Is there a role for dual antiplatelets, rivaroxaban + aspirin or FXIa inhibitors in secondary stroke prevention?

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Disclosures

- Research Funding: Bayer, Bristol Myers Squibb, Janssen, Alexion, Astra Zeneca, Daiichi Sankyo, CIHR, Heart and Stroke Foundation
- Consultant: Bayer, Janssen, Anthos, Astra Zeneca, Novartis

Current Antithrombotics for Stroke Prevention

- ASA + Clopidogrel
- ASA + Ticagrelor

} Minor stroke / TIA short term

- ASA

} Long term – most stroke subtypes

- VKA (warfarin)
- FX inhibitors
  - Rivaroxaban
  - Apixaban
  - Edoxaban
- Direct Thrombin Inhibitors
  - Dabigatran

} Major risk cardiac sources

- ASA + Rivaroxaban

} Atherosclerosis (COMPASS)

CHANCE/POINT Results

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CHANCE (Wang et al. N Engl J Med 2013; 369 (1):1-9)

ASA + Clopidogrel x 21 days superior to Clopidogrel (HR 0.68 (0.57-0.810 p<0.001)*
Clopidogrel loading dose 300 mg
No increase in ICH or major bleeding

POINT (Johnston et al. N Engl J Med 2018; 379 (3): 215-225)

ASA + Clopidogrel x 90 days superior to ASA (HR 0.74 (0.58-0.94) p=0.01)*
Clopidogrel loading dose 600 mg
No increase in ICH; major bleeding was doubled with ASA + clopidogrel vs. ASA alone

* Ischemic and hemorrhagic stroke

Duration of treatment (POINT)

- For every 1000 pts treated for 21 days
  - 20 ischemic events prevented (95% CI 8-32)
  - 2 major hemorrhages caused (95% CI -5 -1)

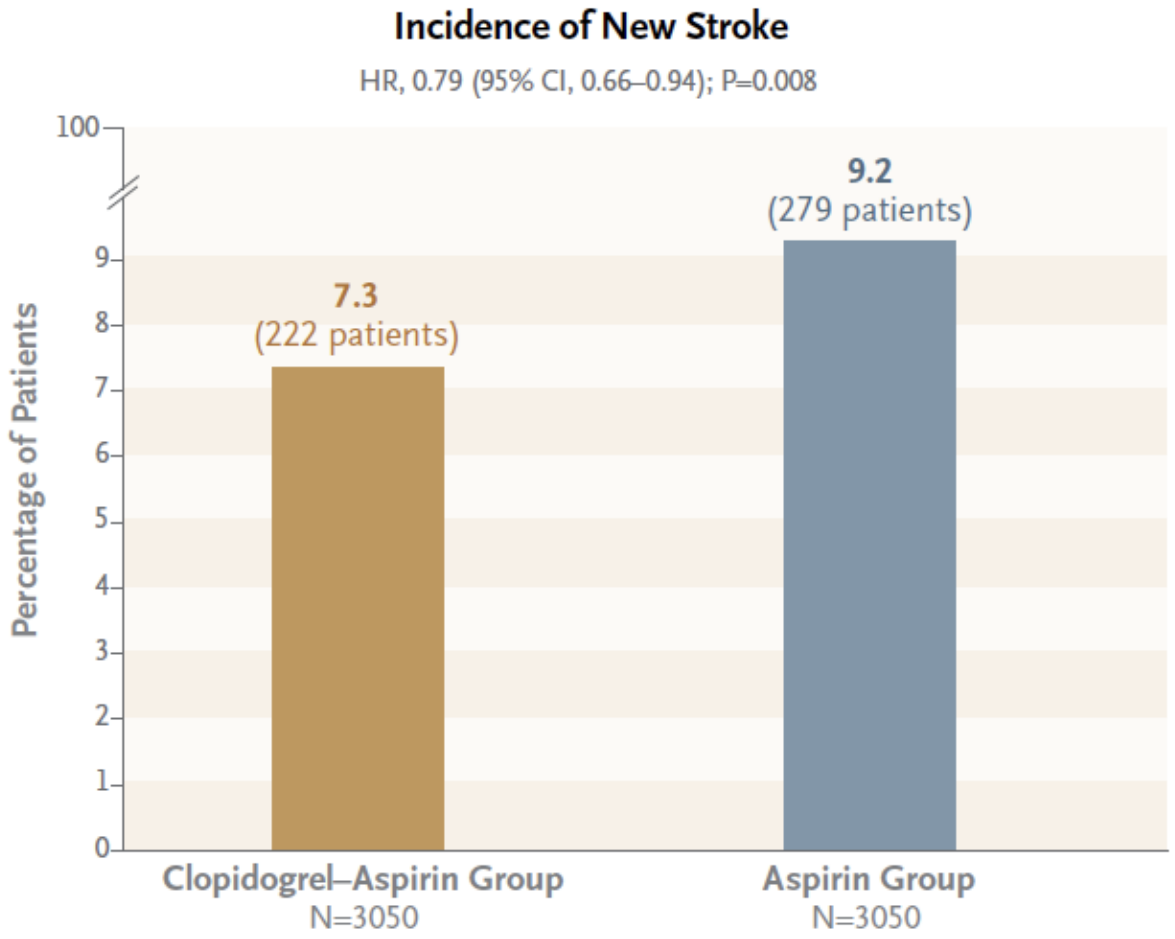
- For every 1000 pts treated for 90 days
  - 16 ischemic events prevented (95% CI 3-28)
  - 5 major hemorrhages caused (95% CI -1–10)

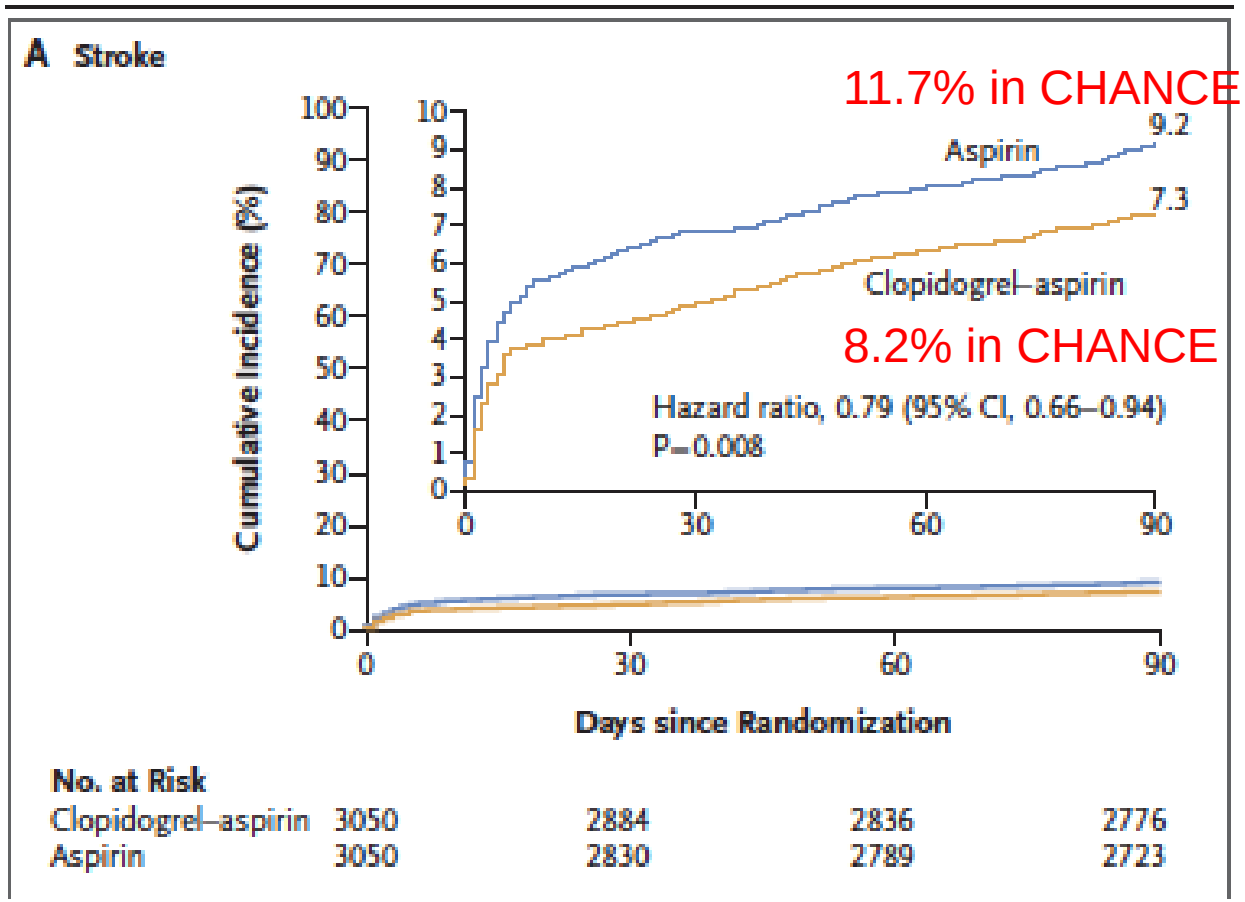
Circulation. 2019;140:658–664.

INSPIRES Eligibility: Inclusion

- Minor ischemic stroke (NIHSS 5 or less) or high-risk TIA ($ABCD^2$ 4 or more)
- 24-72 hours of last known well

- At least one of the following:
  - 50% or greater stenosis of major extracranial/intracranial arteries believed to have contributed to stroke/symptoms
  - Acute multiple infarcts believed to have originated from atherosclerotic disease





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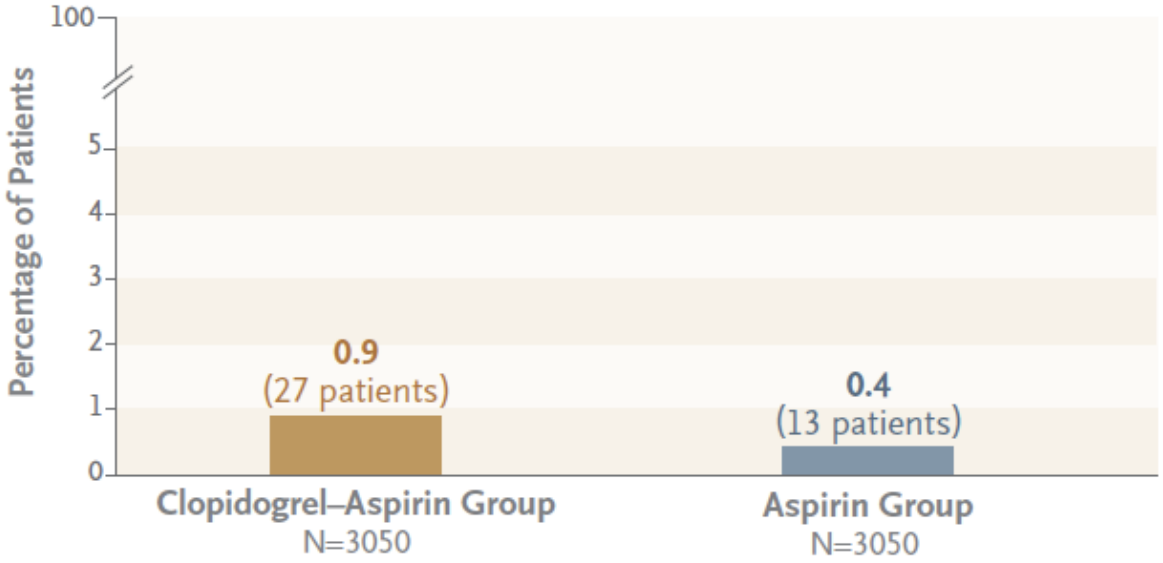

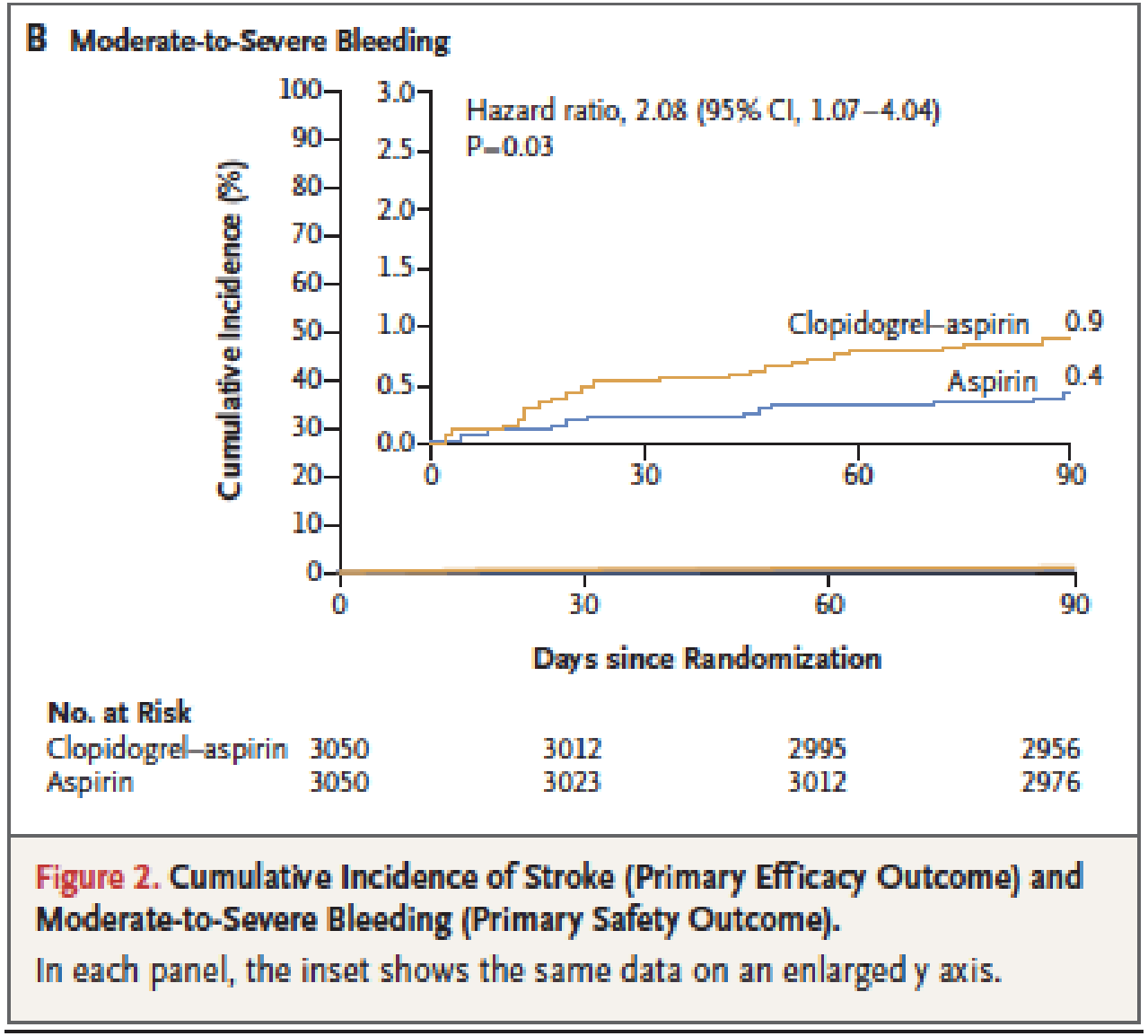

Figure 2. Cumulative Incidence of Stroke (Primary Efficacy Outcome) and Moderate-to-Severe Bleeding (Primary Safety Outcome).

In each panel, the inset shows the same data on an enlarged y axis.

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Genetic influences in Clopidogrel PK/PD

- Can affect absorption and metabolism
  - Clopidogrel is a prodrug that must be converted to an active form
  - Activation occurs in liver CYP2C19

- Loss of function affects 20-30 % of population
  - Perhaps 40-60% Asia

- Influence is variable
  - Not on/off but variable degrees of effect on function of clopidogrel

Ticagrelor (Better, Faster, Stronger)

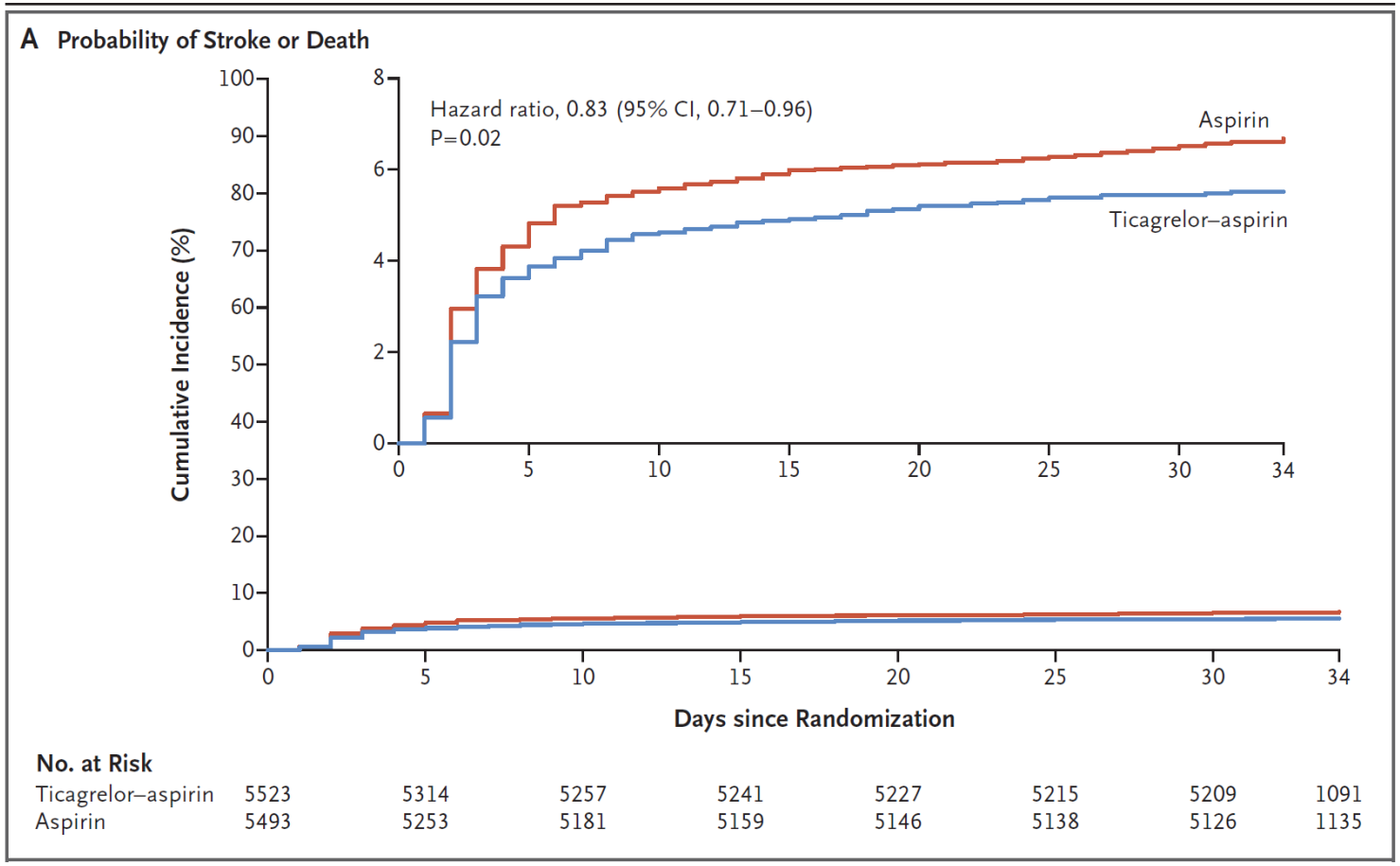
Table 1 Summary of key pharmacokinetic and pharmacodynamic parameters of $P2Y_{12}$ receptor inhibitors

End point	Ticagrelor [19, 20, 29]	Clopidogrel [29, 30]	Prasugrel [31]
Metabolic activation required	No Major metabolite (AR-C124910XX) is equipotent to the parent compound	Yes	Yes
Reversibility of binding to ADP receptor	Reversible	Irreversible	Irreversible
Single-dose pharmacokinetic parameters			
t_{max}	Ticagrelor: 1.3–2 h AR-C124910X: 1.3–3 h	30–60 min[a]	30 min[a]
$t_{½}$	Ticagrelor: 7.7–13.1 h AR-C124910X: 7.5–12.4 h	30 min[a]	7 (2–15) h[a]
Onset of IPA			
40–50 % IPA	30 min	2–4 h	1 h
Maximum IPA	2 h	8 h	3 h
Duration of IPA	3–5 days	7–10 days	5–10 days

ADP adenosine 5′-diphosphate, *IPA* inhibition of platelet aggregation, $t_{½}$ elimination half-life, t_{max} time to reach maximum plasma concentration

[a] Data are for the active metabolite

THALES Outcome



Event Rates:
5.4% vs 6.5%

CHANCE 2 – Effect on Stroke

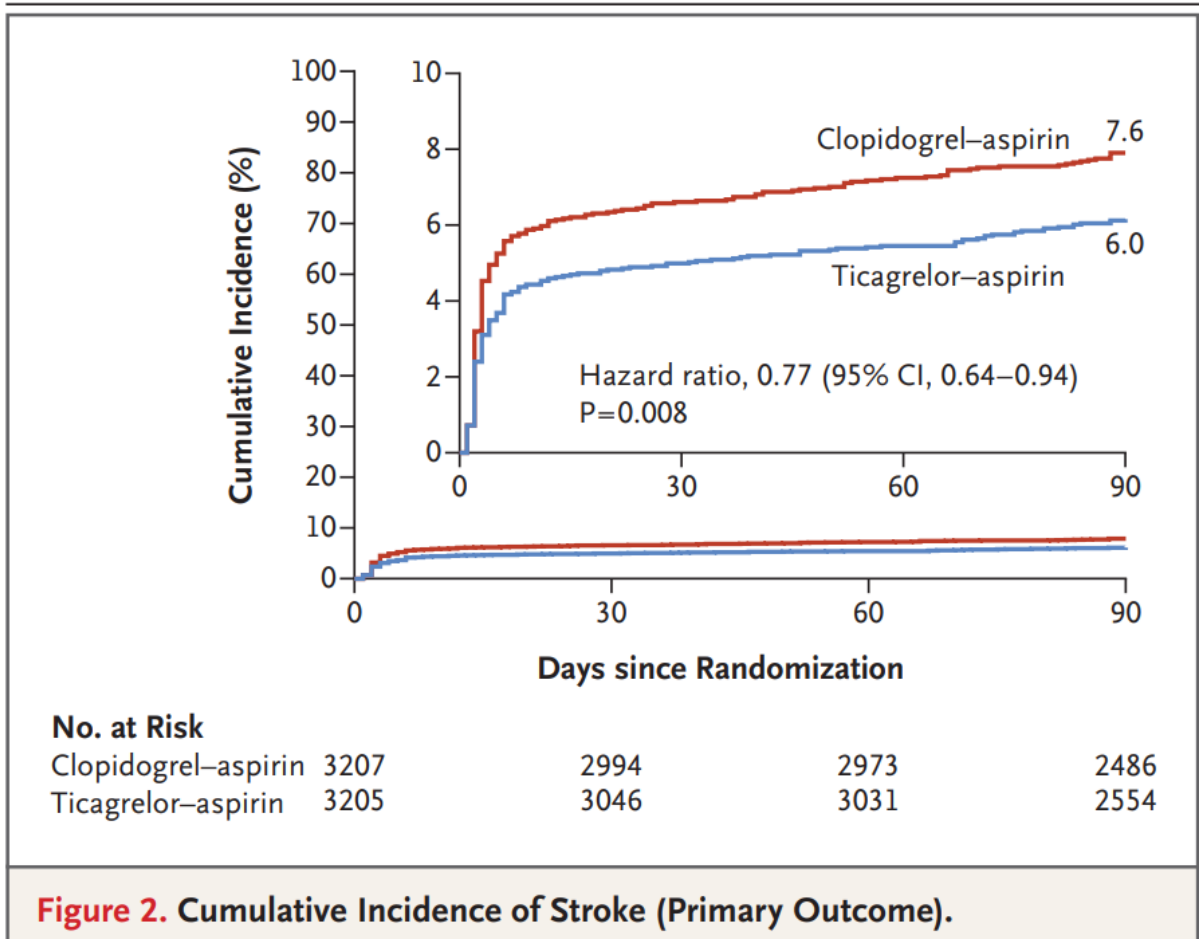


Figure 2. Cumulative Incidence of Stroke (Primary Outcome).

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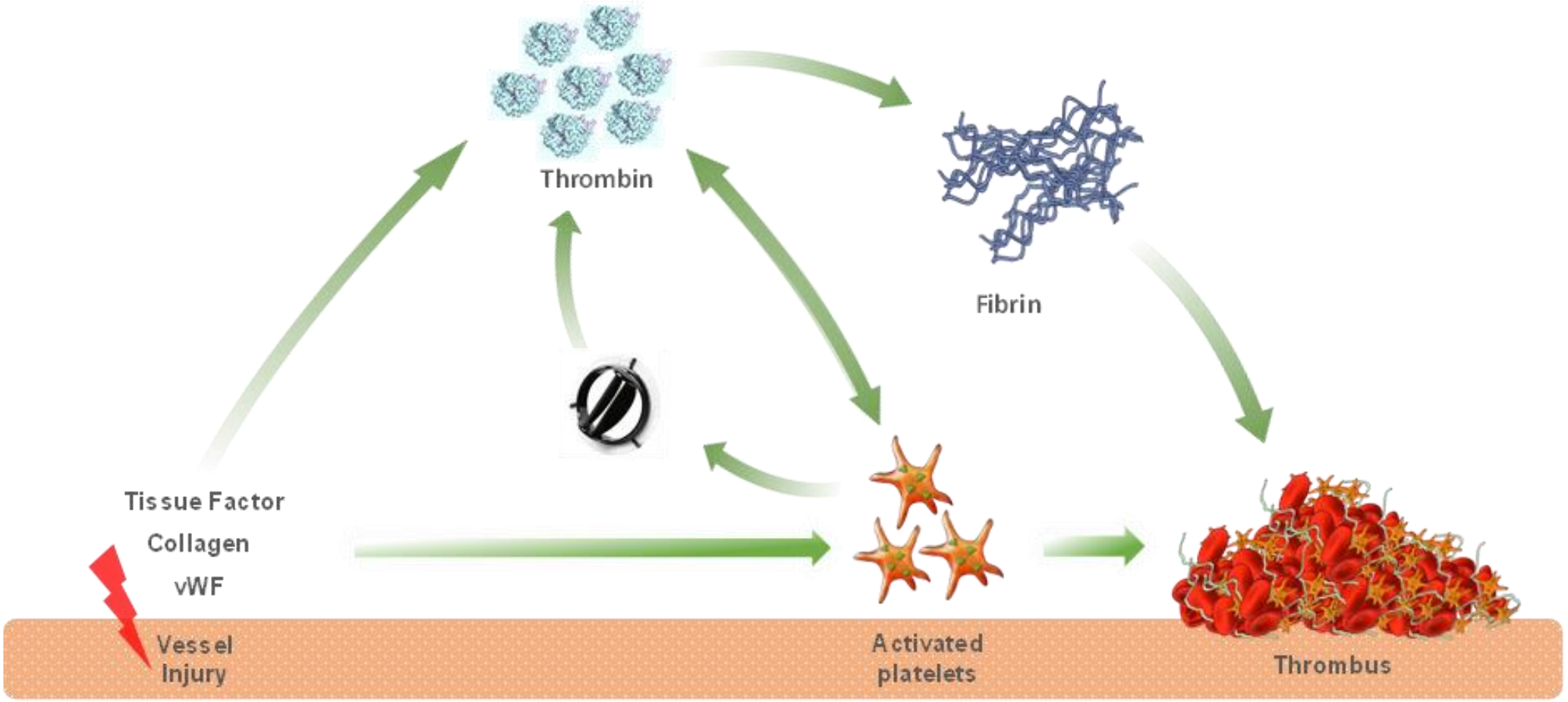
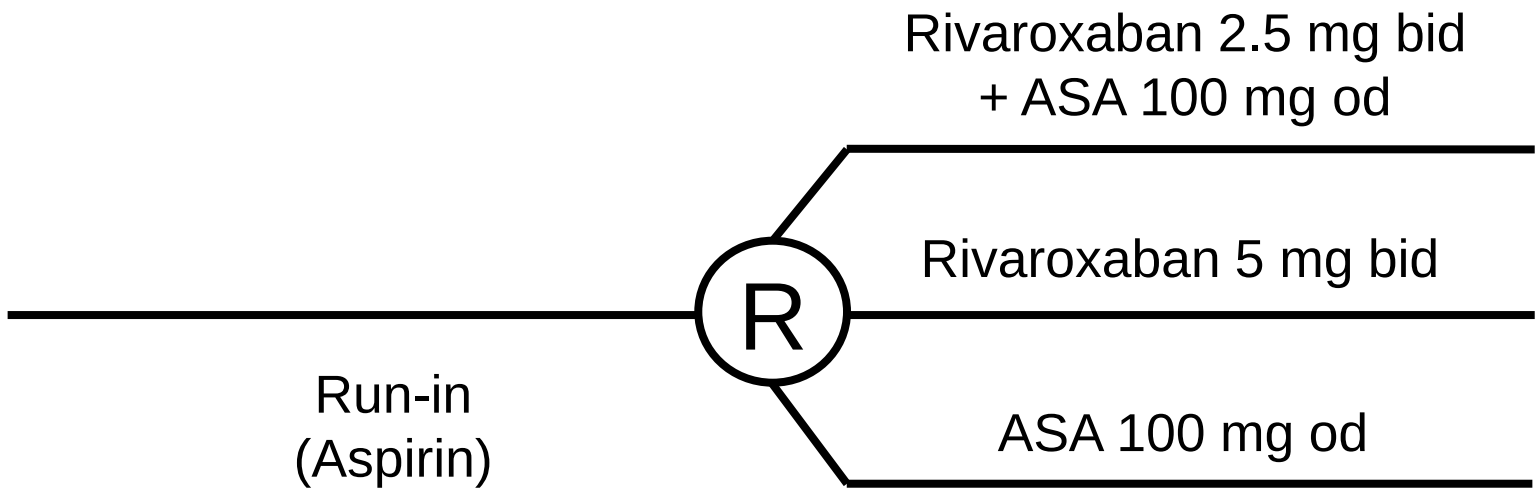
Biological rationale for testing dual pathway approach



Eikelboom JW. *Res Pract Thromb Haemost* 2019

COMPASS Design

- N = 27,395 coronary artery or peripheral artery disease
  - Primary outcome: stroke, MI, cardiovascular death
  - 1,323 participants with a primary outcome event



Mean follow up: 1.9 years

N Engl J Med 2017; 377: 1319-30.

COMPASS Trial

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MAIN INCLUSION CRITERIA

Coronary artery disease:

- MI within 20 years or multivessel disease or multivessel revascularization, plus ≥1 of:
  - age ≥65 or
  - age <65 plus atherosclerosis in ≥2 vascular beds or ≥2 additional risk factors: current smoker, diabetes, eGFR <60 mL/min, heart failure, nonlacunar ischemic stroke ≥1 month ago)

Peripheral artery disease:

- Surgery for PAD including amputation, or
- Intermittent claudication plus one or more of ABI <0.90 or peripheral stenosis ≥50%, or

Carotid artery disease:

- Carotid revascularization or asymptomatic carotid stenosis ≥50%

RELEVANT EXCLUSION CRITERIA

- Stroke within 1 month
- Symptomatic lacunar stroke
  - Asymptomatic lacunes permitted
- Intracerebral hemorrhage
- Atrial fibrillation

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ABI, ankle-brachial index; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease
Eikelboom J *et al*. *N Engl J Med* 2017; 377:1319-30. Anand SS et al. Lancet 2017; pii: S0140-6736(17)32409-1.

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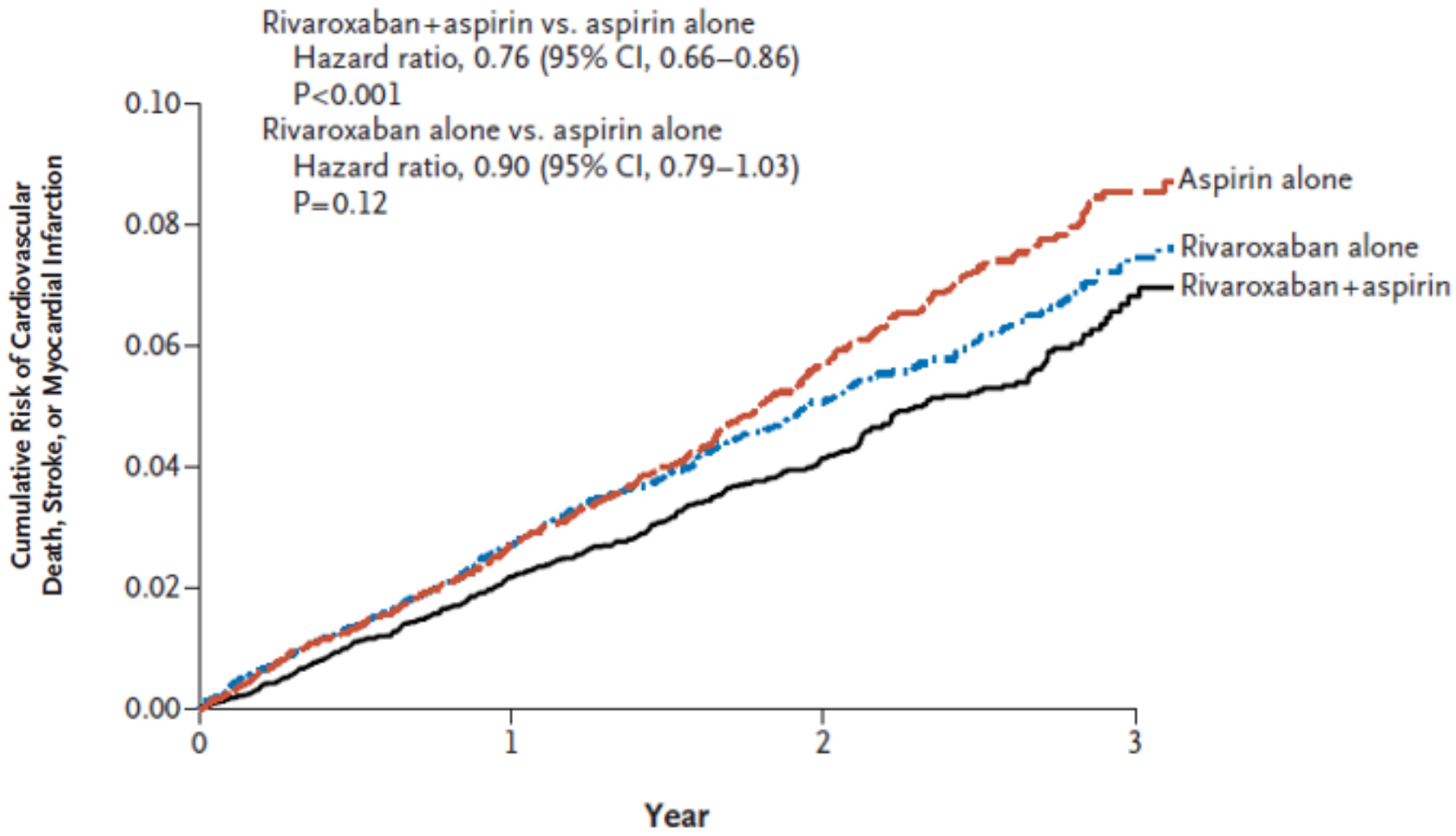
MRI lesions at baseline

	Patients N	Patients with lesions	
		N	%
Infarcts	1,760	612	**34.8%**
Non-lacunar		409	23.2%
Lacunar		315	17.9%
Microbleeds	1,696	497	**29.3%**
Cortical		307	18.1%
Subcortical		321	18.9%

Sharma M, et al. *Int J Stroke* 2019;14:270-281.

COMPASS : Primary outcome



Eikelboom JW, et al. *N Engl J Med* 2017; 377: 1319-30.

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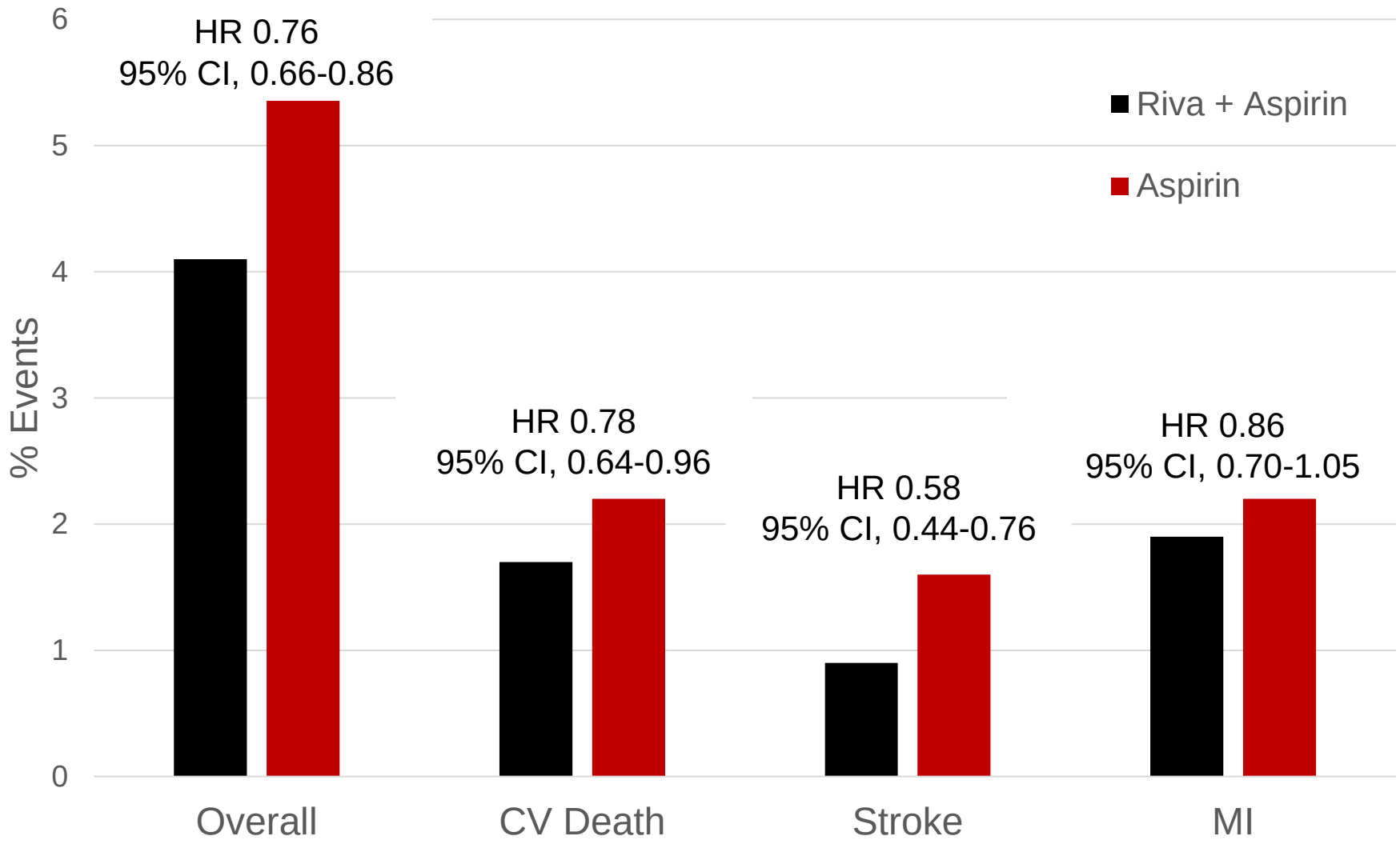
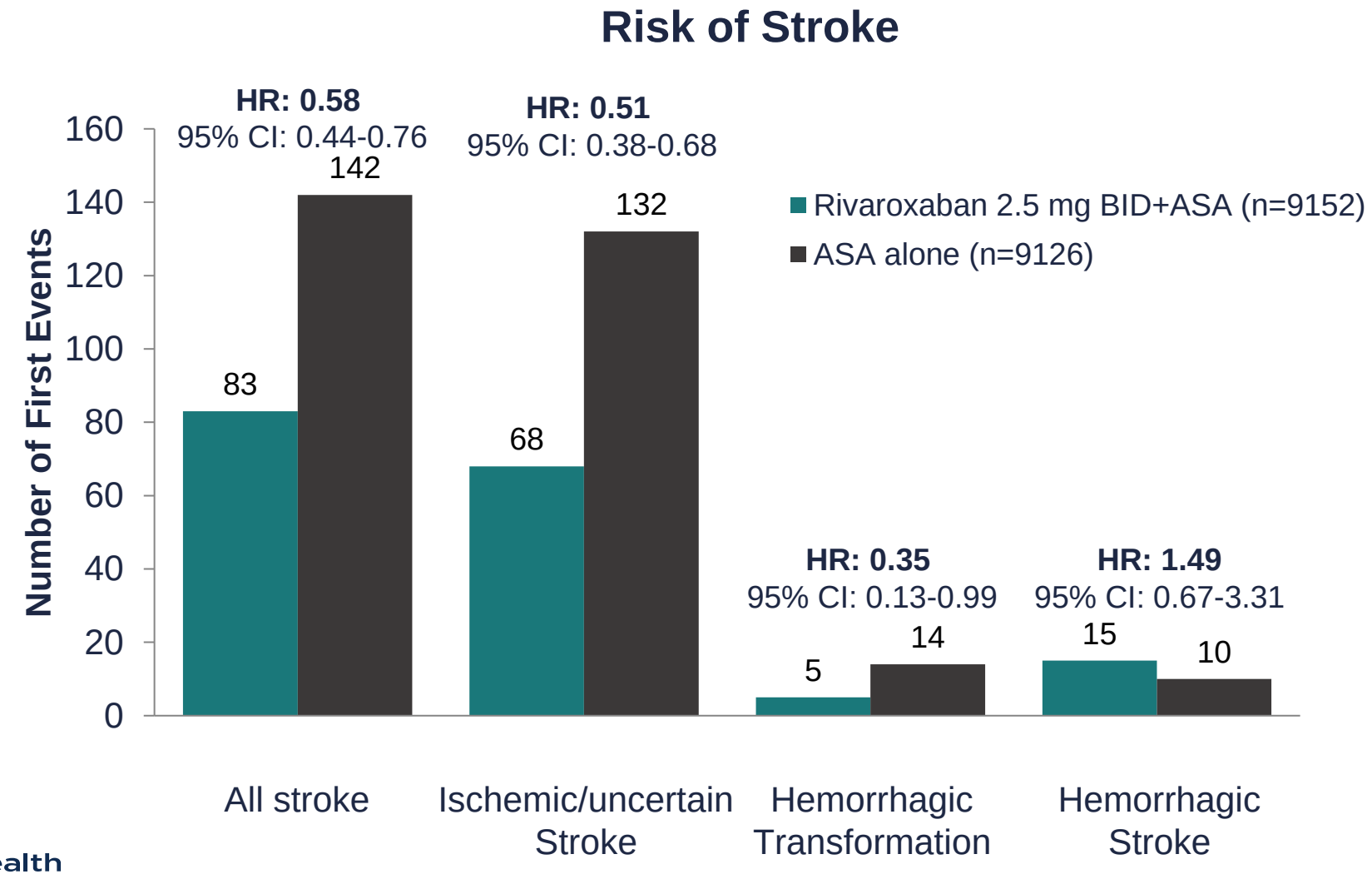
Primary efficacy outcome and components



COMPASS Stroke outcomes



ASA: acetylsalicylic acid; CI: confidence interval; HR: hazard ratio.

1. Sharma et al. Circulation 2019;139:1134-45.

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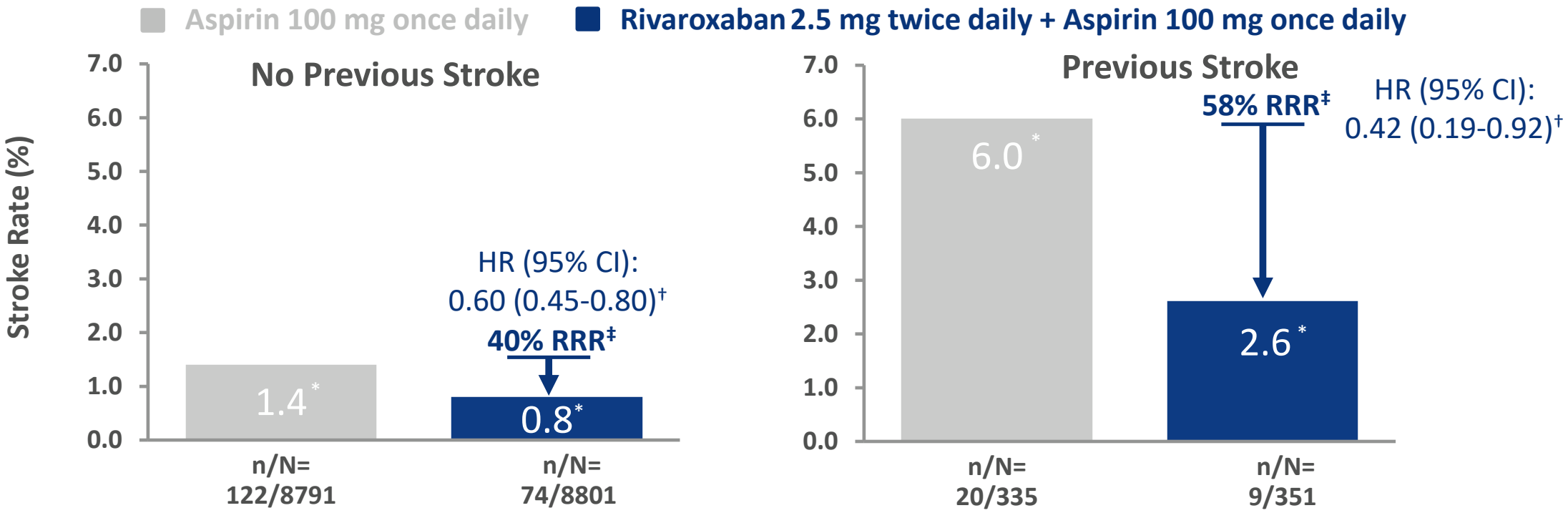
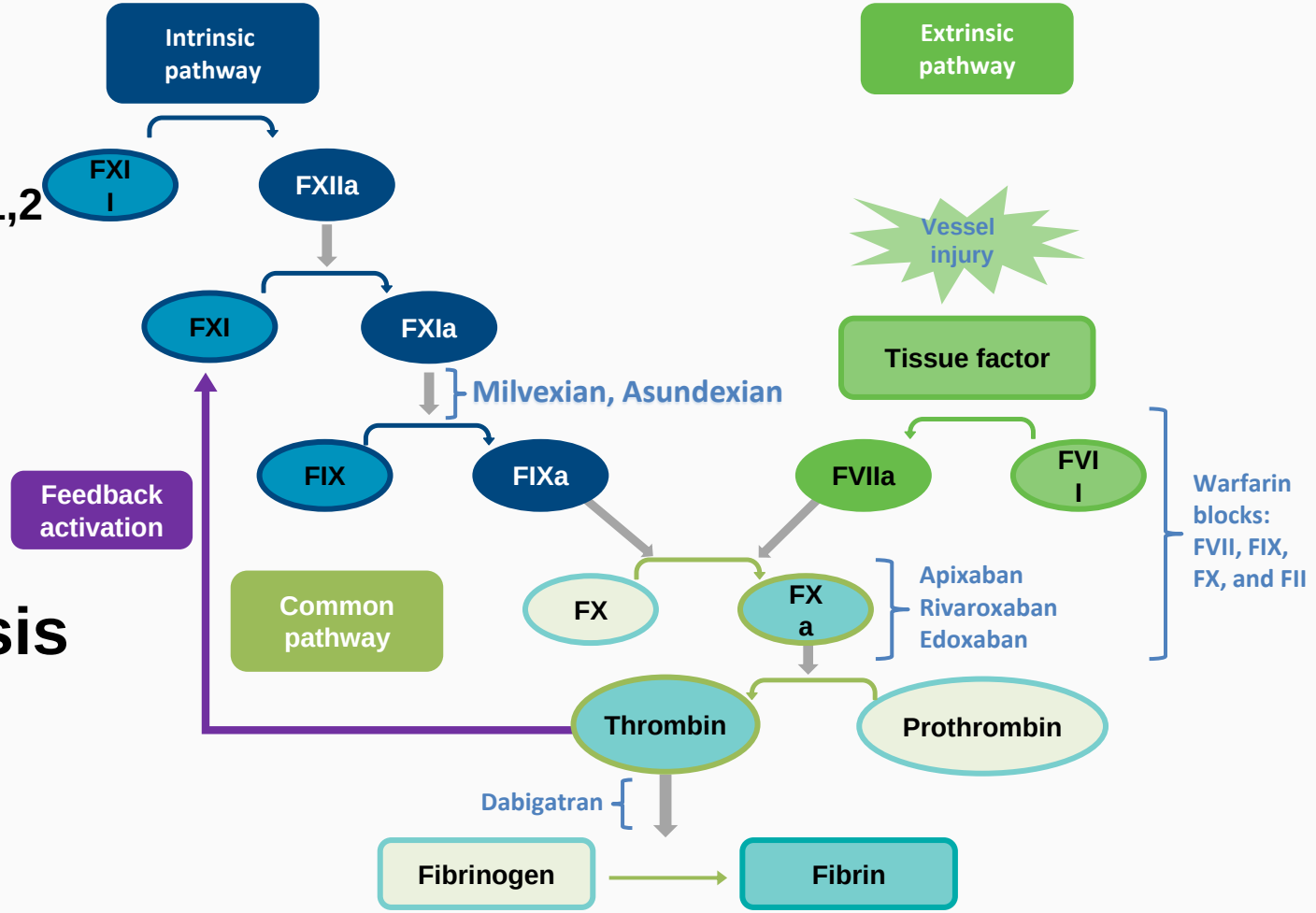
Stroke reduction according to stroke history



Sharma M, et al. *Circulation* 2019;139:1134-45.

FXIa Background and Hypothesis

- **Genetically determined FXI deficiency associated with[1,2]**
  - Decrease in ischemic stroke and VTE
  - No increase in ICH
  - Spontaneous bleeding rare
- **Factor XI plays a less important role in hemostasis than thrombosis**
  - Activated by FXII and thrombin amplification

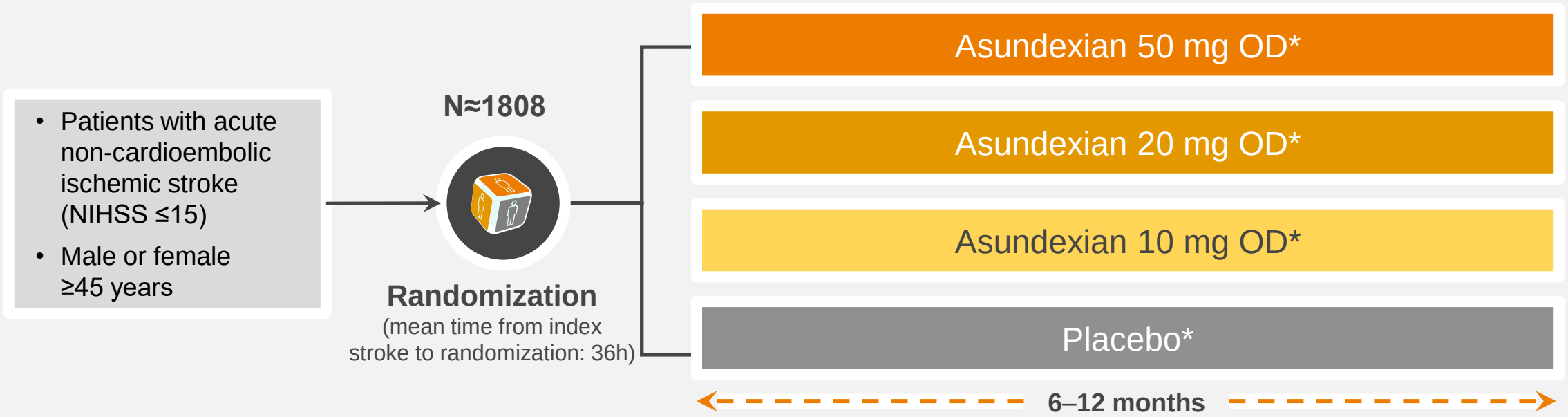


FXI, factor XI; VTE, venous thromboembolism; ICH, intracerebral hemorrhage; FXII, factor XII; FXIIa, activated factor XII; FXIa, activated factor XI; FIX, factor IX; FIXa, activated factor IX; FVIIa, activated FVII; FVII, factor VII; FX, factor X; FXa, activated factor X.

1. Solomon O, et al. *Blood.* 2008;111(8):4113-4117. 2. Preis M, et al. *Blood*. 2017;129(9):1210-1215.

Phase II PACIFIC-STROKE Study Design

Multicenter, randomized, placebo-controlled, double-blind, dose-finding, study of the oral FXIa inhibitor asundexian after acute non-cardioembolic ischemic stroke



TRIAL OBJECTIVE

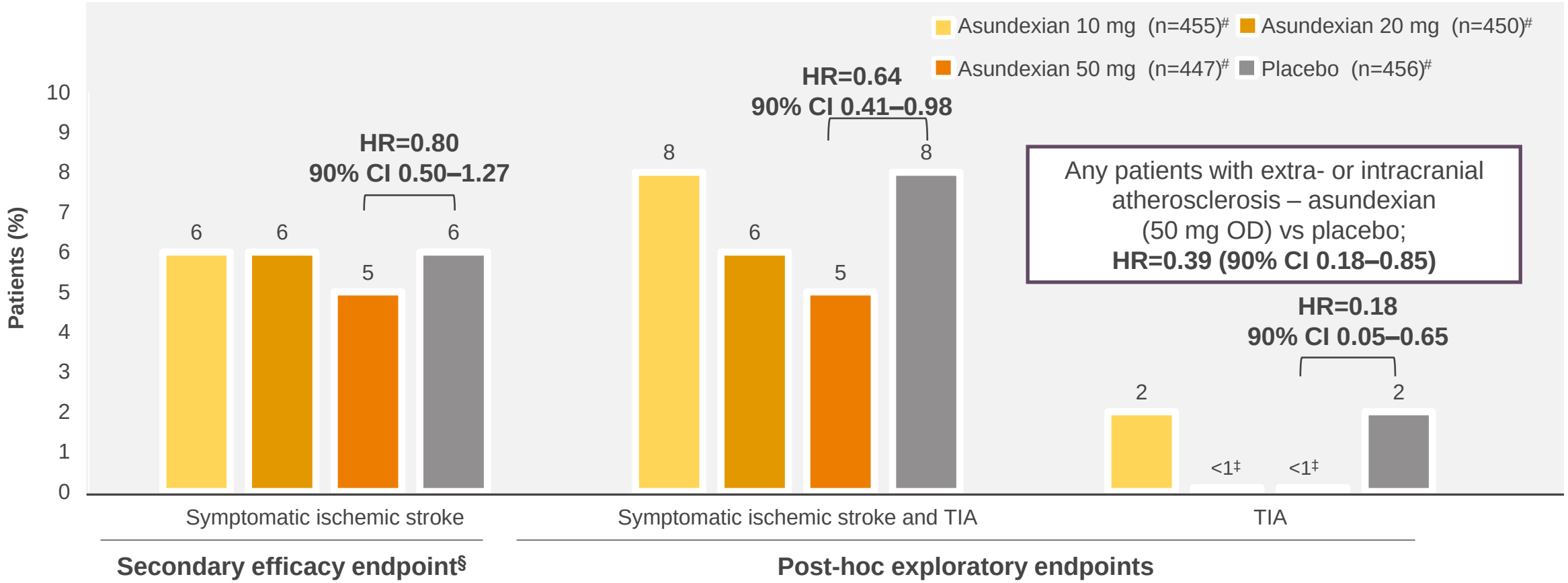
To assess the effect of FXIa inhibition, using asundexian, when added to antiplatelet therapy for secondary prevention of non-cardioembolic ischemic stroke

PRIMARY OUTCOME

Dose-response effect on the composite of incident MRI-detected covert brain infarcts and recurrent symptomatic ischemic stroke

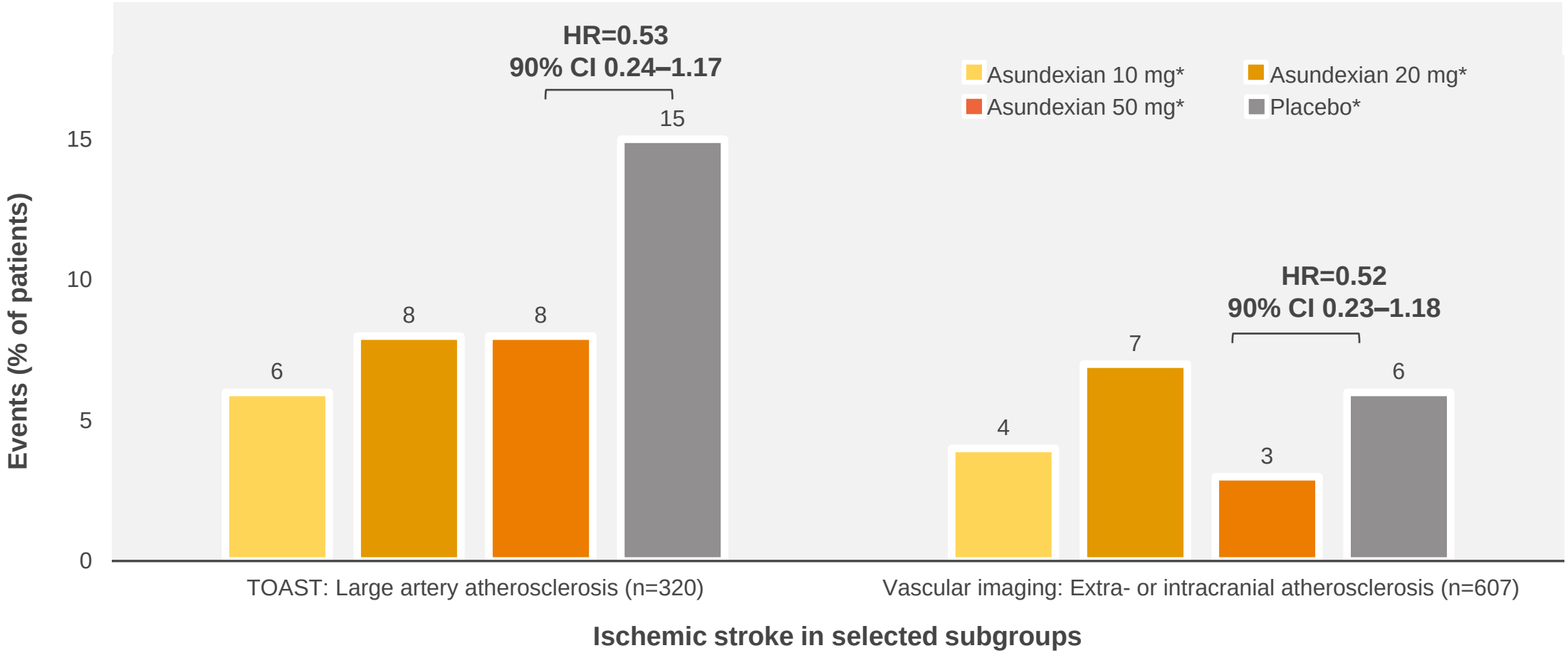
Asundexian is currently undergoing clinical trials and has not yet been approved in Europe.
*Plus antiplatelet background therapy according to standard of care. 43% of patients were on DAPT for a mean duration of 70 days.
DAPT, dual antiplatelet therapy; FXIa, activated Factor XI; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; OD, once daily; R, randomization. Shoamanesh A et al. *Lancet* 2022;400:997–1007.

Reductions in Symptomatic Ischemic Stroke and TIA Were Observed With Asundexian 50 mg Versus Placebo*



Asundexian is currently undergoing clinical trials and has not yet been approved in Europe.
*Post hoc exploratory outcome. #Plus antiplatelet background therapy according to standard of care.
‡Asundexian 20 mg = 2/450 patients, asundexian 50 mg = 2/447 patients. §Proportion of outcomes at end of study. Median follow-up of 46.1 weeks (IQR 35.2, 53.8).
CI, confidence interval; HR, hazard ratio; IQR, interquartile range; TIA, transient ischemic attack.
Shoamanesh A *et al. Lancet* 2022;400:997–1007.

There was a Beneficial Trend With Asundexian in Patients With Atherosclerosis for the Reduction Risk of Ischemic Stroke[1,2]



Asundexian is currently undergoing clinical trials and has not yet been approved in Europe.
*Plus antiplatelet background therapy according to standard of care. CIs not provided are not reported.
CI, confidence interval; HR, hazard ratio; TOAST, trial of ORG 10172 in acute stroke treatment.
1. Shoamanesh A *et al. Lancet* 2022;400:997–1007. 2. Data on file.

The Rates of Intracranial Hemorrhage, Hemorrhagic Transformation And New Microbleeds Were Numerically Less In Patients With Microbleeds On Asundexian vs Placebo[1]

Secondary analysis of PACIFIC-STROKE, response according to microbleed status

Intracranial hemorrhage risk:

- **CMB +ve:** Event rate of 1.7 per 100-person years with asundexian 50 mg daily versus 1.8% with placebo (HR=0.96)[2]
- **CMB -ve:** Event rate of 0.9 per 100-person years with asundexian 50 mg daily versus 0.00 with placebo (HR=N/A)[2]

Hemorrhagic transformation:

- **CMB +ve:** No. of events with asundexian 50 mg daily was 31 (N=96) versus 37 (N=98) with placebo (OR=0.79)[2]
- **CMB -ve:** No. of events with asundexian 50 mg daily was 53 (N=176) versus 60 (N=192) with placebo (OR=0.95)[2]

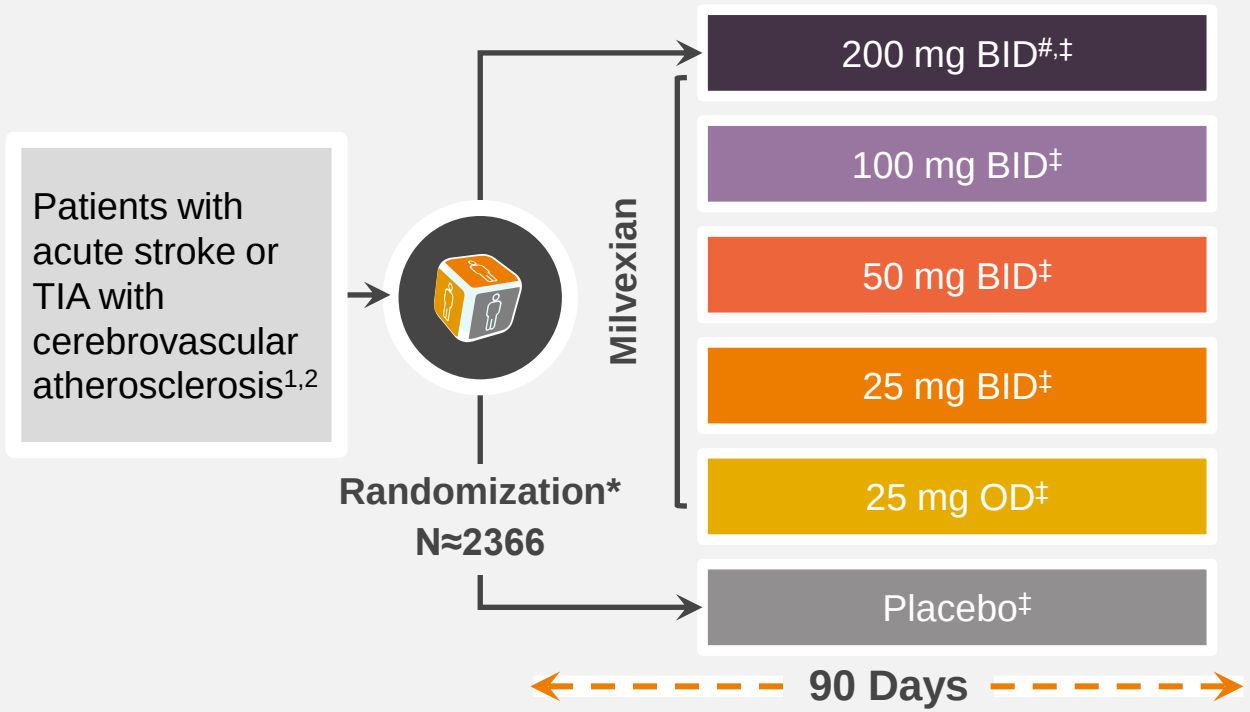
New microbleeds:

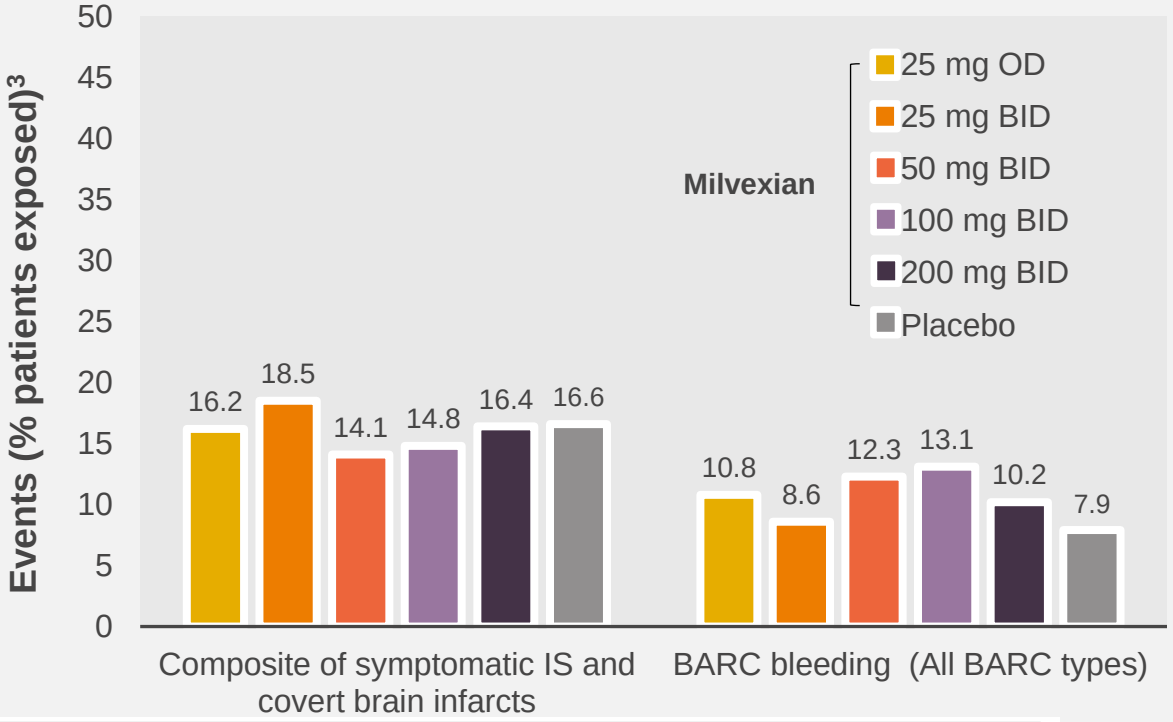
- **CMB +ve:** No. events with asundexian 50 mg daily was 24 (N=128) versus 28 (N=111) with placebo (OR=0.68)[2]
- **CMB -ve:** No. events with asundexian 50 mg daily was 7 (N=240) versus 11 (N=259) with placebo (OR=0.68)[2]

Asundexian is currently undergoing clinical trials and has not yet been approved in Europe.
CI, confidence interval; CMB, cerebral microbleed; HR, hazard ratio; NA, not applicable; OR, odds ratio.
1. Balali P, et al. *Int J Stroke*. 2023. doi:10.1177/17474930231216339. 2. Balali P, et al. *Int J Stroke*. 2023. doi:10.1177/17474930231216339 (Supplementary appendix).

There was No Significant Difference in Primary Outcome or Major Bleeding With Milvexian Compared With Placebo in AXIOMATIC-SSP[1–3]

Randomized, double-blind, dose-finding, placebo-controlled, Phase II study of the oral FXIa inhibitor milvexian for stroke prevention[1]





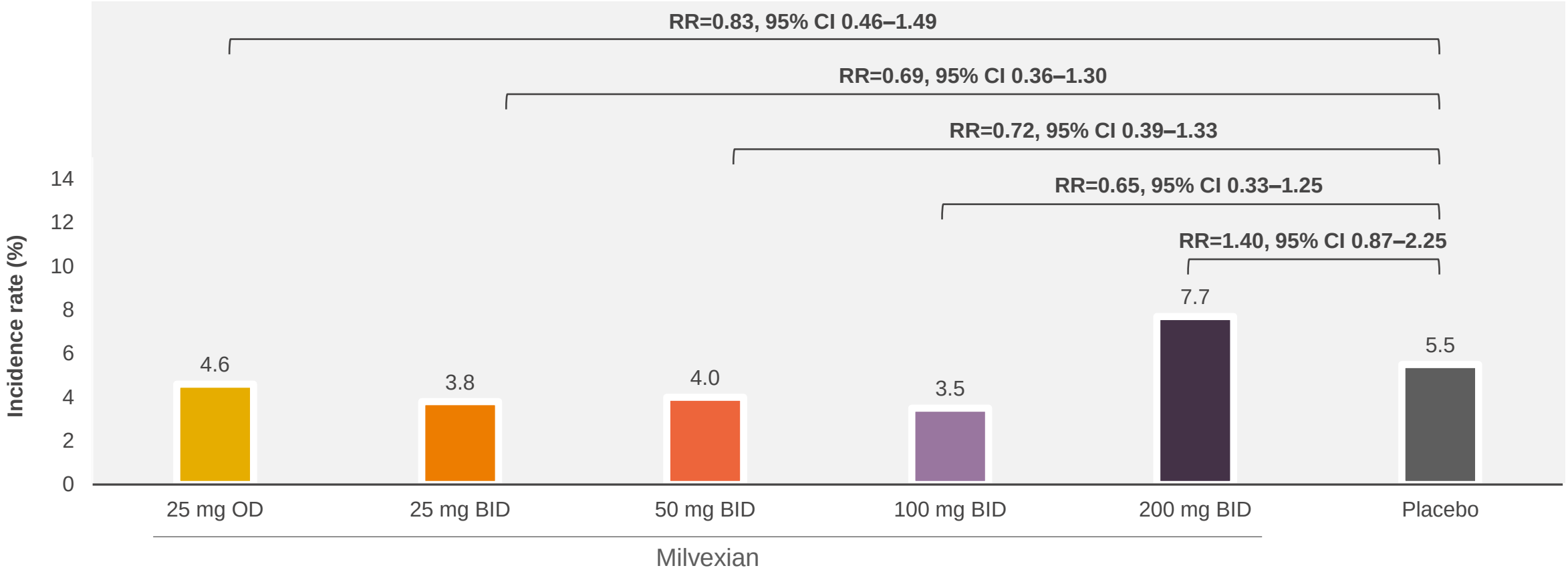
Primary outcome: Composite of new ischemic stroke and new covert brain infarction on MRI up to day 90

Milvexian is currently undergoing clinical trials and has not yet been approved in Europe.

Figure adapted from Sharma M. *et al. J Stroke Cerebrovasc Dis* 2022;31:106742. *300 mg clopidogrel LD + 100 mg aspirin. #The milvexian 200 mg BID cohort (2:1 ratio of milvexian to placebo) was added after 450 participants from the lower doses completed the day 21 visit. ‡All participants were on 75 mg clopidogrel + 100 mg aspirin up to Day 21, followed by 100 mg aspirin to day 90.

BARC, Bleeding Academic Research Consortium; BID, twice daily; FXIa, activated Factor XI; IS, ischemic stroke; LD, loading dose; MRI; magnetic resonance imaging; OD, once daily; R, randomization; TIA, transient ischemic attack. 1. Bristol Myers Squib. 2022. https://clinicaltrials.gov/ct2/show/NCT03766581 [accessed August2023]. 2. Sharma M *et al. J Stroke Cerebrovasc Dis* 2022;31:106742. 3. Sharma M *et al.* ESC. Barcelona, Spain, 26–29 August 2022, Oral Presentation. https://esc365.escardio.org/presentation/255308?query=axiomatic. [accessed August 2023].

Milvexian was Associated with Numerically Fewer Symptomatic Ischemic Strokes* at all Doses Except 200 mg BID

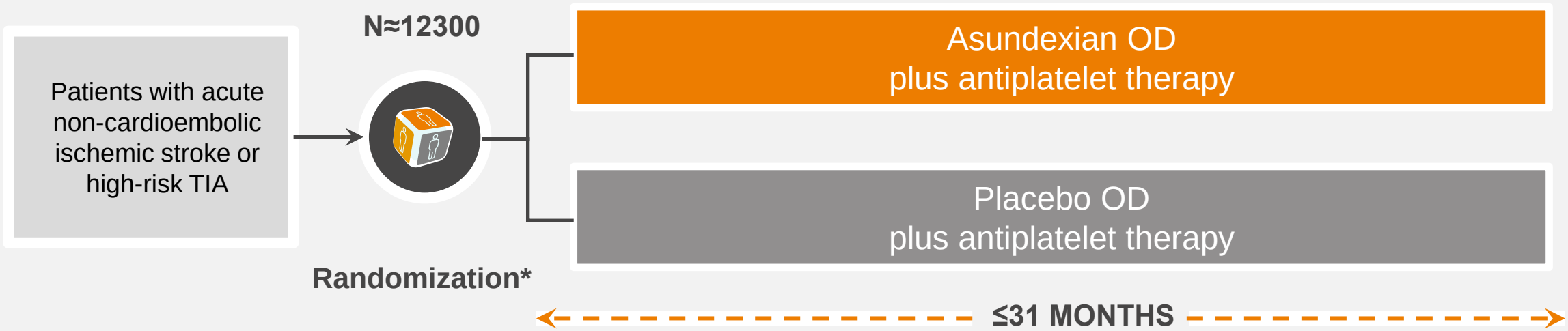


Milvexian is currently undergoing clinical trials and has not yet been approved in Europe.
No hemorrhagic strokes occurred.
*ITT population which included all participants who were randomized to a treatment, regardless of whether they received a study drug or not.
BID, twice daily; CI, confidence interval; OD, once daily; RR, relative risk.
Figure adapted from Sharma M *et al.* ESC. Barcelona, Spain, 26–29 August 2022, Oral presentation. https://esc365.escardio.org/presentation/255308?query=axiomatic

Sharma M *et al.* ESC. Barcelona, Spain, 26–29 August 2022, Oral presentation. https://esc365.escardio.org/presentation/255308?query=axiomatic. [accessed August2023].

Phase III OCEANIC-STROKE Study Design[1,2]

Multicenter, international, randomized, placebo-controlled, double-blind, parallel-group, event-driven, Phase III study of the oral FXIa inhibitor asundexian for the prevention of ischemic stroke (active, recruiting)*

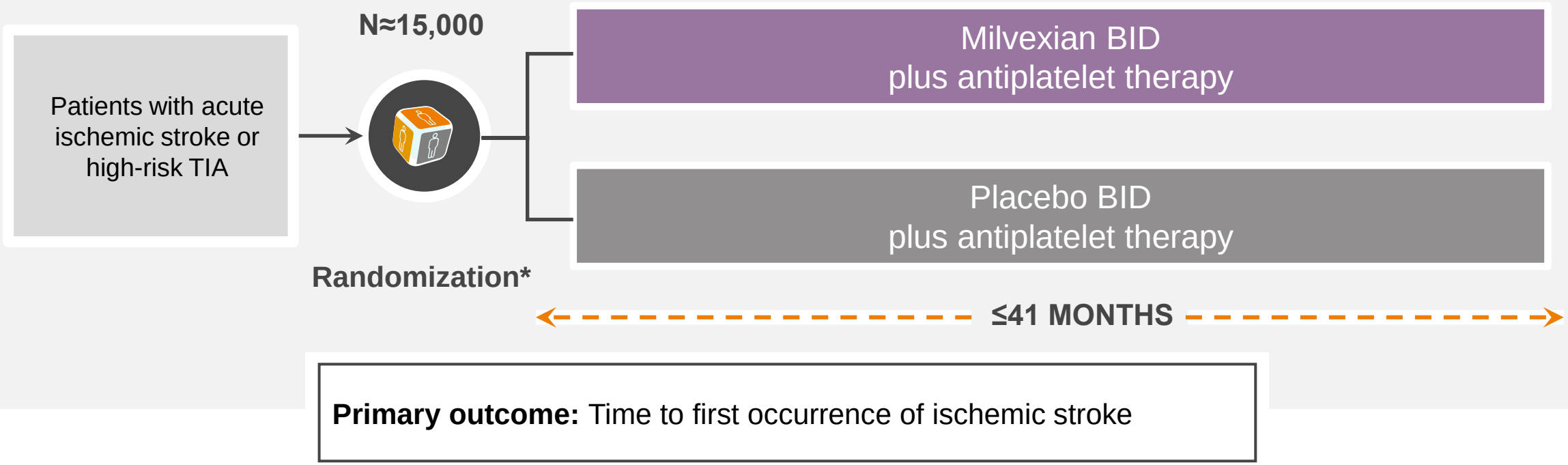


Primary efficacy outcome: Time to first occurrence of ischemic stroke
Primary safety outcome: Time to first occurrence of ISTH major bleeding

*OCEANIC-STROKE is a Phase III study following the Phase II study PACIFIC-STROKE.
FXIa, activated Factor XI; ISTH, International Society on Thrombosis and Haemostasis; OD, once daily; R, randomization; TIA, transient ischemic attack.
1. Bayer. 2023. https://clinicaltrials.gov/ct2/show/NCT05686070 2. Bayer AG. https://www.bayer.com/media/en-us/bayer-initiates-landmark-phase-iii-study-program-to-investigate-oral-fxia-inhibitor-asundexian/ [accessed 10 May 2023].

Phase III LIBREXIA-STROKE Study Design[1,2]

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



*LIBREXIA-STROKE is a Phase III study for ischemic stroke prevention following the Phase II study AXIOMATIC-SSP. BID, twice daily; FXIa, activated Factor XI; R, randomization; TIA, transient ischemic attack. 1. Janssen Research & Development, LLC. 2023. https://clinicaltrials.gov/ct2/show/NCT05702034 2. Bristol Myers Squibb. 2022. https://news.bms.com/news/details/2022/Late-Breaking-Results-From-Phase-2-AXIOMATIC-SSP-Study-of-Milvexian-an-Investigational-Oral-Factor-XIa-Inhibitor-Show-Favorable-Antithrombotic-Profile-in-Combination-With-Dual-Antiplatelet-Therapy/default.aspx [accessed 10 May 2023].

Summary

- DAPT
  - RRR 20-30%
  - Favor Ticagrelor in recurrent events or clopidogrel non-metabolizers
  - Can start up to 3 days after event in large artery athero

- Riva + ASA
  - Very effective
  - Systemic or carotid atherosclerosis
    - Carotid stenosis/revascularization, MI, Multiple stents or CABG

- FXIa Inhibition
  - Epidemiology and Mendelian Randomization suggest benefit
  - Phase II trials encouraging – particularly in atherosclerosis
  - Phase III trials underway