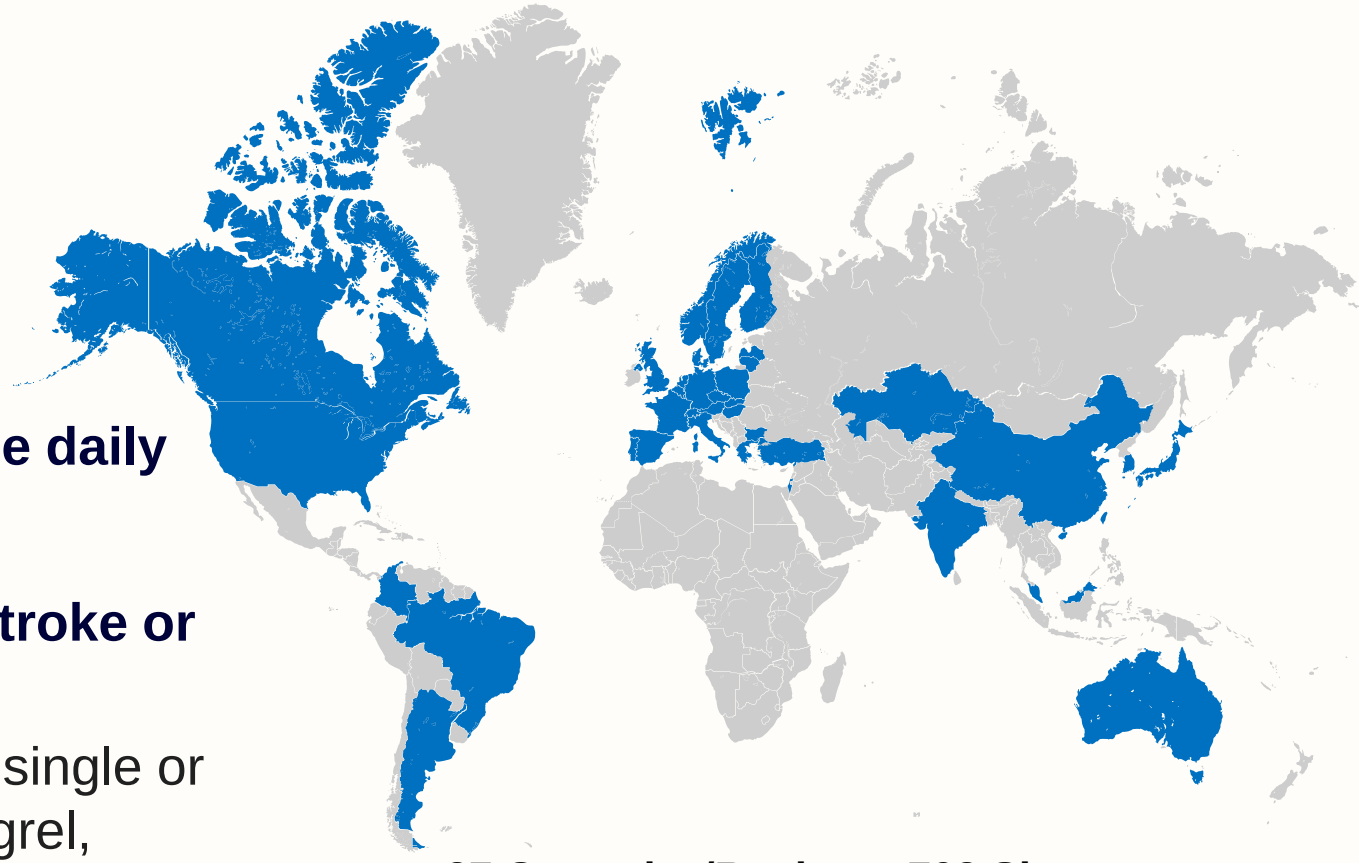
Hamilton, ON

OCEANIC-STROKE: Study Design[1,2]

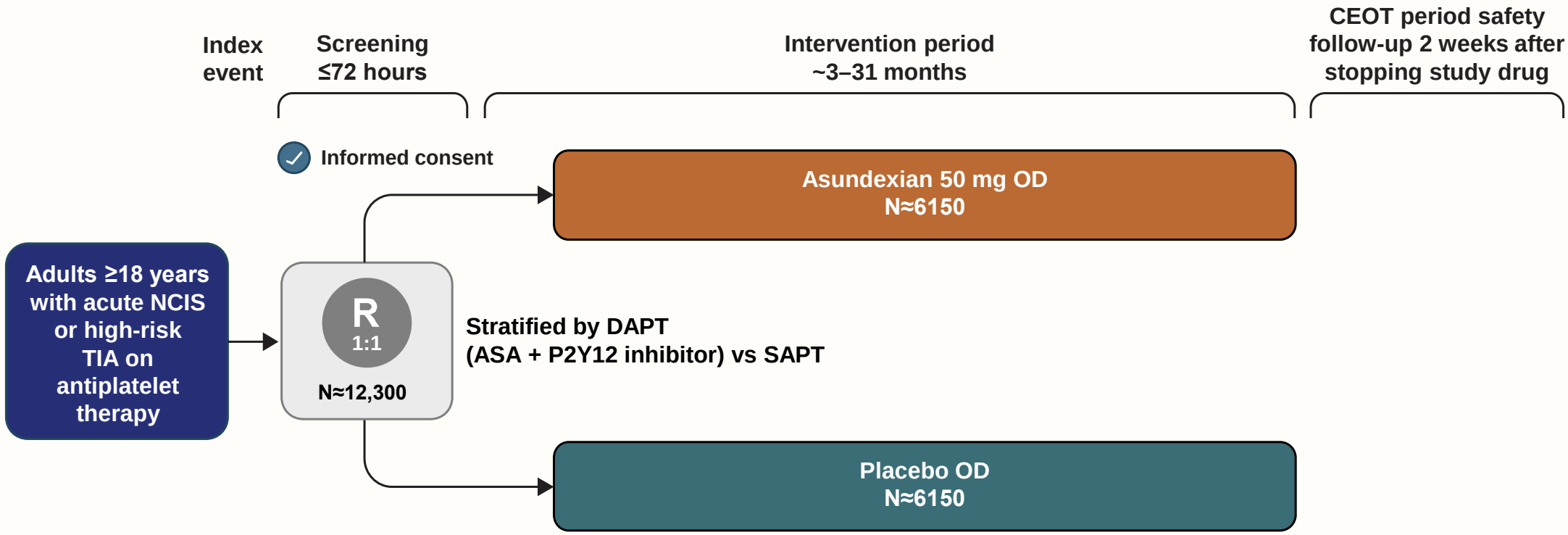
- **OCEANIC-STROKE**
  - Placebo-controlled
  - Double-blinded
  - Event-driven Phase 3 RCT
- **Comparing asundexian 50 mg once daily and placebo**
- **Patients with non-cardioembolic stroke or high-risk TIA**
  - Planned for antiplatelet therapy – single or aspirin + P2Y12 inhibitor (clopidogrel, ticagrelor, prasugrel)



37 Countries/Regions, 702 Sites

Asundexian is not approved for the treatment of stroke.
P2Y12, purinergic receptor Y12; RCT, randomized controlled trial; TIA, transient ischemic atack
1. Sharma M, et al. *Eur Stroke J*. 2026;11(1):aakaf017. **2**. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

OCEANIC-STROKE: Study Design[1,2]



Asundexian is not approved for the treatment of stroke.

ASA, aspirin; CEOT, common end of treatment; DAPT, dual antiplatelet therapy; NCIS, non-cardioembolic ischemic stroke; OD, once daily; P2Y12, purinergic receptor Y12; R, randomization; SAPT, single antiplatelet therapy; TIA, transient ischemic attack.

1. Sharma M, et al. *Eur Stroke J*. 2026;11(1):aakaf017. **2**. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

OCEANIC-STROKE: Key Inclusion and Exclusion Criteria[1,2]

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

Asundexian is not approved for the treatment of stroke.

ABCD^2, age, blood pressure, clinical features, duration of symptoms, and diabetes; AF, atrial fibrillation; CABG, coronary artery bypass grafting; CMB, cerebral microbleed; GI, gastrointestinal; HT, hemorrhagic transformation; ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale; PH 1 or 2, parenchymal hematoma type 1 or type 2; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

1. Sharma M, et al. *Eur Stroke J*. 2026;11(1):aakaf017. **2**. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

OCEANIC-STROKE: Key Endpoints[1,2]

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

Asundexian is not approved for the treatment of stroke.
*Hypothesis testing conducted using strict hierarchy order for efficacy endpoints.
CRNM, clinically relevant non-major; CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; mRS, modified Rankin score.**1**. Sharma M, et al. *Eur Stroke J*. 2026;11(1):aakaf017. **2**. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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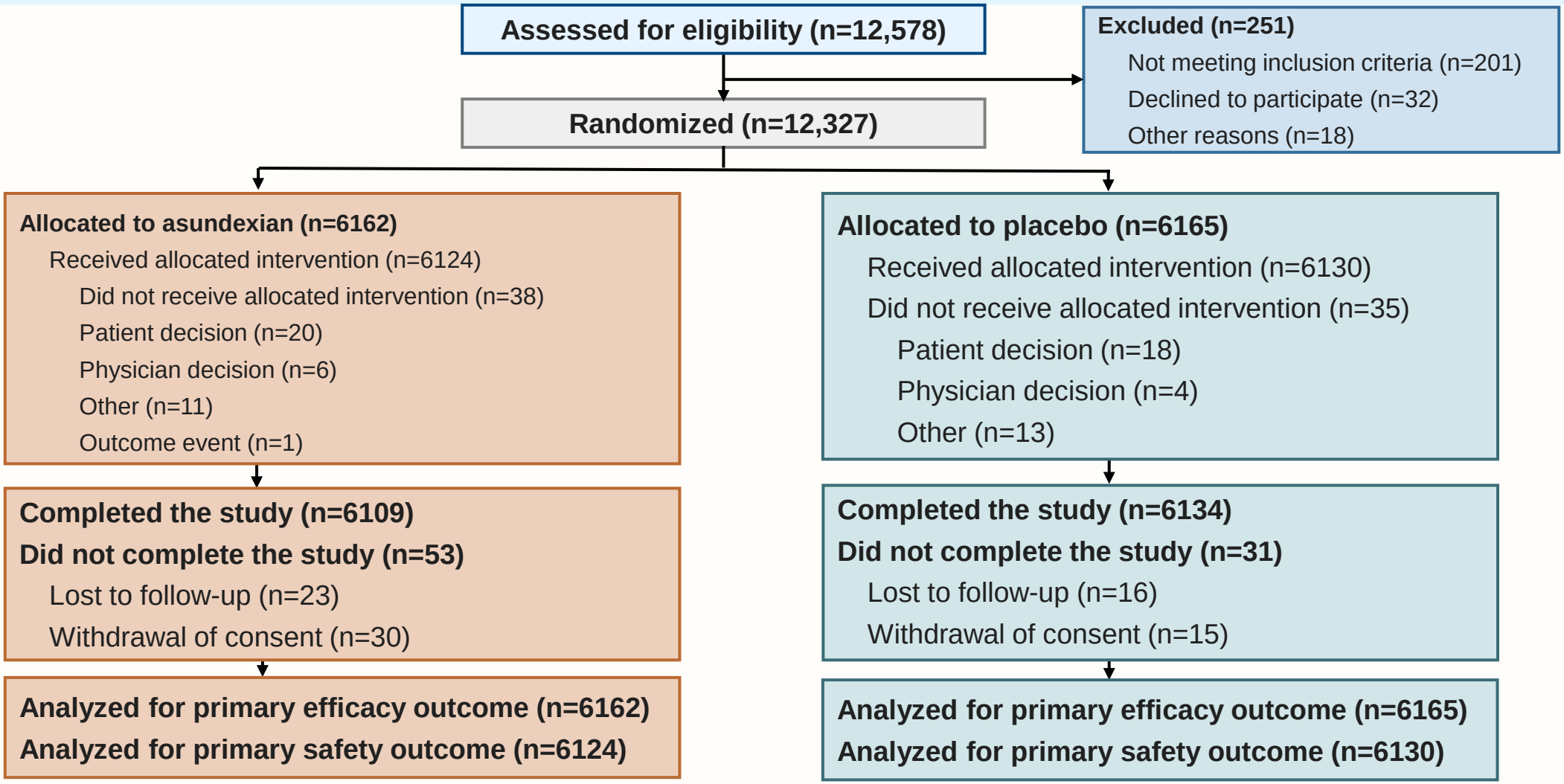
Consort Diagram[1,2]



Asundexian is not approved for the treatment of stroke.

1. Sharma M, et al. *Eur Stroke J*. 2026;11(1):aakaf017. **2**. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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Baseline Characteristics

Characteristics	Asundexian 50 mg	Placebo
Randomized, N	6162	6165
Age, years, mean (SD)	67.7 (10.8)	67.5 (10.9)
Female sex, n (%)	2063 (33.5)	2047 (33.2)
Medical history, n (%)		
Previous history of stroke or TIA	1310 (21.3)	1345 (21.8)
Coronary artery disease	949 (15.4)	1013 (16.4)
Hypertension	4937 (80.1)	4868 (79.0)
Diabetes mellitus	2134 (34.6)	2115 (34.3)
Current smoker	1644 (26.7)	1665 (27.0)
Race, n (%)		
White	4105 (66.6)	4078 (66.1)
Asian	1721 (27.9)	1742 (28.3)
Black	143 (2.3)	139 (2.3)
Other	193 (3.1)	206 (3.3)

Asundexian is not approved for the treatment of stroke.
SD, standard deviation; TIA, transient ischemic attack.
Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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Index Event Characteristics

Characteristics	Asundexian 50 mg	Placebo
Index event, n (%)		
Ischemic stroke	5839 (94.8)	5838 (94.7)
High-risk TIA	323 (5.2)	325 (5.3)
TOAST subtype of index event,† n (%)		
Large-artery atherosclerosis	2512 (43.0)	2484 (42.5)
Stroke of undetermined etiology	1786 (30.6)	1710 (29.3)
Small-vessel occlusion	1290 (22.1)	1349 (23.1)
Stroke of other etiology	161 (2.8)	188 (3.2)
Cardioembolic	89 (1.5)	107 (1.8)
NIHSS at randomization,† median (IQR)	2 (1, 4)	2 (1, 4)
NIHSS at randomization,† n (%)		
≤3	4087 (70.0)	4079 (69.9)
4–7	1385 (23.7)	1375 (23.6)
≥8	365 (6.3)	382 (6.5)
Dual antiplatelet therapy	3859 (62.6)	3853 (62.5)

Asundexian is not approved for the treatment of stroke.

†Stroke index event only. IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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Acute Treatment of Index Stroke

	Overall N=11677	Asundexian 50 mg N=5839	Placebo N=5838
Intravenous thrombolysis and/or endovascular therapy,† n (%)	3201 (27.4)	1608 (27.5)	1593 (27.3)
Intravenous thrombolysis only	2314 (19.8)	1146 (19.6)	1168 (20.0)
Endovascular therapy only	371 (3.2)	202 (3.5)	169 (2.9)
Intravenous thrombolysis and endovascular therapy	516 (4.4)	260 (4.5)	256 (4.4)

Asundexian is not approved for the treatment of stroke.
†Stroke index event only.
Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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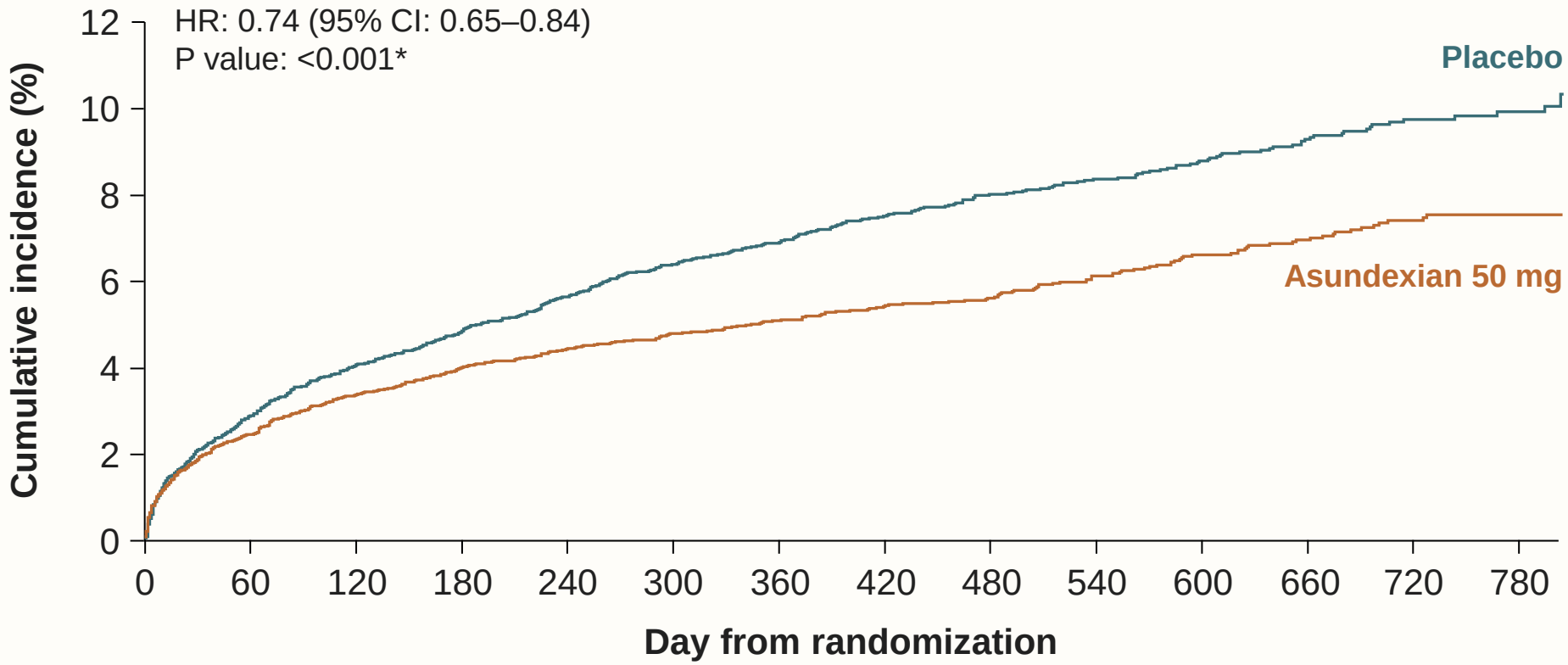
Cumulative Incidence of Ischemic Stroke



No. at risk														
Placebo	6165	5949	5853	5754	5370	4840	4406	3990	3497	3070	2564	1961	1410	792
Asundexian 50 mg	6162	5958	5859	5763	5384	4876	4463	4033	3543	3101	2588	2004	1428	810

Asundexian is not approved for the treatment of stroke.

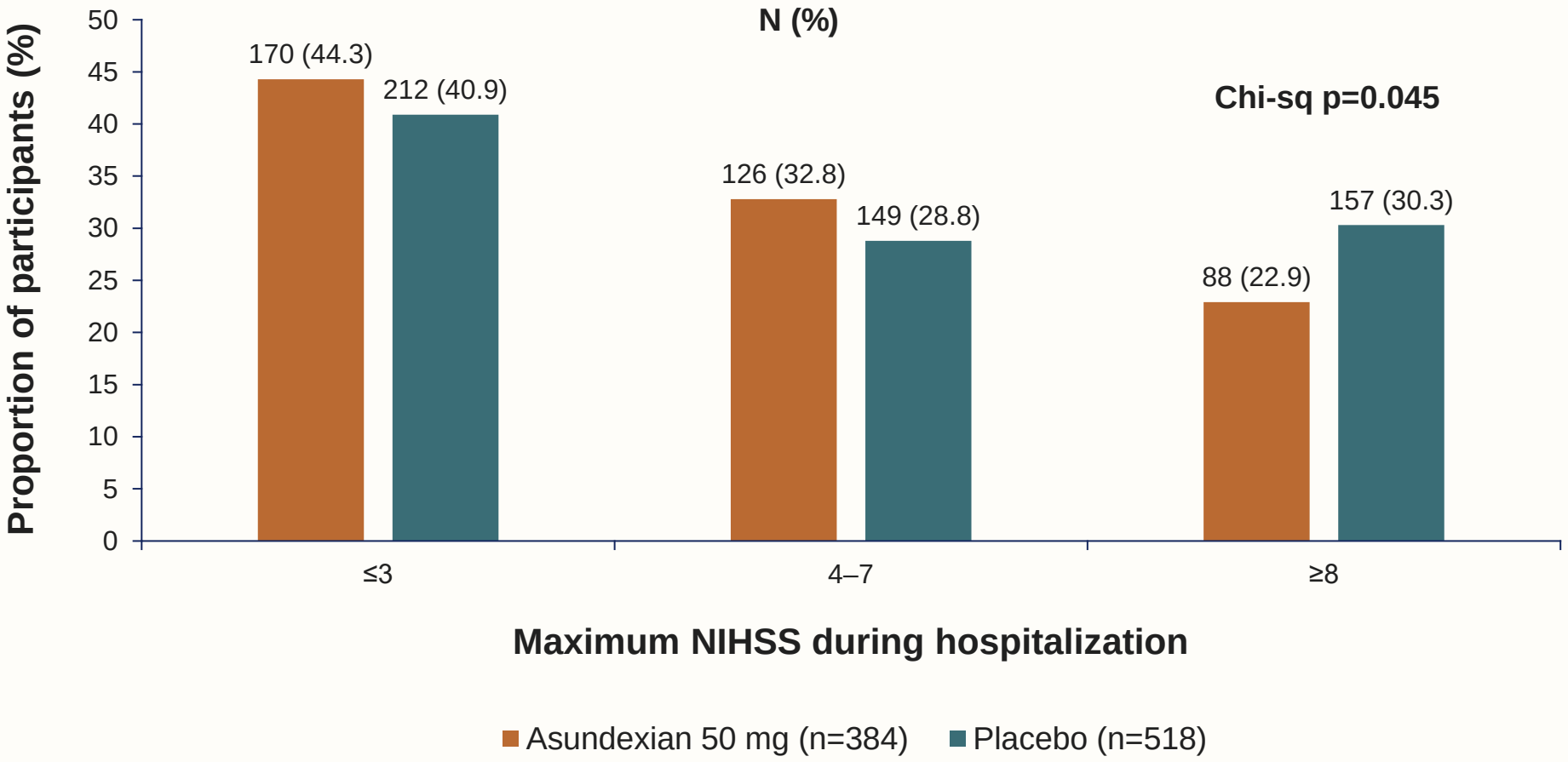
*P value is obtained from stratified log-rank test (stratified by baseline intention of DAPT). csHR and 95% CI are provided here. Absolute risk reduction at 1 year was 1.9%, with a number needed to treat of 53. Cumulative incidence curves are estimated by Aalen–Johansen method, truncated at Day 820. csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

Efficacy Outcomes

Outcome	Asundexian 50 mg (N=6162) n (%)	Placebo (N=6165) 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

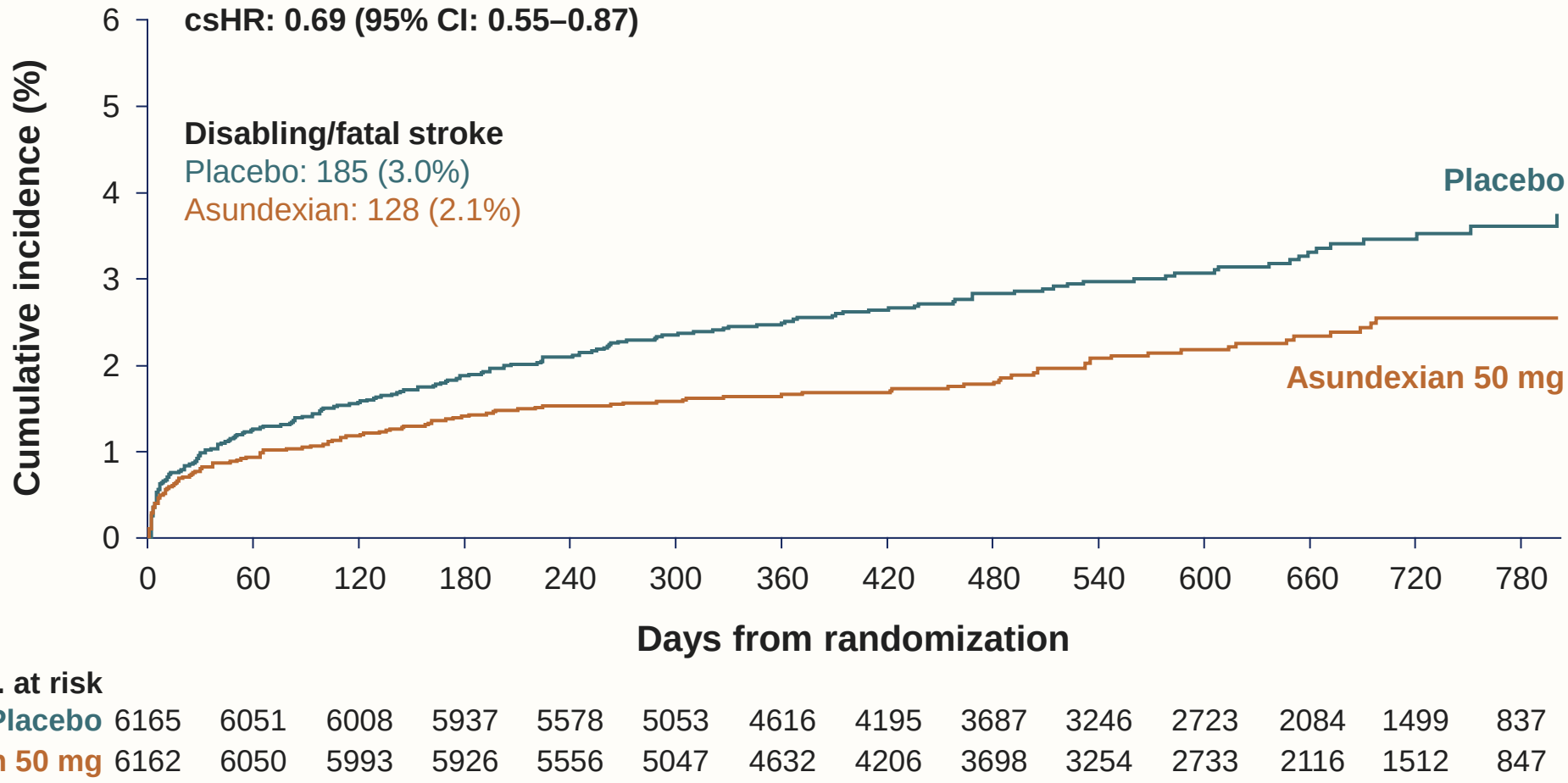
Asundexian is not approved for the treatment of stroke. †csHRs are estimated from stratified cox proportional hazard model (stratified by baseline intention of T); ‡P values are obtained from stratified log-rank test (stratified by baseline intention of T); ¶A disabling stroke is defined as a stroke of any type during the trial associated with a modified Rankin Scale (mRS) of ≥3 at 90 days after the stroke or an increase of 1 point if the last available mRS before the recurrent stroke event was ≥3. csHR, cause-specific hazard ratio; CV, cardiovascular; MI, myocardial infarction; mRS, modified Rankin score.Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

Maximum NIHSS† of Incident Ischaemic Stroke



Asundexian is not approved for the treatment of stroke.
Data displayed is related to first incident ischaemic stroke. †Maximum NIHSS during hospitalization for acute stroke. Multiple imputation used to complete missing NIHSS in n=109/902 (12.1%).
NIHSS, National Institutes of Health Stroke Scale.

Disabling/Fatal Stroke



No. at risk

Placebo	6165	6051	6008	5937	5578	5053	4616	4195	3687	3246	2723	2084	1499	837
Asundexian 50 mg	6162	6050	5993	5926	5556	5047	4632	4206	3698	3254	2733	2116	1512	847

Asundexian is not approved for the treatment of stroke.
A disabling/fatal stroke is defined as a stroke of any type during the trial associated with a mRS of ≥3 at 90 days after the stroke or an increase of 1 point if the last available mRS before the recurrent stroke event was ≥3. csHR (95% CI) from Cox proportional hazards model stratified by baseline intention of DAPT. Cumulative incidence curves are estimated by Aalen–Johansen method. Plot truncated at Day 820. csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy; mRS, modified Rankin Scale. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

Safety Outcomes

Outcome	Asundexian 50 mg (N=6162) n (%)	Placebo (N=6165) 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)

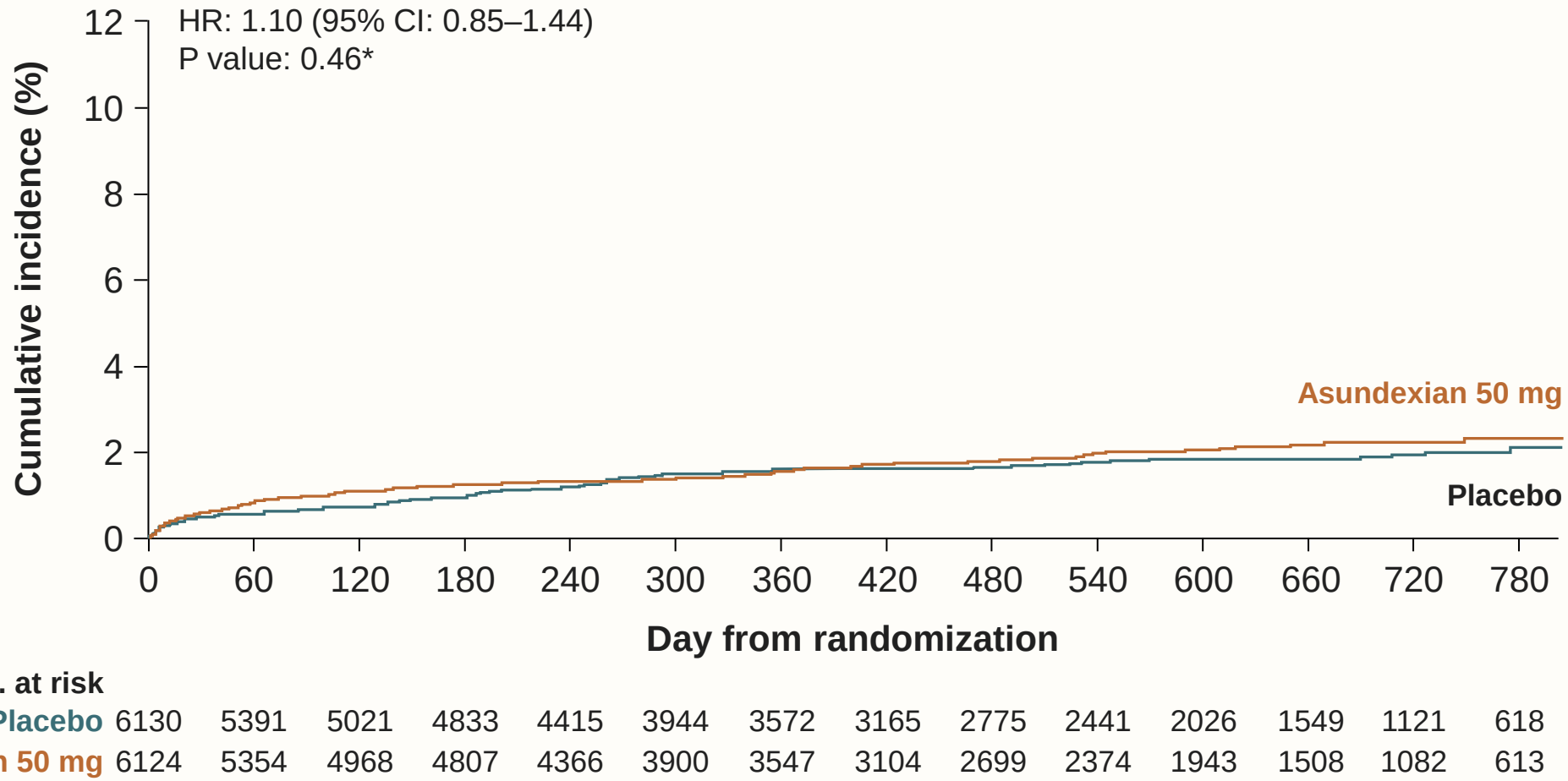
Asundexian is not approved for the treatment of stroke.

†csHRs are estimated from stratified Cox proportional hazards model (stratified by baseline intention of DAPT).

csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy; ISTH, International Society on Thrombosis and Haemostasis.

Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

Cumulative Incidence of ISTH Major Bleeding



No. at risk

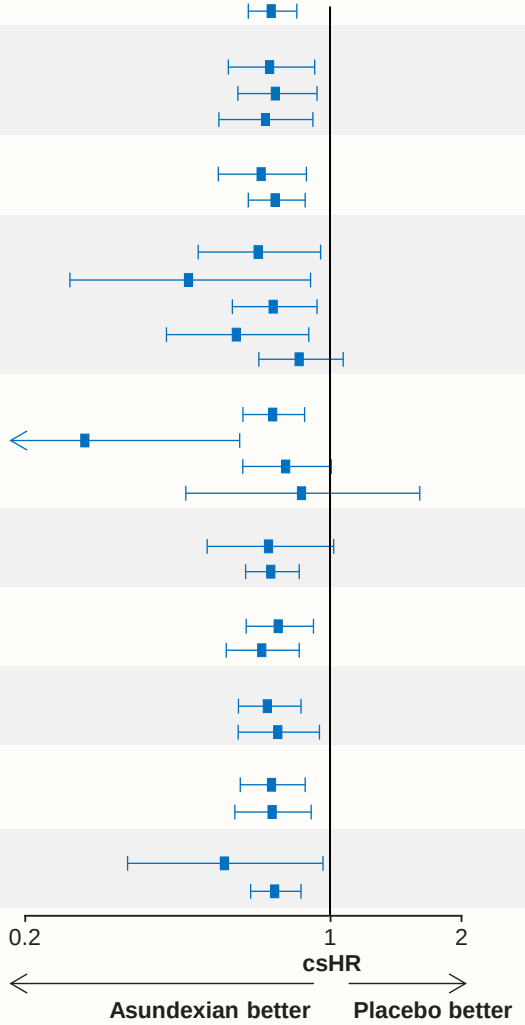
Placebo	6130	5391	5021	4833	4415	3944	3572	3165	2775	2441	2026	1549	1121	618
Asundexian 50 mg	6124	5354	4968	4807	4366	3900	3547	3104	2699	2374	1943	1508	1082	613

Asundexian is not approved for the treatment of stroke.

*P value is obtained from stratified log-rank test (stratified by baseline intention of DAPT). csHR and 95% CI are provided here. Cumulative incidence curves are estimated by Aalen–Johansen method, truncated at Day 820. csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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)



Asundexian is not approved for the treatment of stroke.
CIs are unadjusted for multiplicity and may not be used for inference.
csHR, cause-specific hazard ratio; TIA, transient ischemic attack.
Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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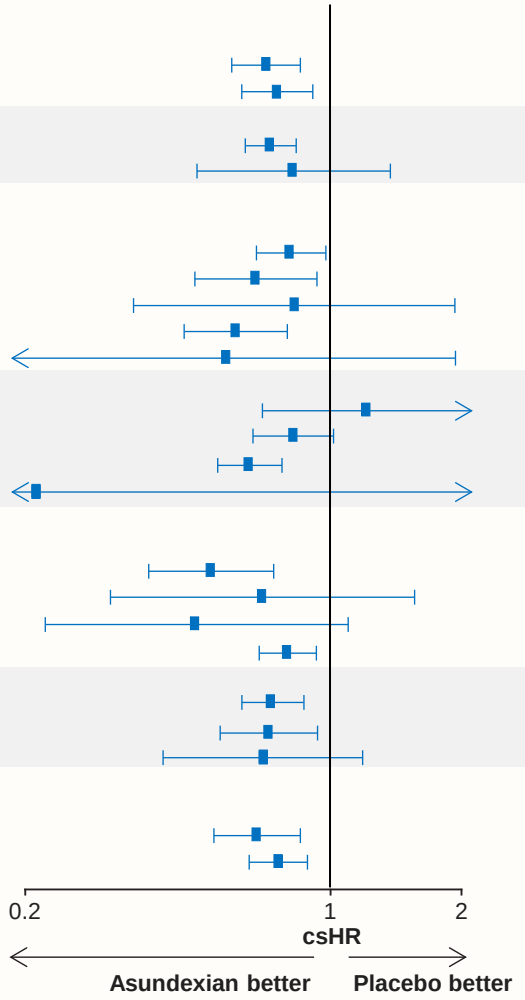
HEALTH THROUGH KNOWLEDGE

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)



Asundexian is not approved for the treatment of stroke.

*For index event of ischemic stroke. CIs are unadjusted for multiplicity and may not be used for inference.

csHR, cause-specific hazard ratio; NIHSS, National Institutes of Health Stroke Scale; P2Y12, purinergic receptor Y12; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479.

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LIBREXIA-STROKE: Study Design[1,2]

Ongoing randomized, double-blind, parallel-group, placebo-controlled, Phase III study of the oral FXIa inhibitor milvexian for stroke prevention after acute non-cardioembolic ischemic stroke or high-risk TIA (active, recruiting completed)*

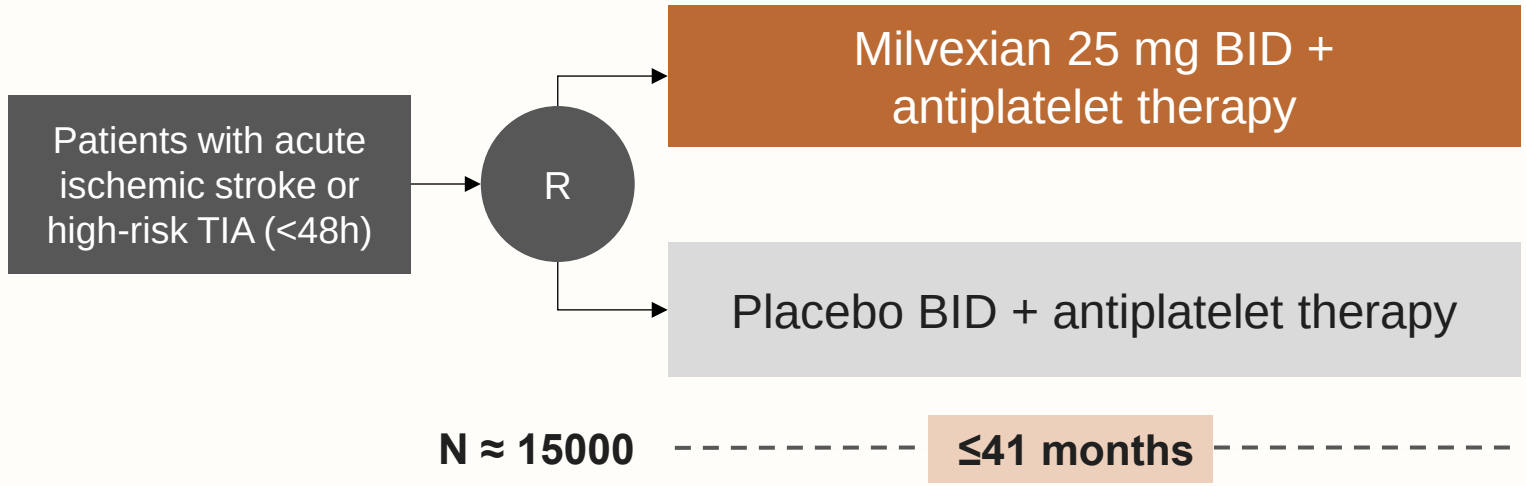
1 Primary endpoint

- Time to first occurrence of ischemic stroke

2 Secondary endpoints

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 MAVE[#]



Milvexian is not approved for the treatment of stroke.

*LIBREXIA-STROKE is a Phase III study for ischemic stroke prevention following the Phase II study AXIOMATIC-SSP. [#]MAVE is a composite of CVD, MI, ischemic stroke, major adverse limb events, symptomatic pulmonary embolism, or deep vein thrombosis. BID, twice daily; CVD, cardiovascular death; FXIa, activated factor XI; MAVE, major adverse vascular events; MI, myocardial infarction; R, randomization; TIA, transient ischemic attack. **1**. Janssen Research & Development, LLC. 2025. https://clinicaltrials.gov/ct2/show/NCT05702034 [accessed March 2025]. **2**. Johnston SC. *et al.* ISC. Los Angeles, USA, February 4–7 2025. Presentation Number: OGCTP18.

Conclusion

- **In patients with non-cardioembolic ischemic stroke or high-risk TIA treated with antiplatelet therapy, asundexian 50 mg reduced the occurrence of ischemic stroke**[1]
  (csHR 0.74; 95% CI, 0.65 to 0.84; p<0.001)
  - The difference between the treatment arms began early and continued throughout the treatment period.
  - A consistent effect was seen in subgroups.
- **Asundexian was associated with a reduction in disabling or fatal stroke (mRS ≥ 3)**[1]
- **Asundexian was not associated with an increase in bleeding**[1]
  - Including ISTH major,
  - CRNM, minor or intracranial bleeding
- **LIBREXIA-STROKE outcome pending**[2,3]

Asundexian is not approved for the treatment of stroke. Milvexian is not approved for the treatment of stroke.

csHR, cause-specific hazard ratio; CRNM, clinically relevant non-major; ISTH, International Society on Thrombosis and Haemostasis; mRS, modified Rankin score; TIA, transient ischemic attack.**1**. Sharma M, et al. *N Engl J Med*. 2026;394(15):1467-1479. **2**. Janssen Research & Development, LLC. 2025. https://clinicaltrials.gov/ct2/show/NCT05702034 [accessed March 2025]. **3**. Johnston SC. *et al.* ISC. Los Angeles, USA, February 4–7 2025. Presentation Number: OGCTP18.

Audience Q&A

All Faculty

Moderator: Dr. Ashkan Shoamanesh

Apply the Evidence in Canadian Stroke Clinic Models of Care

Dr. Laura Gioia, MD, MSc
Stroke Neurologist, CHUM
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University of Montreal, Montreal, QC

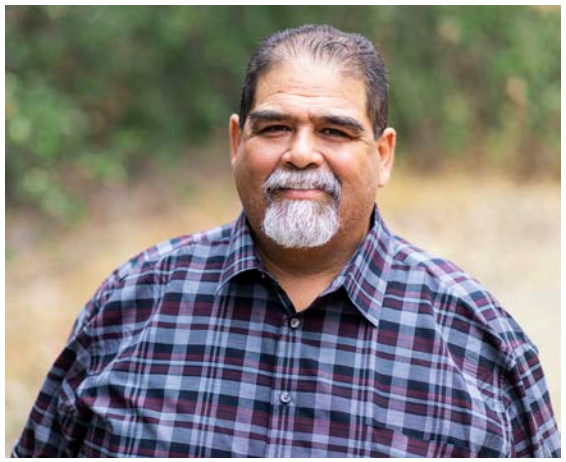
Disclosure of Conflict of Interest

Laura Gioia, MD, MSc

The following financial relationships have been disclosed:

- **AstraZeneca Canada Inc., Bayer Inc.** – Speaker honoraria / advisory board
- **FRQS, Heart and Stroke Foundation, CIHR** – Research funding / grants

Case 1: “Code Stroke”



Josh

Patient profile

- 56 M independent
- PMHx: Smoker, uncontrolled BP, dyslipidemia

Clinical Presentation

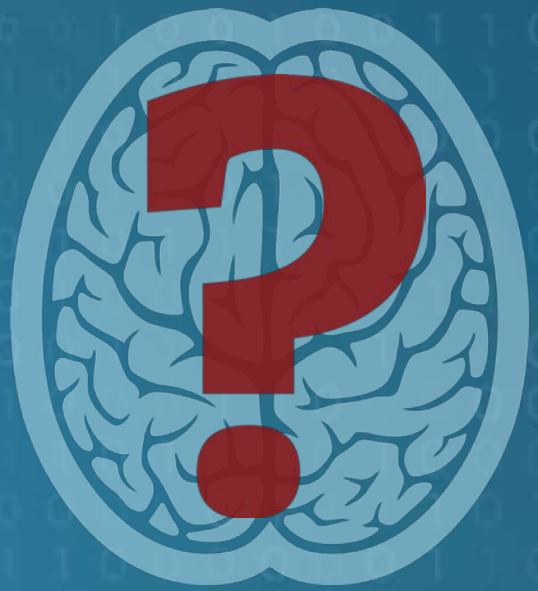
- Develops Right arm-face paresis, resolved en route to ED (duration 15 minutes)
- **NIHSS 0** at **2 hours** post-onset
- NSR on heart monitor
- NCCT unremarkable
- Neck-willis CTA: left carotid atherosclerotic plaque with ulceration (40% stenosis)
- TTE/Holter pending
- Brain MRI (protocol TIA: DWI and FLAIR): negative (DWI-)

Medical treatment

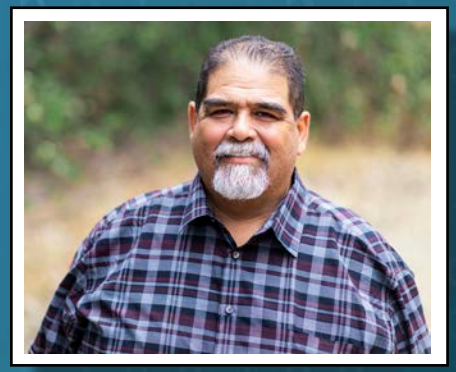
- Perindopril 4 mg po qd
- Rosuvastatin 20 mg po qd
- ASA 80 mg po qd

Dx: High-risk TIA due to left carotid sync

BP, blood pressure; CTA, Computed Tomography Angiography; DWI, diffusion-weighted imaging; Dx, diagnosis; NCCT, non-contrast computed tomography; NIH, National Institutes of Health Stroke Scale; NSR, National Scouting Report; po, per os (by mouth/orally); PMHx, past medical history; qd, once-daily; TIA, transient ischemic attack; TTE, transthoracic echocardiogram.



Case 1: What is your recommended antithrombotic regimen?



Josh

What would be your next management step?

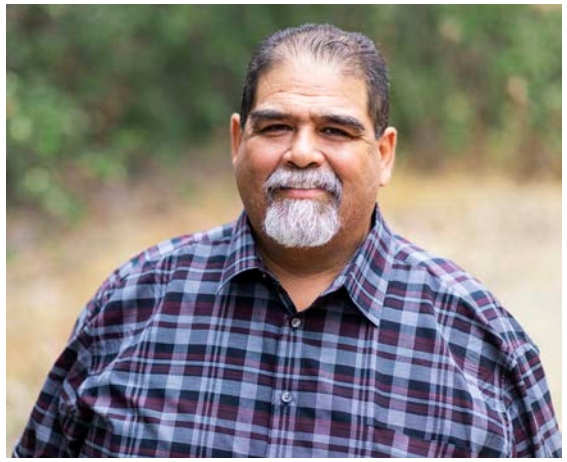
A. DAPT (aspirin + clopidogrel)

B. Dual pathway: aspirin + asundexian

C. Triple therapy: aspirin + clopidogrel + asundexian

Asundexian is not approved for the treatment of stroke.
ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy.

Case 1: What is your recommended antithrombotic regimen?



Josh

Let's discuss the rationale for the management steps

1. DAPT (aspirin + clopidogrel)
   Rationale:
   - Only 5% of patients in OCEANIC STROKE were TIAs
   - DAPT remains standard of care for TIAs within 24 hours (median time onset to treatment in OCEANIC-STROKE = 50.5 ± 15.3 hours)

2. Dual pathway: aspirin + asundexian
   Rationale:
   - Dual pathway inhibition may confer an added advantage for secondary stroke prevention

3. Triple therapy: aspirin + clopidogrel + asundexian
   Rationale:
   - 66% of subjects were on DAPT at the time of randomization in OCEANIC STROKE...triple therapy is the new standard of care?

Asundexian is not approved for the treatment of stroke.
ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; TIA, transient ischemic attack.

Case 2: “Code Stroke”

David

Patient profile

- 56 M independent
- PMHx: Smoker, uncontrolled BP, dyslipidemia

Clinical Presentation

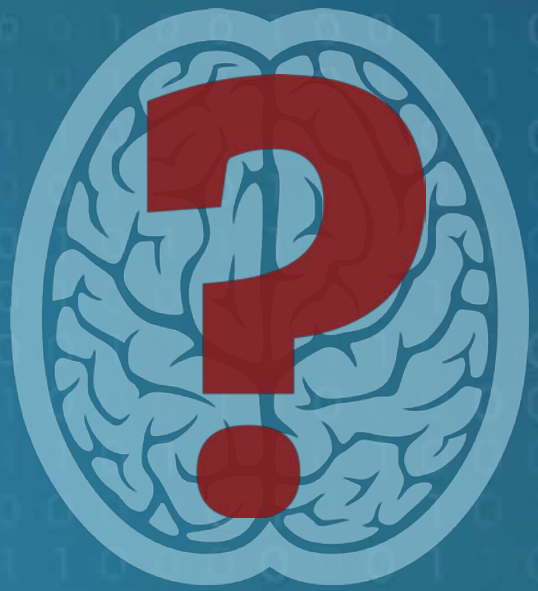
- **Delayed presentation: 4-day** history of mild right arm-face paresis, with worsening upon awakening this morning
- **NIHSS 3**
- NSR on continuous heart monitoring
- NCCT unremarkable
- Neck-willis CTA: left carotid atherosclerotic plaque (40% stenosis)
- TTE/Holter pending
- Brain MRI: DWI+ lesion in left precentral gyrus

Medical treatment

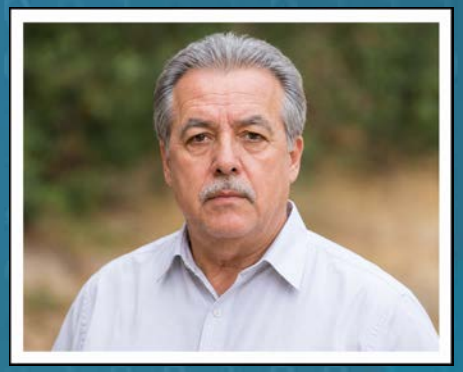
- Perindopril 4 mg po qd
- Rosuvastatin 20 mg po qd
- ASA 80 mg po qd

Dx: Minor ischemic stroke due to left carotid sync

BP, blood pressure; CTA, Computed Tomography Angiography; DWI, diffusion-weighted imaging; Dx, diagnosis; MRI, magnetic resonance imaging; NCCT, non-contrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; NSR, National Scouting Report; po, per os (by mouth/orally); PMHx, past medical history; qd, once-daily; TIA, transient ischemic attack; TTE, transthoracic echocardiogram.



Case 2: What is your recommended antithrombotic regimen?



David

What would be your next management step?

A. Aspirin monotherapy

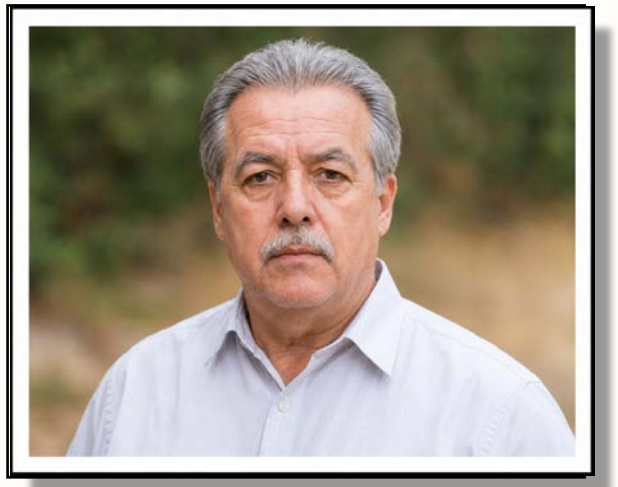
B. Aspirin + asundexian

C. DAPT (Aspirin + clopidogrel)

D. Triple therapy (dual pathway) aspirin + clopidogrel + asundexian

Asundexian is not approved for the treatment of stroke.
ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy.

Case 2: What is your recommended antithrombotic regimen?



David

Let's discuss the rationale for the management steps

1. Aspirin monotherapy
   Rationale: Patient is out-of-window for other treatments, and is considered at lower risk of future events at this stage

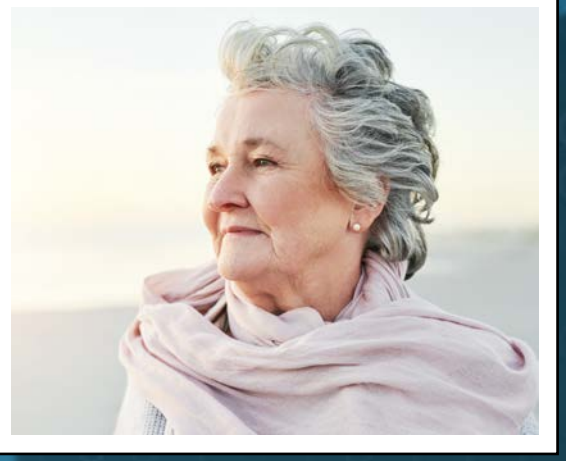
2. Aspirin + asundexian
   Rationale: The patient does not respect trial population (<72 hours from stroke onset), but compelling given robust medium-long term secondary stroke prevention

3. DAPT (aspirin + clopidogrel)
   Rationale: Minor stroke just beyond recommended time windows (time window creep)

4. Triple therapy (aspirin + clopidogrel + asundexian)
   Rationale: Minor stroke just beyond recruitment window in OCEANIC-STROKE (<72 hours) from stroke onset), but compelling given robust medium-long term secondary stroke prevention

Asundexian is not approved for the treatment of stroke.
ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; TIA, transient ischemic attack.

Case 3



Jenny

Patient profile

- 72 F independent
- PMHx: dyslipidemia

Clinical Presentation

- Last seen well at 16:30, then found aphasic with right hemiplegia at 19:00
- **NIHSS 16**
- NCCT unremarkable
- CTA: Left proximal **M1 occlusion**, normal proximal left ICA
- NSR on heart monitor
- Treated acutely with **IV TNK + EVT**
- DTN : 20 minutes, DTP: 70 minutes

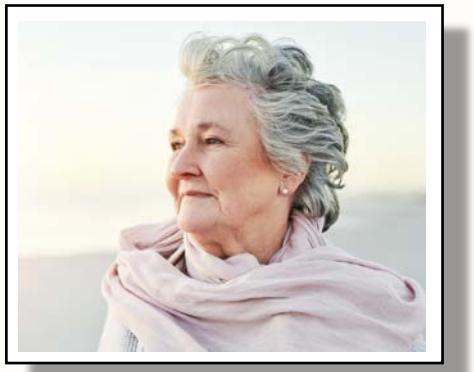
Medical treatment

- Hormone replacement therapy (estradiol patch)
- Rosuvastatin 10 mg po HS

Dx: Embolic ischemic stroke of undetermined source

CTA, CT angiography; DLP, dyslipidemia (abnormal cholesterol/lipid levels); DTN, door-to-needle time; DTP, door-to-puncture time; Dx, diagnosis; HS, hora somni (at bedtime); IV, intravenous; M1 occlusion, blockage of the M1 segment of the middle cerebral artery; NIHSS 16, National Institutes of Health Stroke Scale score of 16; NCCT, non-contrast computed tomography; NSR, normal sinus rhythm; PMHx, past medical history; po, per os (by mouth/oral).

Case 3: At 24 hours



Jenny

NIHSS 14

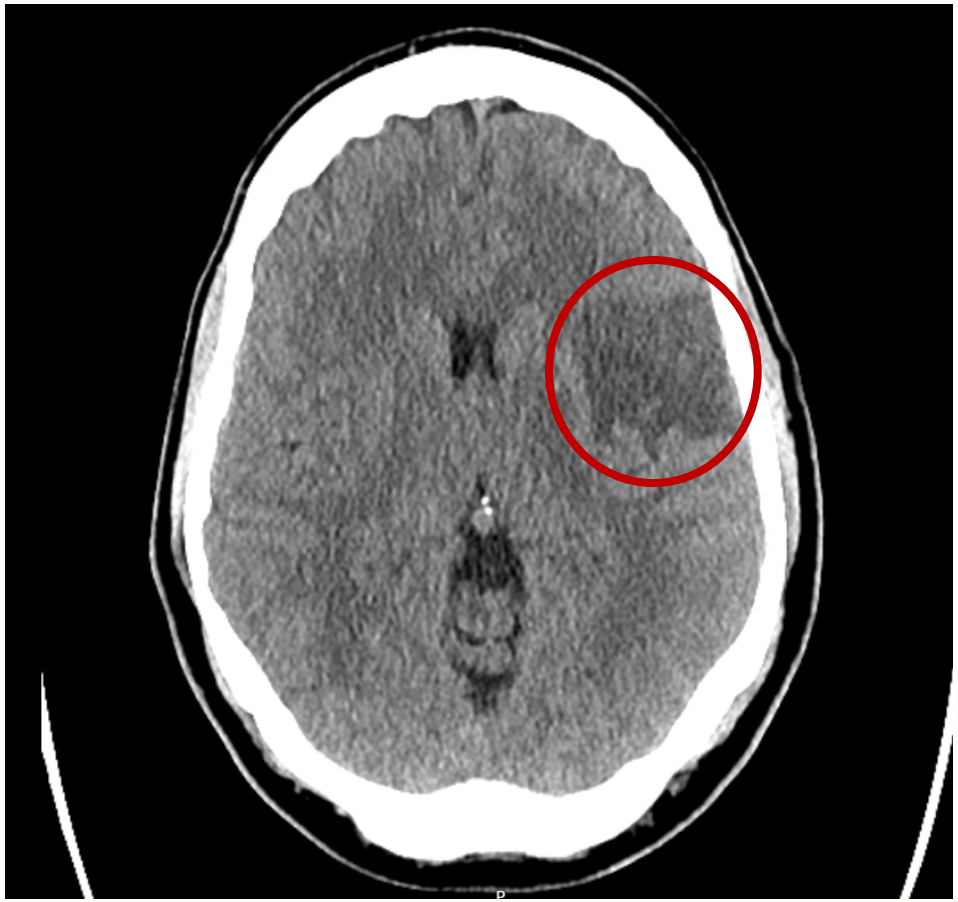
- Severe expressive aphasia
- Right hemiparesis

Control NCCT:

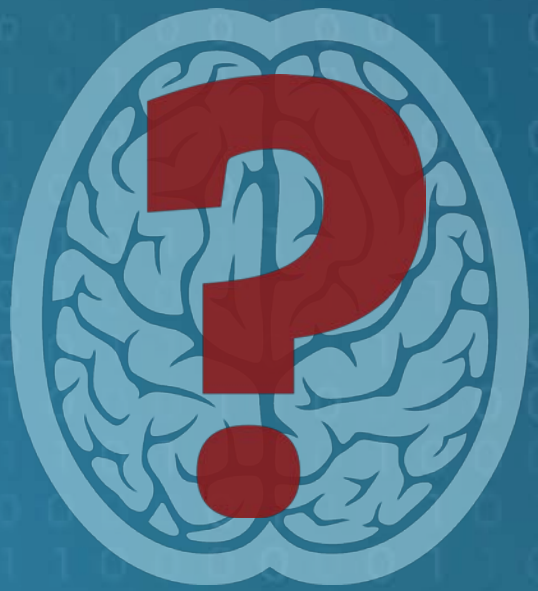
- Left opercular frontal infarct of moderate size

TTE: within normal limits

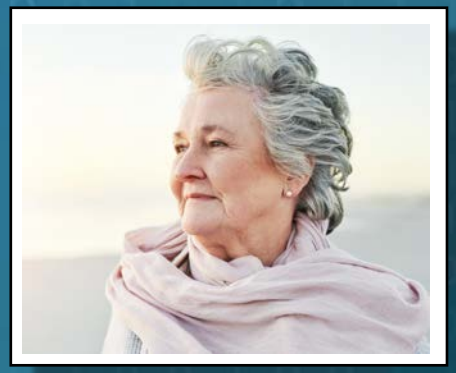
Holter: pending



NCCT, non-contrast computed tomography; NIHSS 16, National Institutes of Health Stroke Scale score of 16; TTE, transthoracic echocardiogram.



Case 3: What is your recommended antithrombotic regimen?



Jenny

What would be your next management step?

A. Aspirin + prophylactic low molecular weight heparin (LMWH)

B. Aspirin + prophylactic LMWH for first 24 hours, with re-evaluation at 48-72 hours to consider addition of asundexian

C. ASA + asundexian + LMWH starting at 24 hours

Asundexian is not approved for the treatment of stroke.
ASA, acetylsalicylic acid; LMWH, low molecular weight heparin.

Case 3: What is your recommended antithrombotic regimen?

Jenny

Let's discuss the rationale for the management steps

1. Aspirin + prophylactic LMWH
   Rationale:
   - Median NIHSS 2 (1-4) in OCEANIC-STROKE, does not reflect our patient's profile
   - A minority (7%) of subjects recruited in OCEANIC-STROKE were treated with both thrombolysis and EVT

2. ASA + prophylactic LMWH for first 24 hours, with re-evaluation at 48-72 hours to consider addition of asundexian
   Rationale:
   - Median time from symptom onset to randomization was 50 ± 15 hours, not 24 hours
   - An estimated higher risk of hemorrhagic transformation in the first 24-48 hours in our patient

3. ASA + asundexian + LMWH starting at 24 hours
   Rationale: Patient corresponds to OCEANIC-STROKE inclusion criteria

Asundexian is not approved for the treatment of stroke.
ASA, acetylsalicylic acid; LMWH, low molecular weight heparin; NIHSS, National Institutes of Health Stroke Scale.

Panel Discussion

Moderator:

Dr. Mike Sharma

Speakers:

Dr. Laura Gioia &

Dr. Ashkan Shoamanesh

A NEW CHAPTER IN SECONDARY STROKE PREVENTION

Clinical Insights from Phase III FXIa Inhibitor Trials

Thank you for joining us today!