

Setting the Stage: The Residual Risk Problem After Stroke

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Disclosures

Stocks

- None

Drug trials (< 5 years)

- PACIFIC-Stroke
- PACIFIC-AF
- OCEANIC-Stroke
- OCEANIC-AF

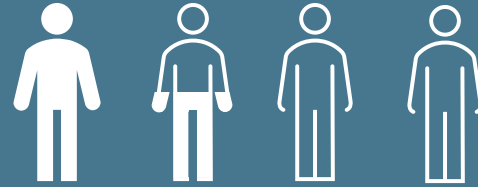
Advisory boards & speaker fees (< 3 years)

- Bayer*
- Boston Scientific
- Daiichi Sankyo*
- Ever Neuro Pharma*
- Novartis*
- Pfizer/BMS*

***FEES ARE PAID TO ARS UMBRIA**

The Risk of Mortality and Poor Patient Outcomes Increases With Each Recurrent Stroke

The risk of a second stroke is
~9-fold greater
in patients who have experienced a prior stroke than the general population¹



Up to **37%** of strokes reoccur at 3 years^{2*}



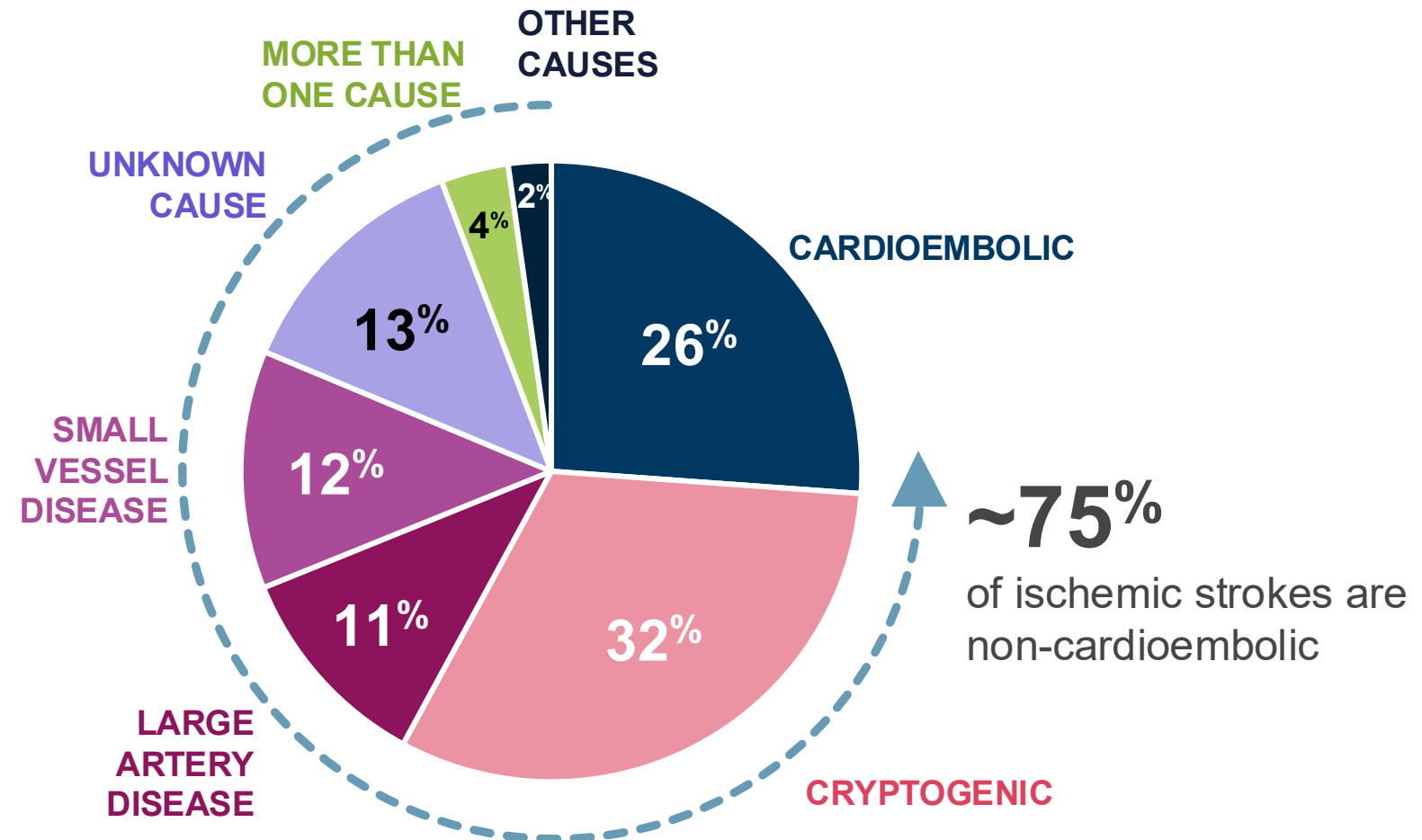
Stroke patients were **2.4 times more likely to be hospitalized** in follow-up compared with controls³

*Based on a systematic review and meta-analysis of 3 studies.

1. Velleca M, et al. *EMJ Cardiol.* 2019;7(1):110-118. 2. Kolmos M, et al. *J Stroke Cerebrovasc Dis.* 2021;30(8):105935. 3. Engel-Nitz NM, et al. *Vasc Health Risk Manag.* 2010;6:905-913.

The Majority of Ischemic Strokes Are Non-Cardioembolic^{1,2}

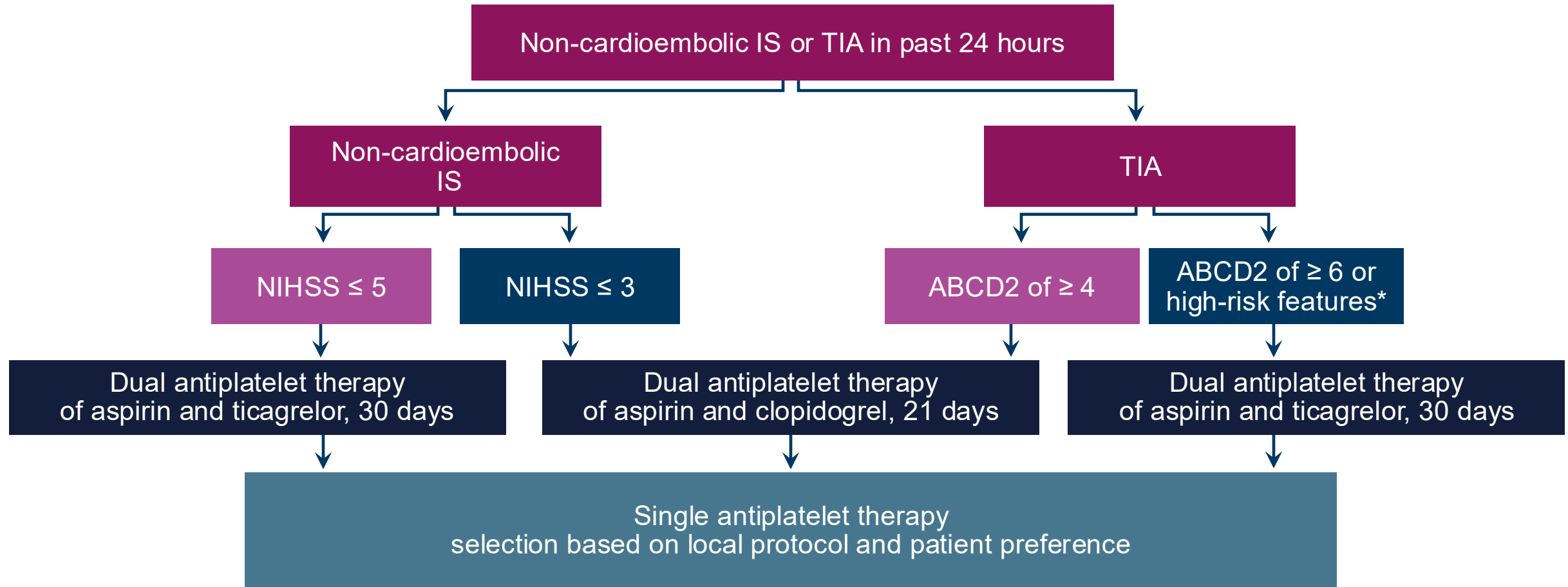
Data from Oxford Vascular Study: first ischemic stroke or TIA (N = 2,555)



TIA, transient ischemic attack.

1. Li L, et al. *Lancet Neurol.* 2015;14(9):903-913. 2. Adams HP Jr, et al. *Stroke.* 1993;24(1):35-41.

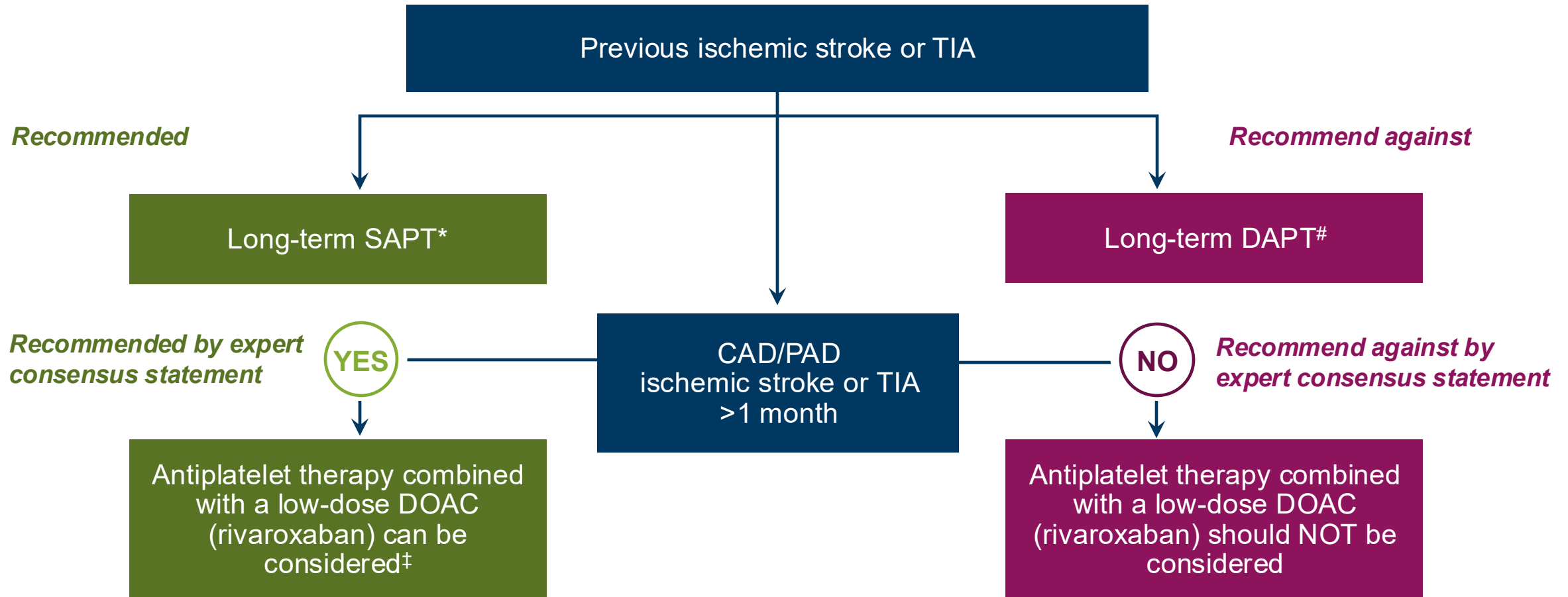
ESO 2021 Guidelines Recommend Antiplatelet Therapy and Dual Antiplatelet Therapy *Early* After Minor Non-Cardioembolic Ischemic Stroke or High-Risk TIA¹



¹Either intracranial atherosclerotic disease or at least 50% stenosis on ICA that could account for presentation.

ABCD2, Age, Blood Pressure, Clinical features, Duration of symptoms, Diabetes history; ESO, European Stroke Organisation; ICA, internal carotid artery; IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack. Dawson J, et al. *Eur Stroke J*. 2021;6(2):CLXXXVII-CXCI.

ESO 2022 Guidelines for *Long-Term* Secondary Prevention After Ischemic Stroke or TIA



*Additional treatment recommendations and expert consensus statements include statins, dual therapy with two blood pressure-lowering drugs, pioglitazone and a target level of <53 mmol/mol for HbA1c in patients with IS/TIA and type 2 diabetes. #Recommended avoidance of DAPT with aspirin and clopidogrel after the first 90 days. ‡In adults, there is continued uncertainty over use of antiplatelet therapy combined with low-dose DOAC. CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; ESO, European Stroke Organisation; HbA1c, glycated hemoglobin; IS, ischemic stroke; PAD, peripheral artery disease; SAPT, single antiplatelet therapy; TIA, transient ischemic attack. Dawson J, et al. *Eur Stroke J*. 2022;7(3):I-XLI.

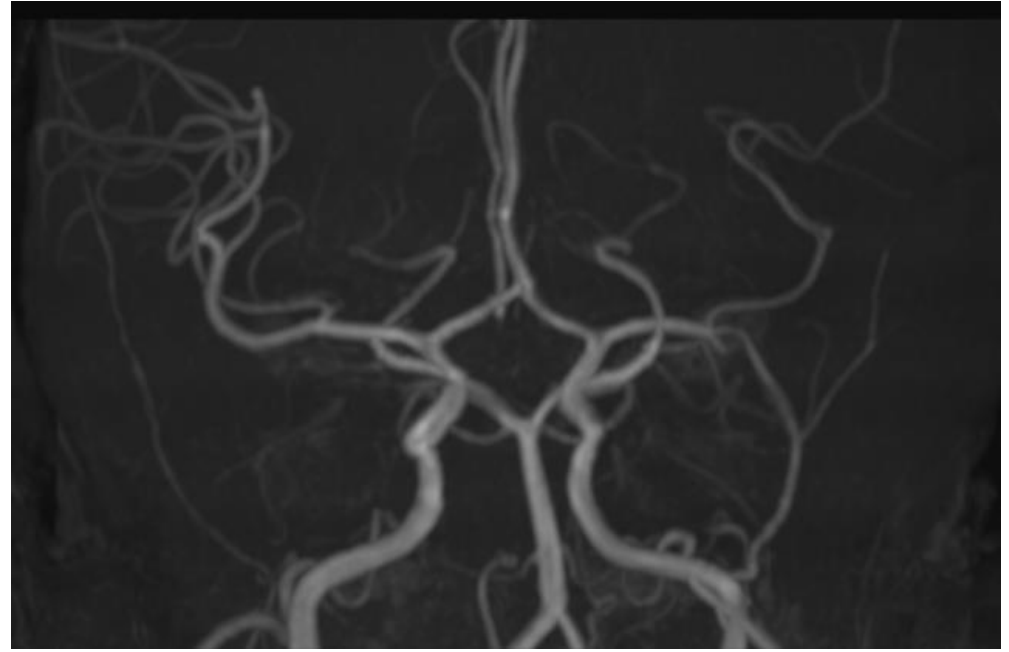
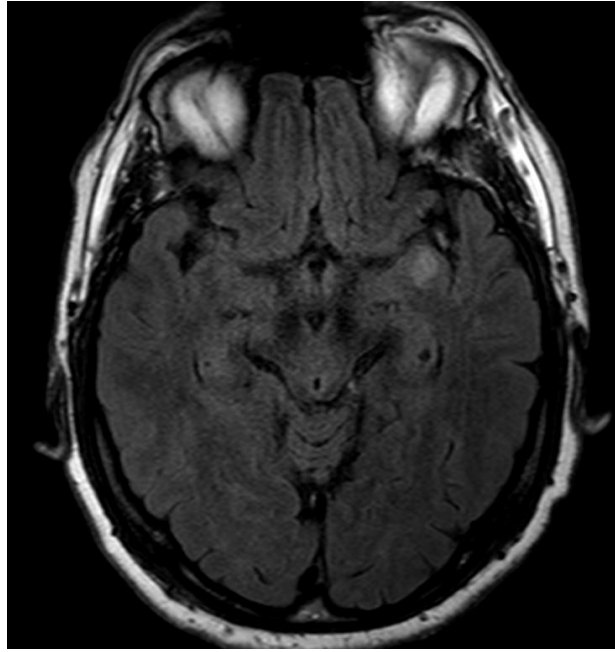
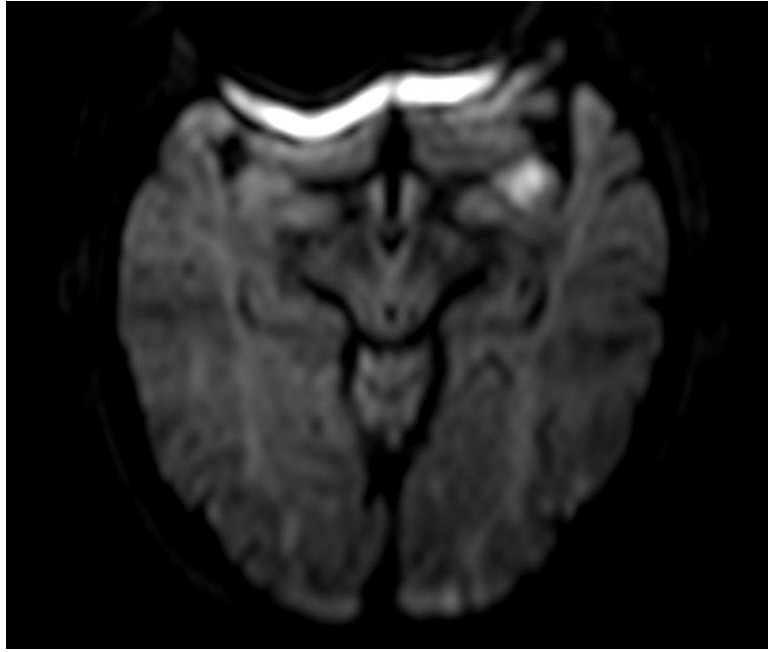
January 6th, 6 pm

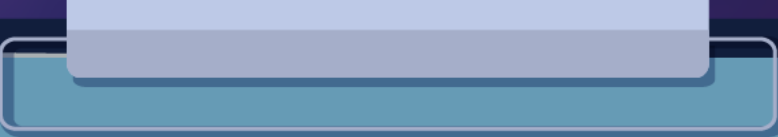
MARCO, 65-YEAR-OLD

- Sudden-onset transient aphasia and right hemiparesis
- Admitted to hospital after 12 hours without neurological symptoms
- CT at admission: negative for acute ischemic stroke

Clinical History

- Smoking, hypertension, diabetes mellitus, smoking, BMI > 35
- Ramipril 5 mg, metformin

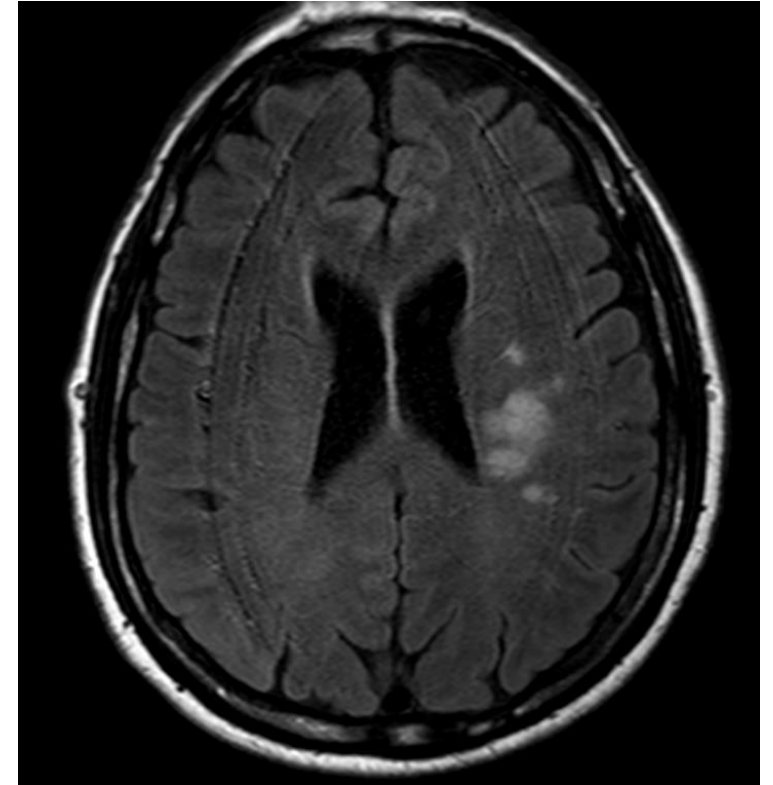
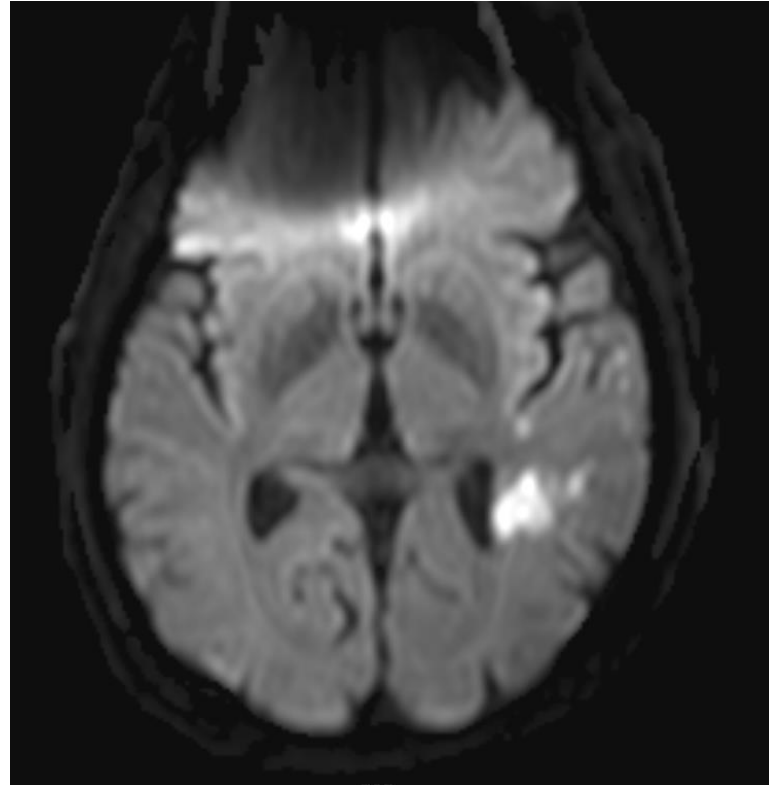
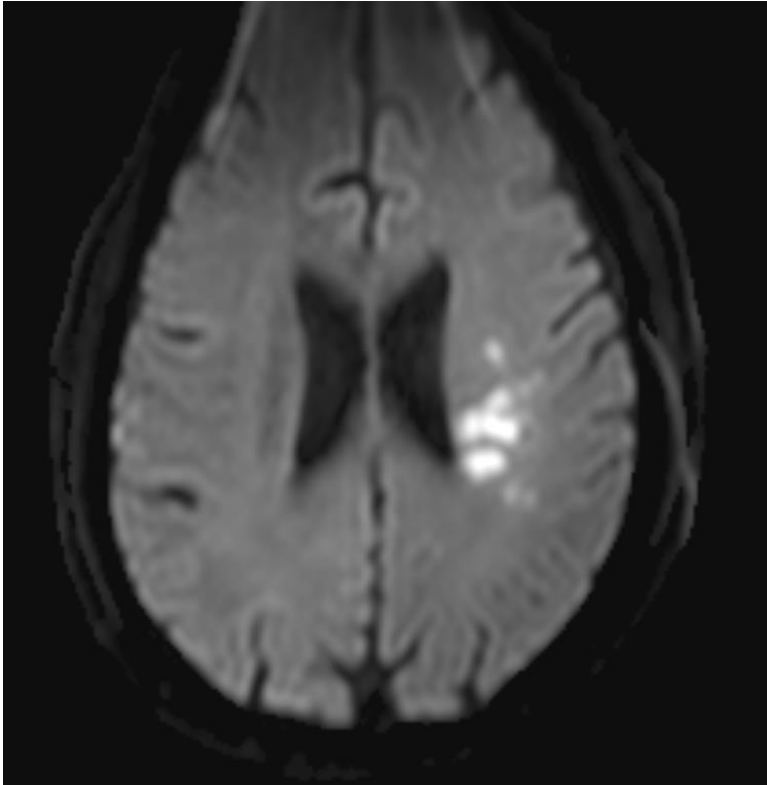




MARCO, 65-YEAR-OLD

- NIHSS: 0
- DAPT was started after a loading dose of clopidogrel (300 mg and aspirin 300 mg) followed by clopidogrel 75 mg for 21 days and aspirin for long-term treatment
- Statins, indications to stop smoking and lose weight

Patient's Neurological Examination Worsened With Right Hemiparesis

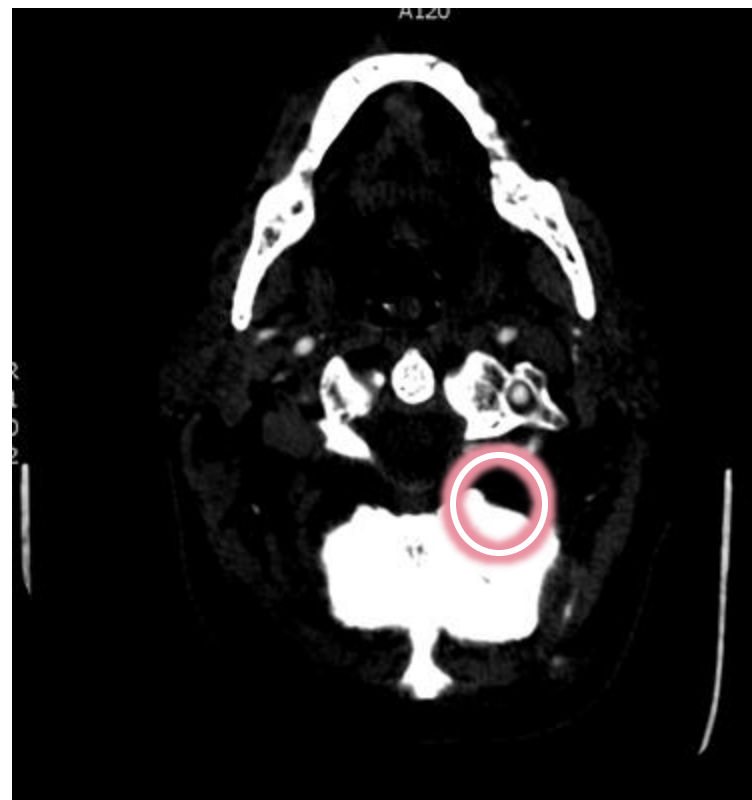


Clinical Practice

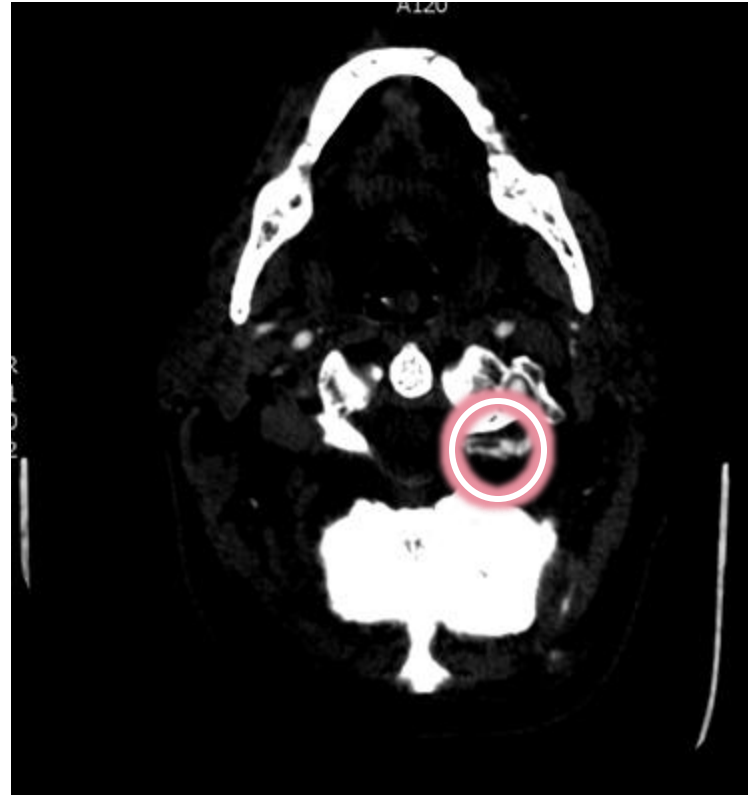
A 72-year-old patient presenting with conjugate gaze deviation to the right and right homonymous hemianopia

NIHSS score: 4

Aspirin 300 mg and clopidogrel 300 mg



Clinical Practice



Global Expert Consensus on the Importance of Secondary Stroke Prevention: Challenges, Care Coordination, and Unmet Needs for Non-Cardioembolic Ischemic Stroke Survivors

We aimed to assess the concept of 'information needs' in recurrent stroke prevention and to summarize the information needs of people with stroke.

METHODS



Scoping review
Medline, CINAHL,
and PsycINFO up to
June 5, 2023



People ≥ 18 years
who suffered a stroke
or TIA within the past
five years



Information needs of
people with stroke

RESULTS

Top 10 information needs

1. Treatment
2. Etiology of stroke
3. Personalized information
4. Prognosis/recovery
5. Community/social support
6. Effects of stroke
7. Care role
8. Rehabilitation
9. Emotional support
10. Discharge



**Most important
influencing factor**
Time of information
provision



**Preferred
information source**
Healthcare professionals

CONCLUSION

**Primary
information needs:**
Clinical information
about the stroke (e.g.
treatment and etiology)



**A clear concept of
information needs is
required**

The Importance of Secondary Stroke Prevention

Global Expert Consensus

Challenges, care coordination, and unmet needs for non-cardioembolic stroke survivors

“

Statement 11:

Sustained investment in SSP management, support and new treatment options are needed to improve quality of life for patients and carers and achieve long-term cost savings.

National stroke plans that include SSP, supported by clear guidelines and policies, will be required to support this goal.

”

Evidence in Focus: OCEANIC-Stroke and What It Changes

Ashkan Shoamanesh, MD

Associate Professor of Medicine

McMaster University

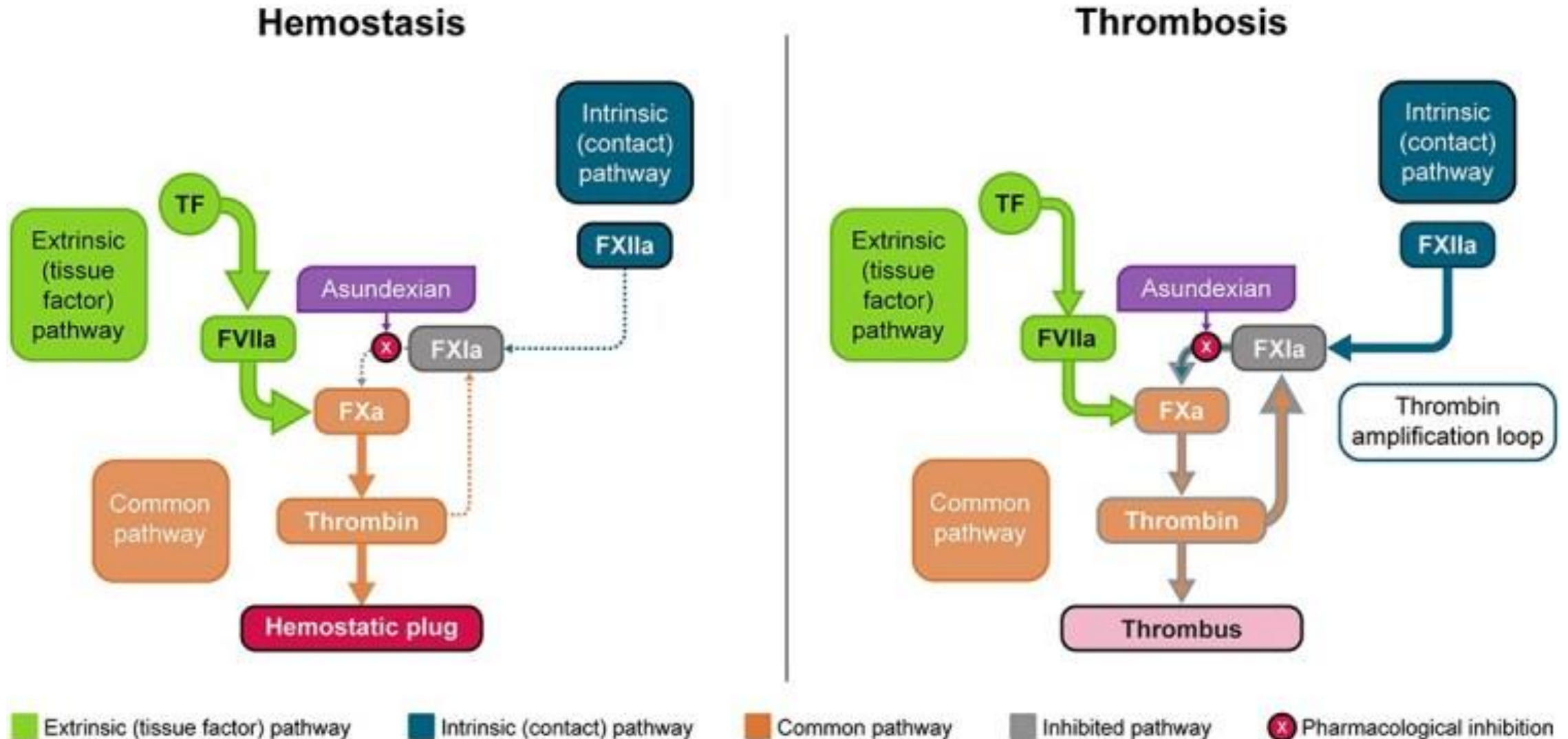
Hamilton, ON, Canada

Disclosures

Relationships With Financial Sponsors

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GRANTS/RESEARCH SUPPORT:	Bayer AG , BHF, BMS/Pfizer, C-SPIN, CaSTOR, CIHR, Daiichi Sankyo Ltd, HSFC, Javelin Inc., MRFF, NIH, Octapharma Canada, PHRI, Portola Pharmaceuticals, Servier Canada Inc.
OTHER:	Marta and Owen Boris Foundation

FXI inhibition: Potential to uncouple pathologic thrombus formation from hemostasis

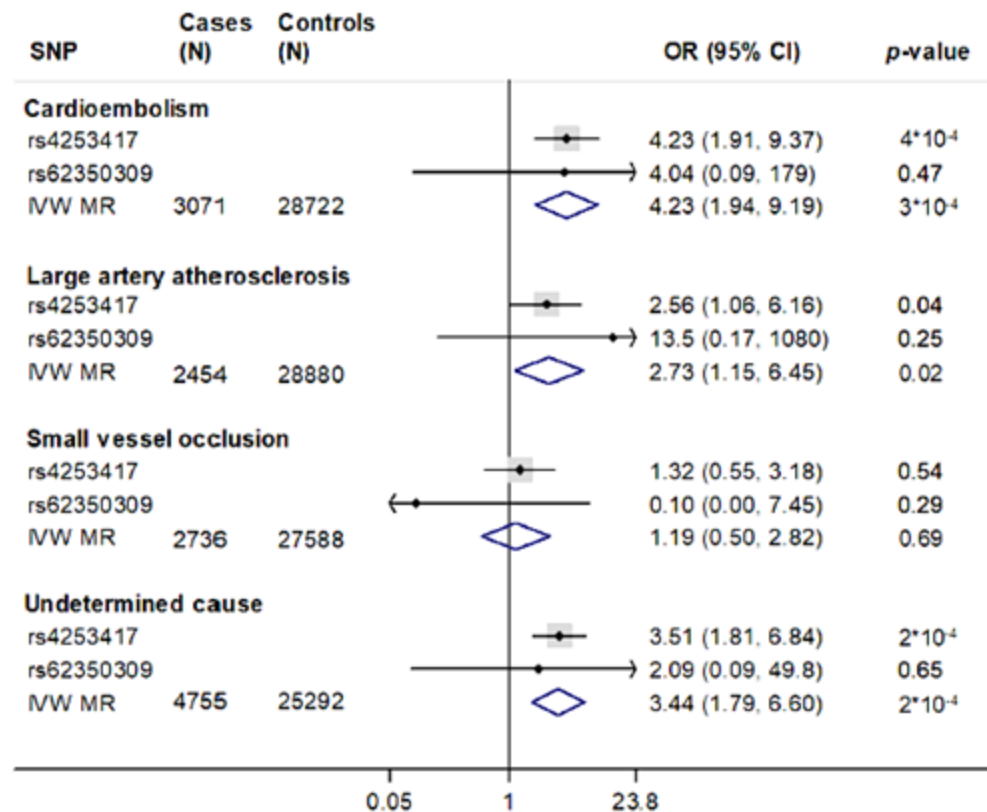


Evidence Supporting FXIa Inhibition as a Target

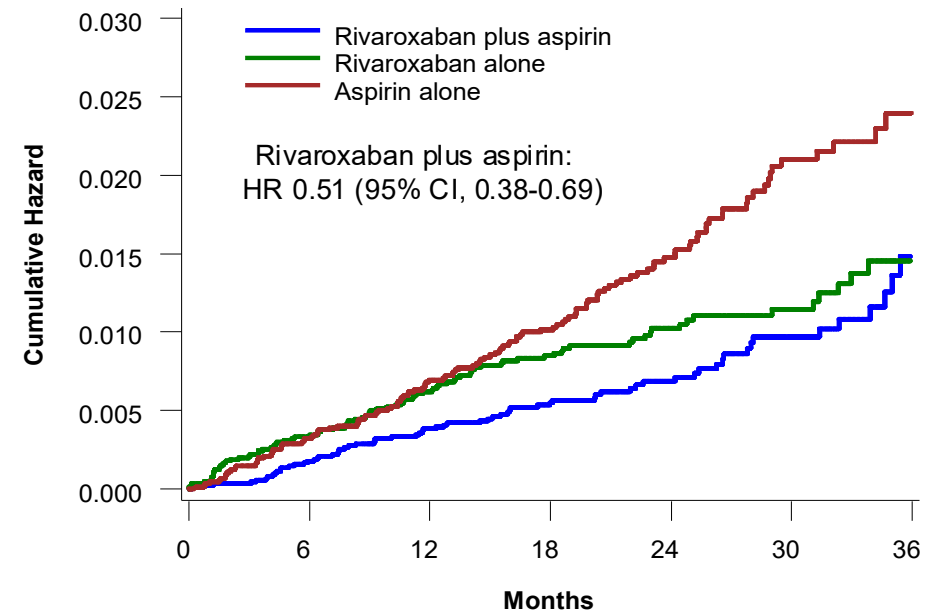
CONDITION	OBSERVATION
Inherent FXI deficiency ¹	• Reduced rates of ischemic stroke and VTE • Spontaneous major bleeding, rare
FXI-knockout mice ²	• Homozygous FXI-knockout mice are protected from thrombosis • At the same time, they do not show a bleeding phenotype differing from wild-type mice
<i>In vivo</i> animal models ³	• Reducing/inhibiting FXI showed strong antithrombotic effects <i>in vivo</i> • No increase in bleeding time even at very high doses or on top of dual antiplatelet therapy

Human Genetic Data as Well as Clinical Data Support the Testing of Asundexian, a FXIa Inhibitor, for Secondary Stroke Prevention

Significant reduced risk for CV events and ischemic stroke in FXI-deficient individuals

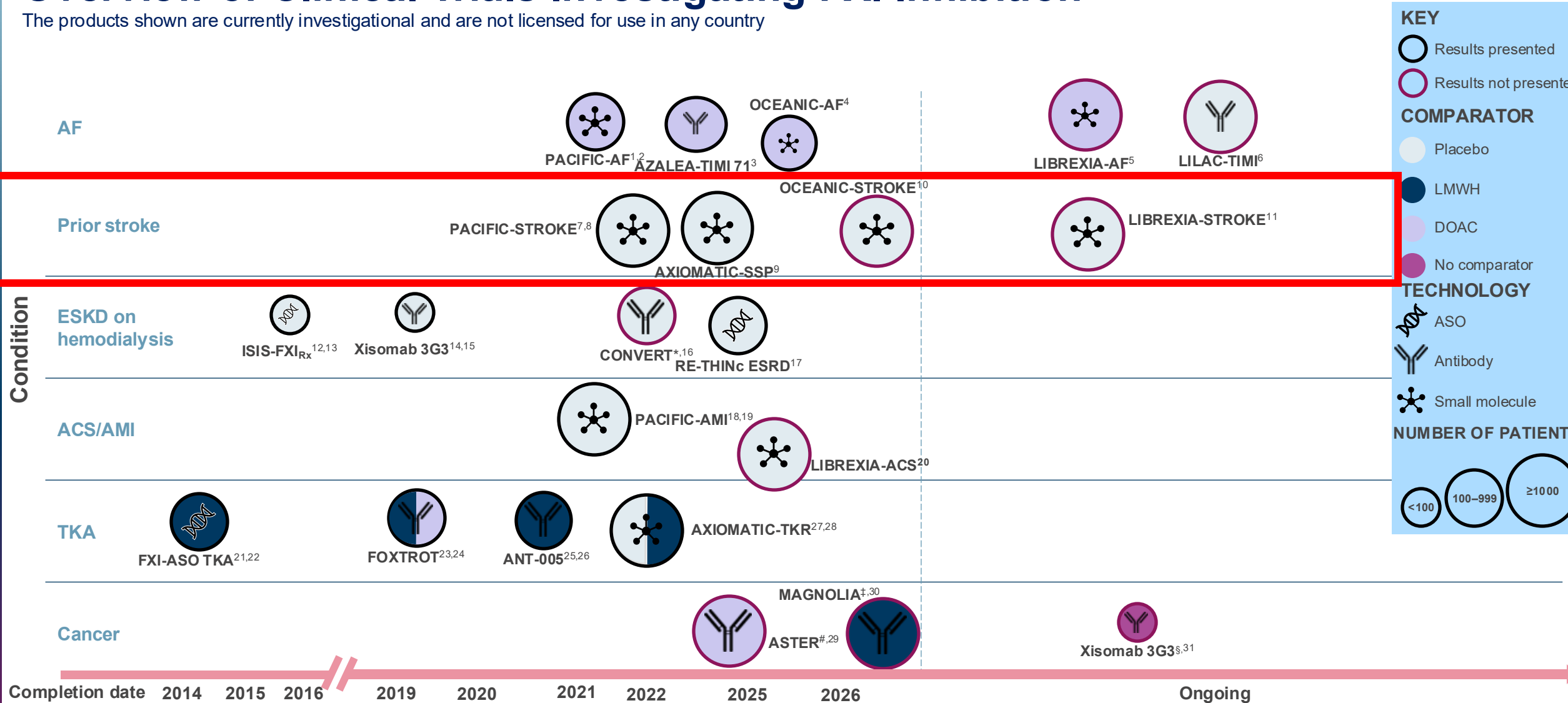


Significant reduced risk for ischemic stroke in patients with CAD and PAD treated with dual pathway inhibition (rivaroxaban and aspirin)



Overview of Clinical Trials Investigating FXI Inhibition

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

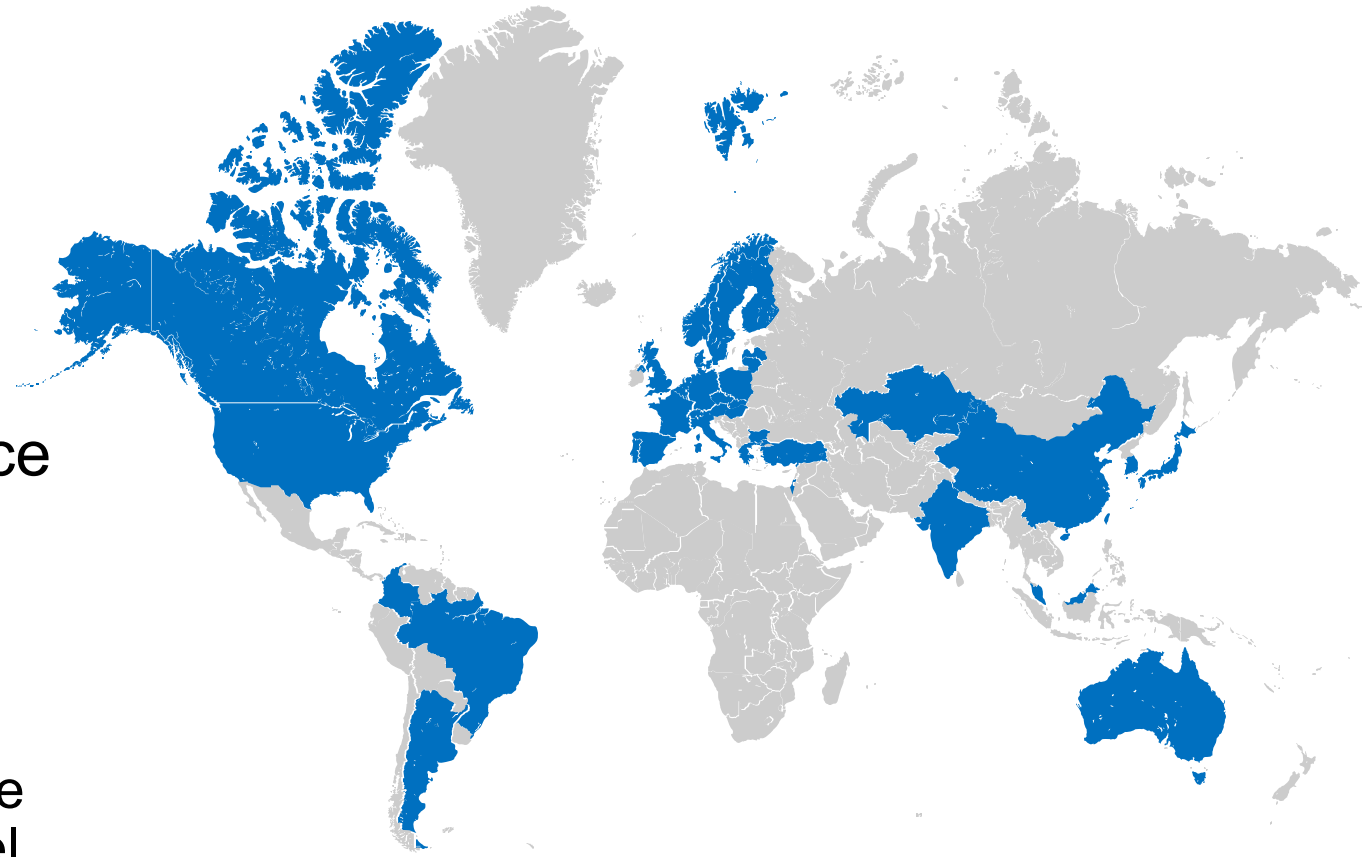


*Osocimab. #Patients with CAT currently receiving or having received anticancer therapy in the last 6 months. †Patients with GI or GU cancer and CAT receiving LMWH for ≥6 months. §Patients with cancer receiving chemotherapy. ACS, acute coronary syndrome; AF, atrial fibrillation; AMI, acute myocardial 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.

1. Bayer. 2022. NCT04218266. 2. Piccini JP, et al. *Lancet*. 2022;399(10333):1383-1390. 3. Anthos Therapeutics, Inc. 2022. NCT04755283. 4. Bayer. 2022. NCT05643573. 5. Bristol Myers Squibb. 2023. NCT05757869. 6. Anthos Therapeutics, Inc. 2023. NCT05712200. 7. Bayer. 2022. NCT04304508. 8. Shoamanesh A, et al. *Lancet*. 2022;400(10357):997-1007. 9. Bristol Myers Squibb. 2022. NCT03766581. 10. Bayer. 2023. NCT05686070. 11. Janssen Research & Development, LLC. 2023. NCT05702034. 12. Ionis Pharmaceuticals, Inc. 2016. NCT02553889. 13. Walsh M, et al. *Kidney Int Rep*. 2021;7(2):200-209. 14. Aronora, Inc. 2022. NCT03612856. 15. Lorentz CU, et al. *Blood*. 2021;138(22):2173-2184. 16. Bayer. 2022. NCT04523220. 17. Bayer. 2023. NCT04534114. 18. Bayer. 2022. NCT04304534. 19. Rao SV, et al. *Circulation*. 2022;146(16):1196-1206. 20. Janssen Research & Development, LLC. 2023 NCT05754957. 21. Ionis Pharmaceuticals, Inc. 2014. NCT01713361. 22. Büller HR, et al. *N Engl J Med*. 2015;372(3):232-240. 23. Bayer. 2020. NCT03276143. 24. Weitz JI, et al. *JAMA*. 2020;323(2):130-139. 25. Anthos Therapeutics, Inc. 2022. EudraCT 2019-003756-37. 26. Verhamme P, et al. *N Engl J Med*. 2021;385(7):609-617. 27. Janssen Research & Development, LLC. 2022. NCT03891524. 28. Weitz JI, et al. *N Engl J Med*. 2021;385(23):2161-2172. 29. Anthos Therapeutics, Inc. 2023. NCT05171049. 30. Anthos Therapeutics, Inc. 2023. NCT05171075. 31. OHSU Knight Cancer Institute. 2022. NCT04465760.

OCEANIC-Stroke

- Design
 - 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

Key Inclusion and Exclusion Criteria

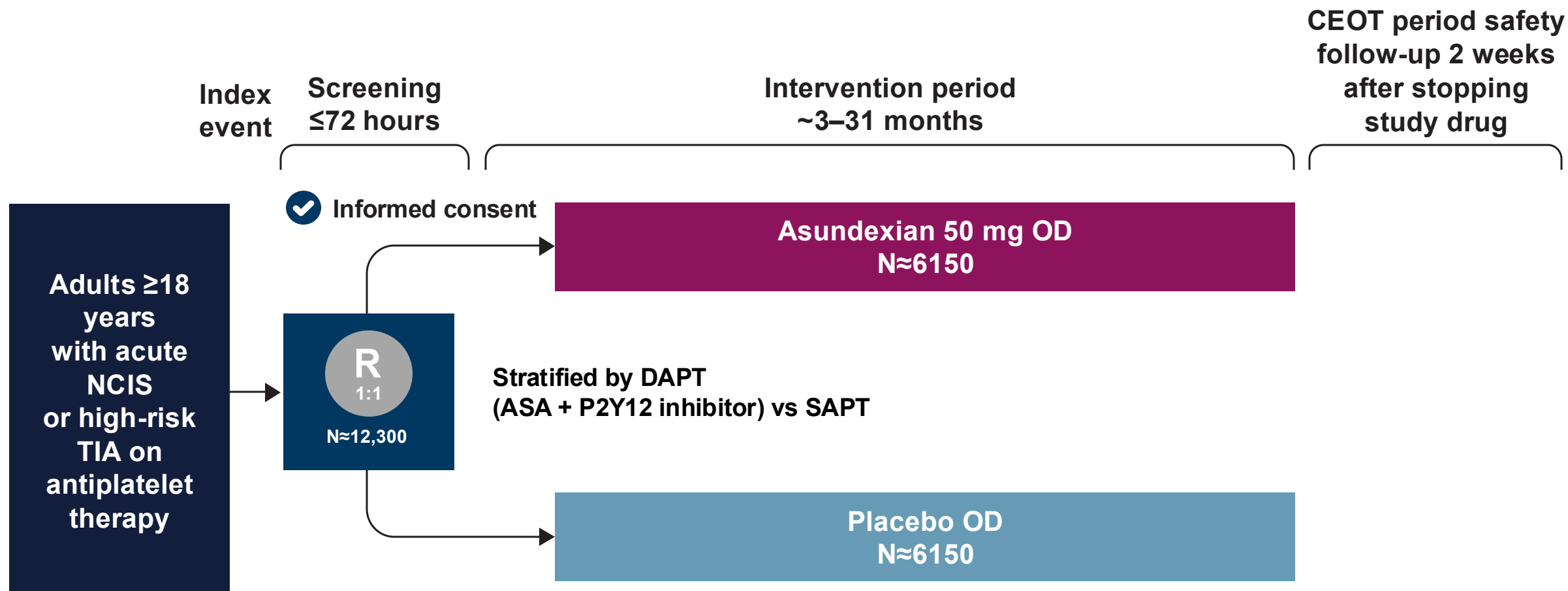
Key inclusion:

- Participants aged ≥ 18 years, within 72 hours of symptom onset:
 - Non-cardioembolic ischemic stroke (NIHSS ≤ 15) or high-risk TIA (ABCD² 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 (eg, vasculitis)
- End-stage renal disease requiring dialysis
- Active nontrivial bleeding (eg, PH1 or PH2); asymptomatic HT and CMB permitted
- History of nontraumatic ICH; significant GI bleeding within 6 months

OCEANIC-Stroke: Study Design



OCEANIC-Stroke: Key Endpoints

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

*Hypothesis testing conducted using strict hierarchy order for efficacy endpoints.

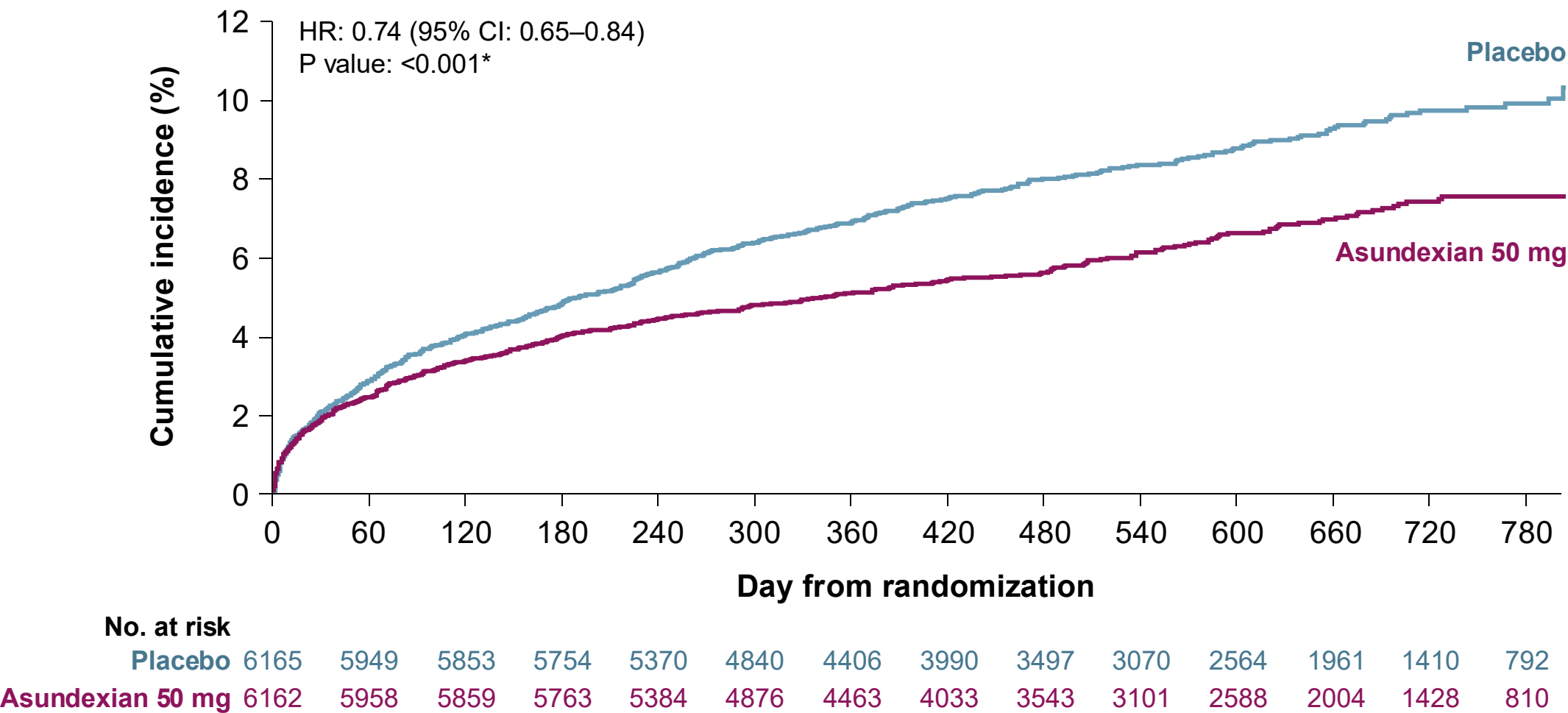
CRNM, clinically relevant non-major; CV, cardiovascular; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; mRS, modified Rankin score.

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)

[†]Stroke index event only.

Cumulative Incidence of Ischemic 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.
 CI, confidence interval; csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy; HR, hazard ratio.

Efficacy Outcomes

Outcome	Asundexian 50 mg (N = 6162)	Placebo (N = 6165)	csHR (95% CI) [†]	P value [‡]
	n (%)	n (%)		
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

[†]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; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; mRS, modified Rankin score.

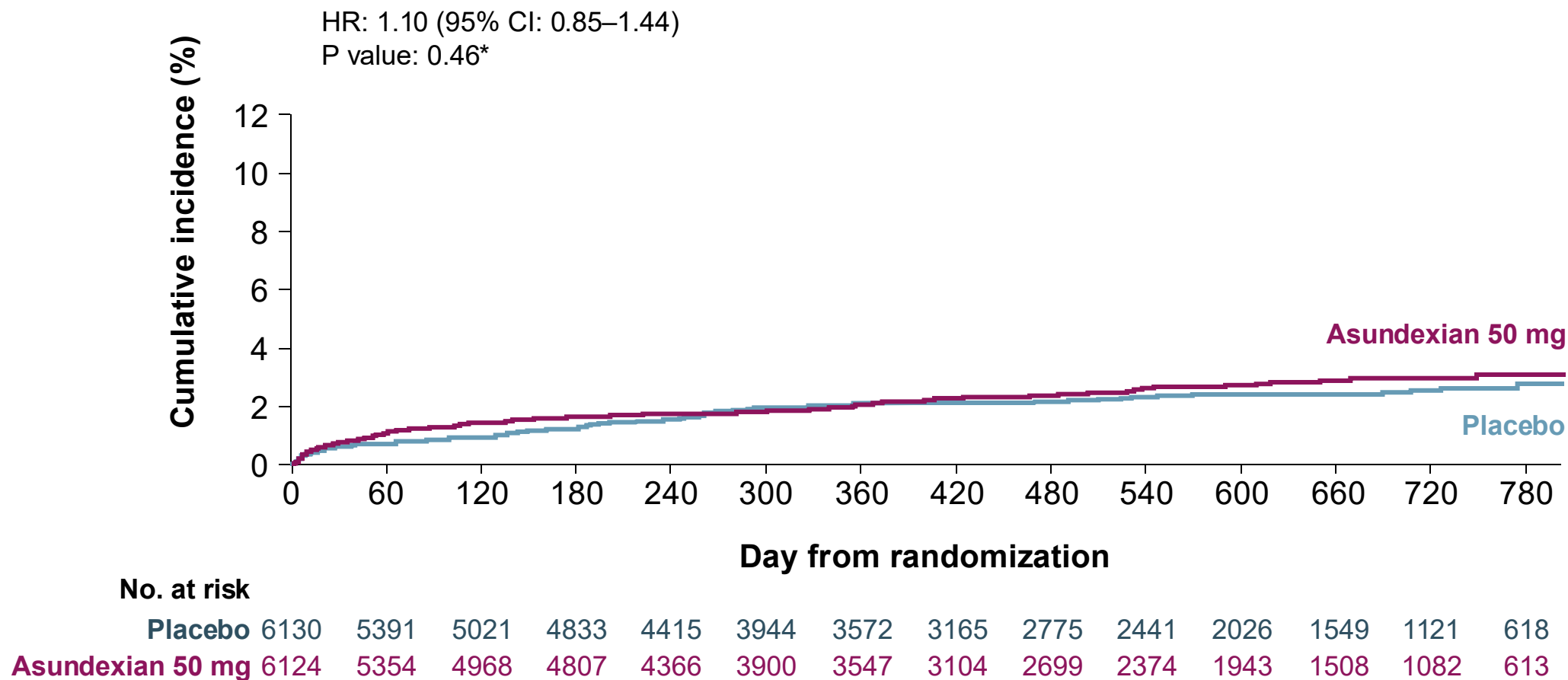
Safety Outcomes

Outcome	Asundexian 50 mg (N = 6162)	Placebo (N = 6165)	csHR (95% CI) [†]
	n (%)	n (%)	
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)

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

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

Cumulative Incidence of ISTH Major Bleeding

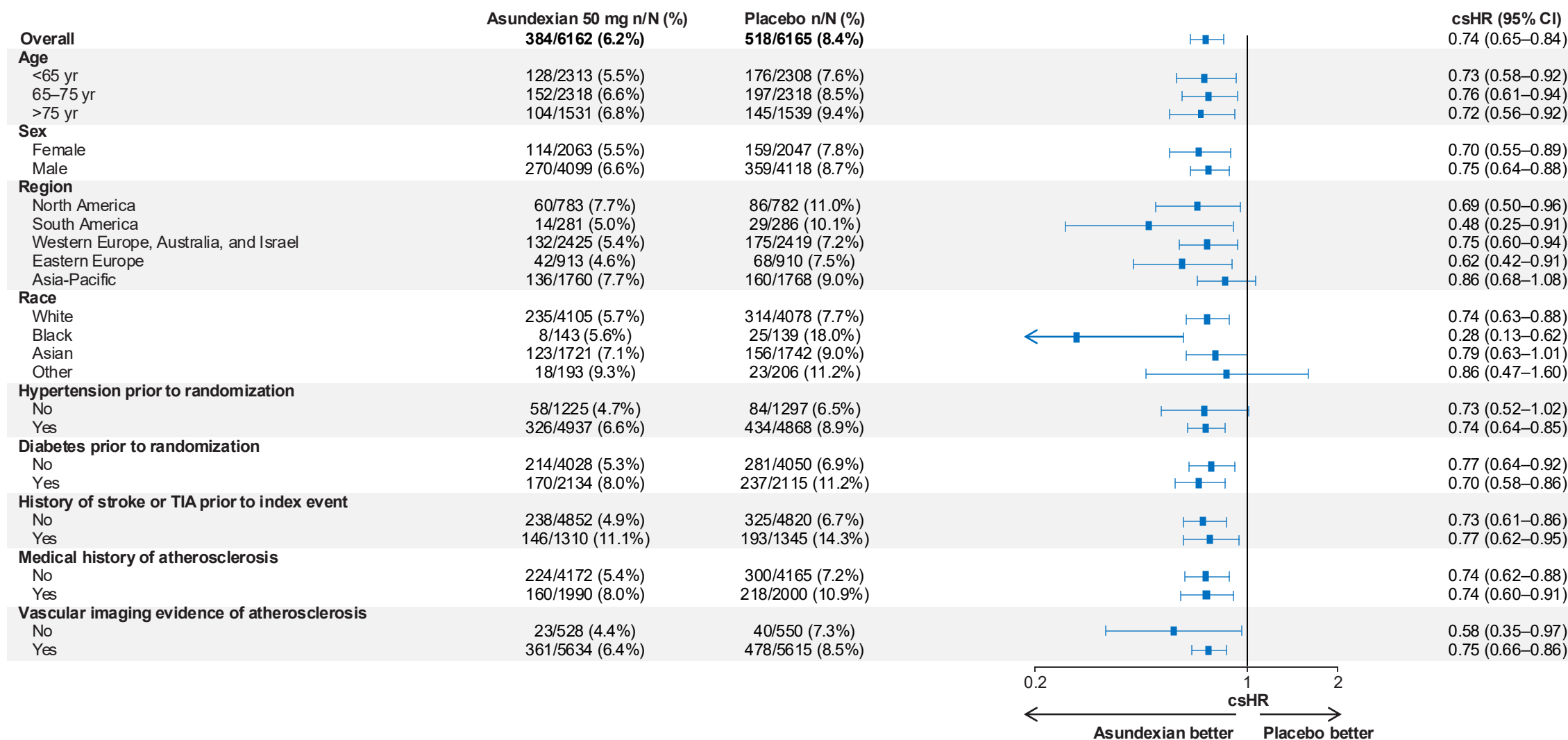


*P value is obtained from stratified log-rank test (stratified by baseline intention of DAPT). csHR and 95% CI are provided here.

Cumulative incidence curves are estimated by Aalen–Johansen method, truncated at Day 820.

CI, confidence interval; csHR, cause-specific hazard ratio; DAPT, dual antiplatelet therapy; HR, hazard ratio.

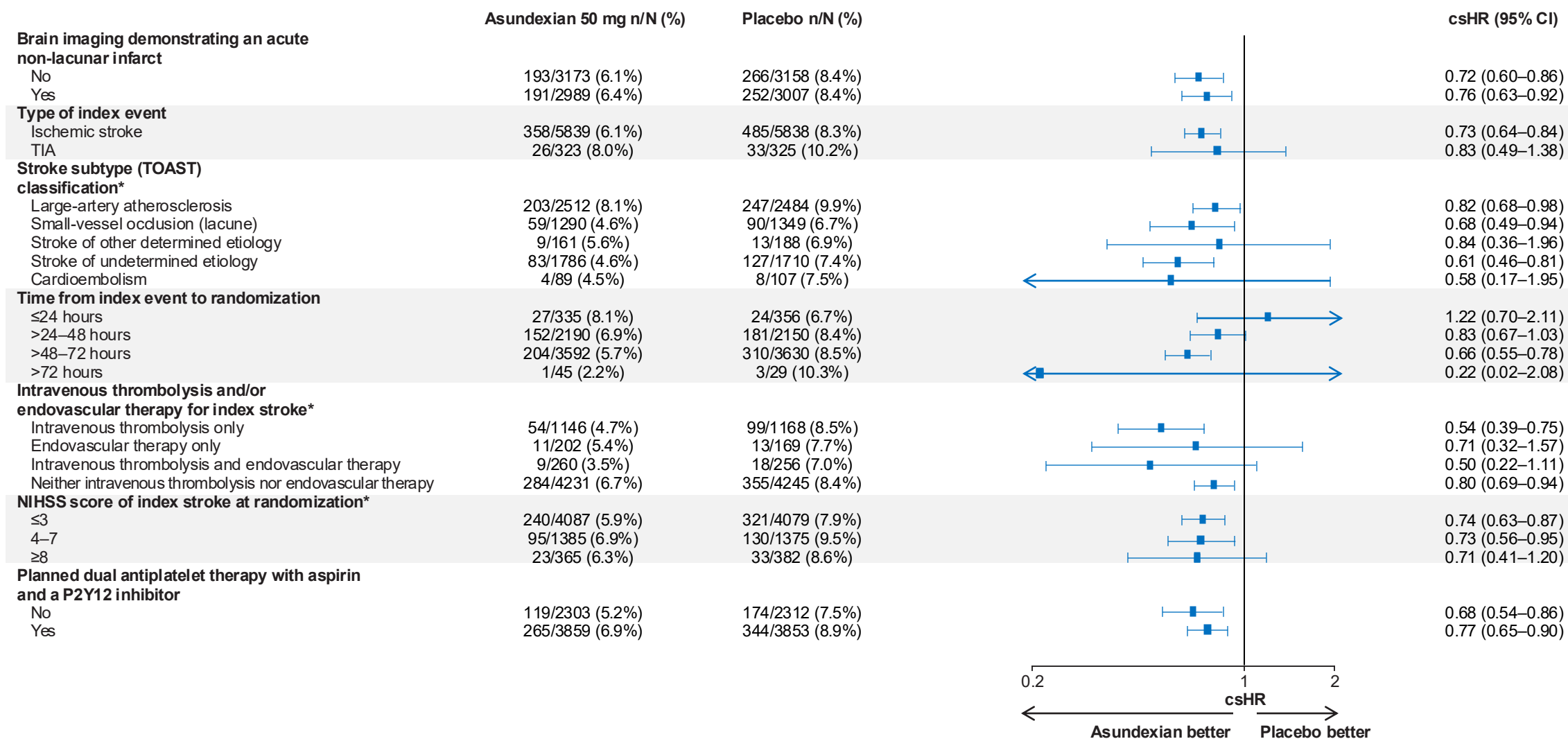
Subgroup Analyses for Ischemic Stroke



CIs are unadjusted for multiplicity and may not be used for inference.

CI, confidence interval; csHR, cause-specific hazard ratio; TIA, transient ischemic attack.

Subgroup Analyses for Ischemic Stroke



*For index event of ischemic stroke.

CIs are unadjusted for multiplicity and may not be used for inference.

CI, confidence interval; 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.

Prespecified Secondary Analysis of Patients With Qualifying Non-Cardioembolic Ischemic Stroke

- According to qualifying non-cardioembolic ischemic stroke subtype (TOAST Criteria)¹
 - Large artery atherosclerosis
 - Small-vessel occlusion*
 - Stroke of undetermined etiology
 - Including sensitivity analysis confined to patients with embolic stroke of undetermined source (ESUS)

*Patients with small-vessel occlusion were required to have a clinical history or vascular imaging evidence of atherosclerosis for eligibility.

TOAST, Trial of Org 10172 in Acute Stroke Treatment.

1. Adams HP Jr, et al. *Stroke*. 1993;24(1):35-41.

No Treatment Interaction for Efficacy Outcomes Across Ischemic Stroke Subtypes

Efficacy endpoints	Large-artery atherosclerosis			Small-vessel occlusion			Stroke of undetermined etiology			Inter. P-value
	Asundexian n (%) (N = 2512)	Placebo n (%) (N = 2484)	Asundexian vs Placebo HR (95% CI) [†]	Asundexian n (%) (N = 1290)	Placebo n (%) (N = 1349)	Asundexian vs Placebo HR (95% CI) [†]	Asundexian n (%) (N = 1786)	Placebo n (%) (N = 1710)	Asundexian vs Placebo HR (95% CI) [†]	
Primary efficacy endpoint (ischemic stroke) [§]	203 (8.08)	247 (9.94)	0.82 (0.68–0.98)	59 (4.57)	90 (6.67)	0.68 (0.49–0.94)	83 (4.65)	127 (7.43)	0.61 (0.46–0.81)	0.21
All strokes (ischemic and hemorrhagic)	211 (8.40)	257 (10.3)	0.82 (0.68–0.98)	65 (5.04)	99 (7.34)	0.68 (0.50–0.93)	87 (4.87)	132 (7.72)	0.62 (0.47–0.81)	0.21
Disabling or a fatal stroke*	72 (2.87)	86 (3.46)	0.83 (0.61–1.14)	19 (1.47)	25 (1.85)	0.80 (0.44–1.46)	26 (1.46)	51 (2.98)	0.48 (0.30–0.77)	0.15

[†]Cause-specific hazard ratios are estimated from stratified cox proportional hazards model (stratified by baseline intention of T). [§]Ischemic stroke here includes undetermined stroke. *Stroke of any type during the trial associated with a mRS of ≥ 3 at 90 days after the recurrent stroke or an increase of 1 point if the last available mRS before the recurrent stroke event was ≥ 3 .

CI, confidence interval; HR, hazard ratio; mRS, modified Rankin scale.

No Treatment Interaction for Efficacy Outcomes Across Ischemic Stroke Subtypes

Safety endpoints	Large-artery atherosclerosis			Small-vessel occlusion			Stroke of undetermined etiology			Inter. P-value
	Asundexian n (%) (N=2496)	Placebo n (%) (N=2468)	Asundexian vs Placebo HR (95% CI) [†]	Asundexian n (%) (N=1280)	Placebo n (%) (N=1342)	Asundexian vs Placebo HR (95% CI) [†]	Asundexian n (%) N=1777	Placebo n (%) N=1705	Asundexian vs Placebo HR (95% CI) [†]	
Primary safety endpoint: ISTH major bleeding	53 (2.1)	44 (1.8)	1.20 (0.80–1.79)	23 (1.8)	30 (2.2)	0.82 (0.48–1.42)	29 (1.6)	25 (1.5)	1.11 (0.65–1.90)	0.52
Symptomatic intracranial hemorrhage (including intracerebral hemorrhage)	14 (0.6)	12 (0.5)	1.17 (0.54–2.54)	13 (1.0)	12 (0.9)	1.19 (0.54–2.60)	9 (0.5)	9 (0.5)	0.95 (0.38–2.40)	0.93
Hemorrhagic stroke	4 (0.2)	5 (0.2)	0.80 (0.21–2.98)	6 (0.5)	8 (0.6)	0.82 (0.28–2.37)	2 (0.1)	5 (0.3)	0.38 (0.07–1.98)	0.72

[†]Cause-specific hazard ratios are estimated from stratified cox proportional hazards model (stratified by baseline intention of T).
CI, confidence interval; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

Consistent Results in Patients With Embolic Stroke of Undetermined Source

Endpoints	ESUS			No ESUS			Inter. P-value
	Asundexian n (%)	Placebo n (%)	Asundexian vs Placebo HR (95% CI) [†]	Asundexian n (%)	Placebo n (%)	Asundexian vs Placebo HR (95% CI) [†]	
Primary efficacy endpoint (ischemic stroke) [§]	N = 924 42 (4.5)	N = 920 76 (8.3)	— 0.53 (0.37–0.78)	N = 4914 316 (6.4)	N = 4918 409 (8.3)	— 0.77 (0.67–0.89)	0.07
ISTH major bleeding	N = 923 16 (1.7)	N = 918 14 (1.5)	— 1.11 (0.54–2.27)	N = 4878 90 (1.8)	N = 4885 89 (1.8)	— 1.02 (0.76–1.37)	0.80

[§]Ischemic stroke here includes undetermined stroke.

[†]Cause-specific hazard ratios are estimated from stratified cox proportional hazards model (stratified by baseline intention of DAPT).

CI, confidence interval; DAPT, dual antiplatelet therapy; ESUS, embolic stroke of undetermined source; HR, hazard ratio;

ISTH, International Society on Thrombosis and Haemostasis.