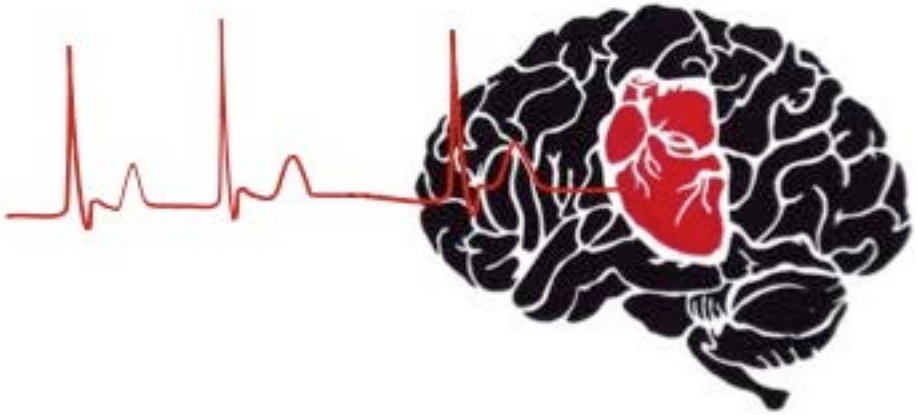
ENRICH-AF



EdoxabaN foR IntraCranial Hemorrhage survivors with Atrial Fibrillation

November 14, 2019

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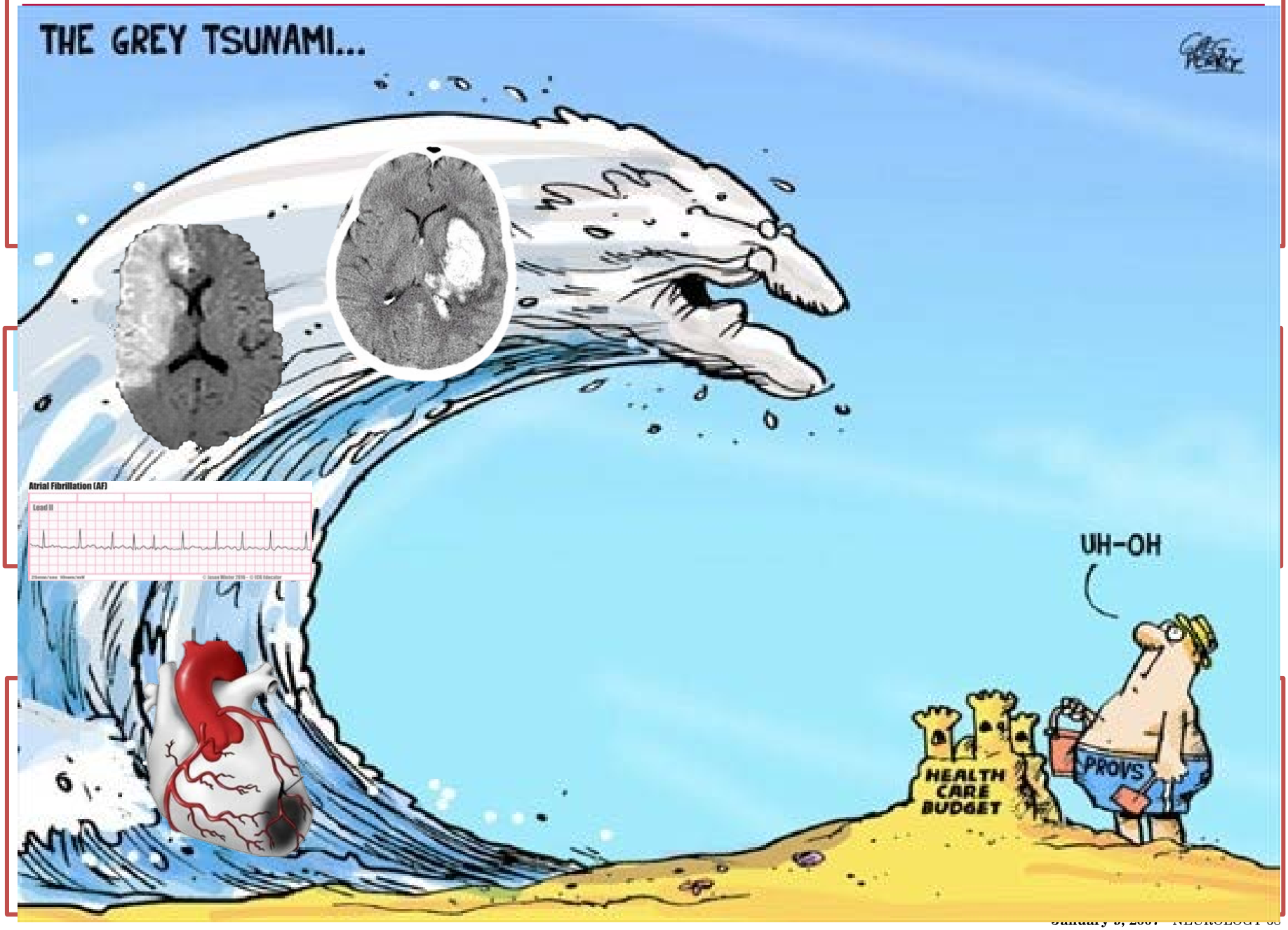
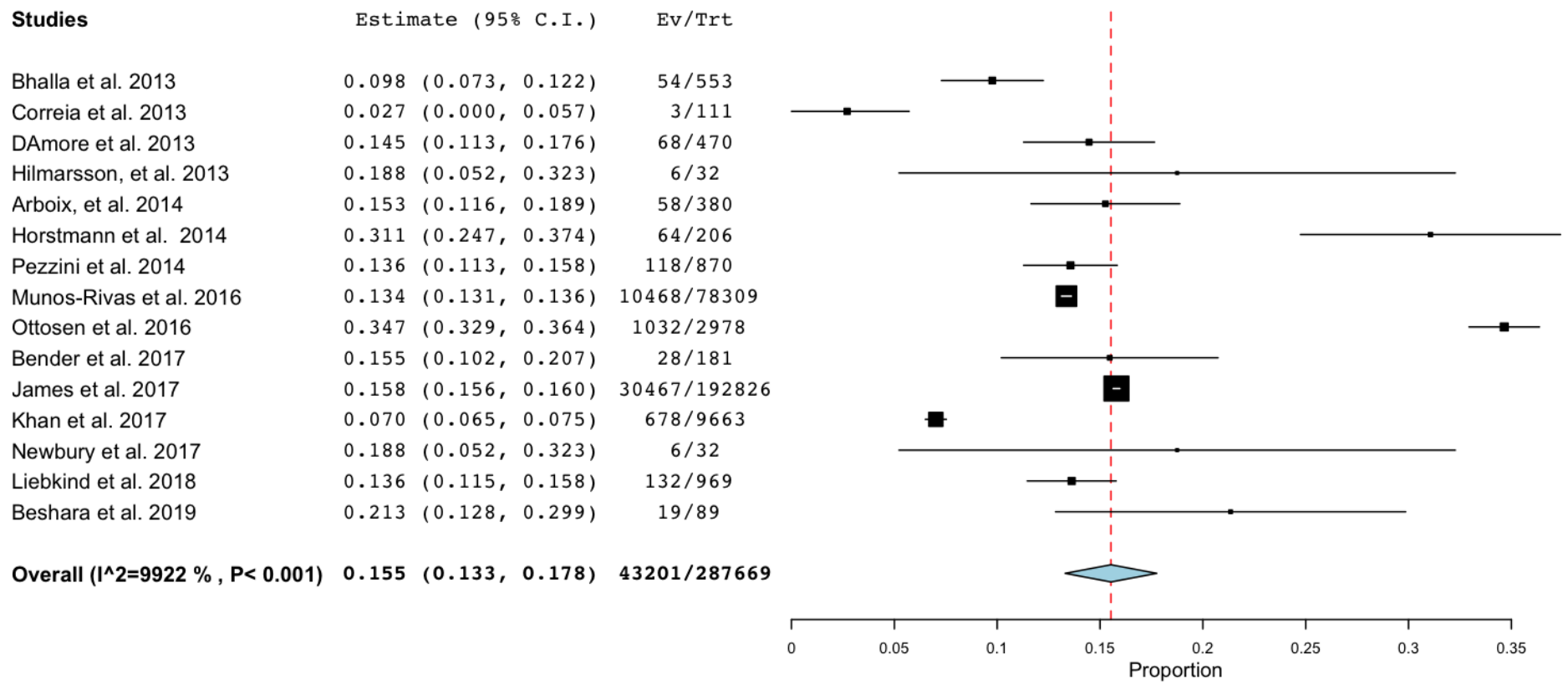

THE GREY TSUNAMI...
Atrial Fibrillation (AF)
Lead II
UH-OH
HEALTH CARE BUDGET
PROVS

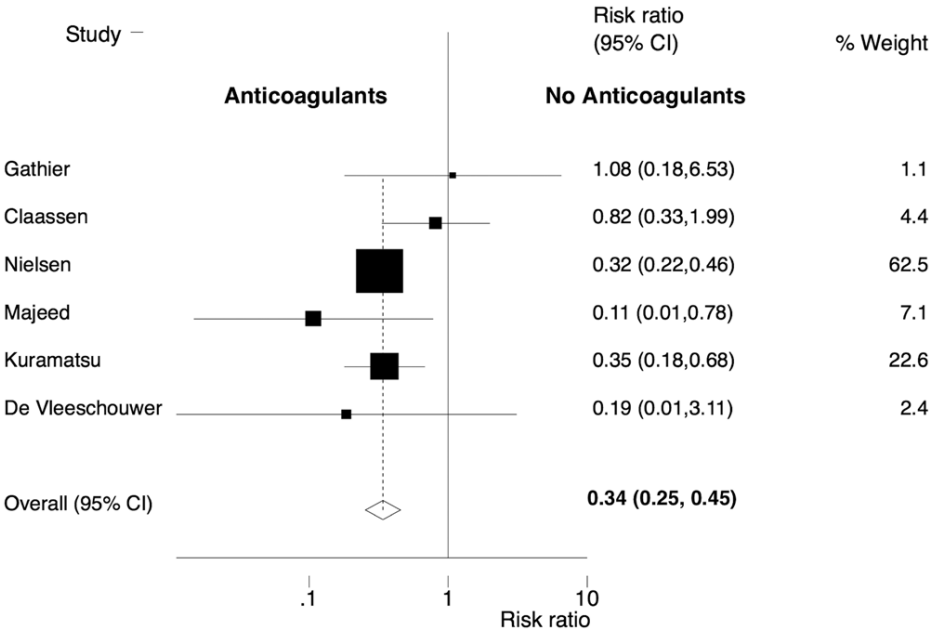
Prevalence of AF in incident ICH: ~16%

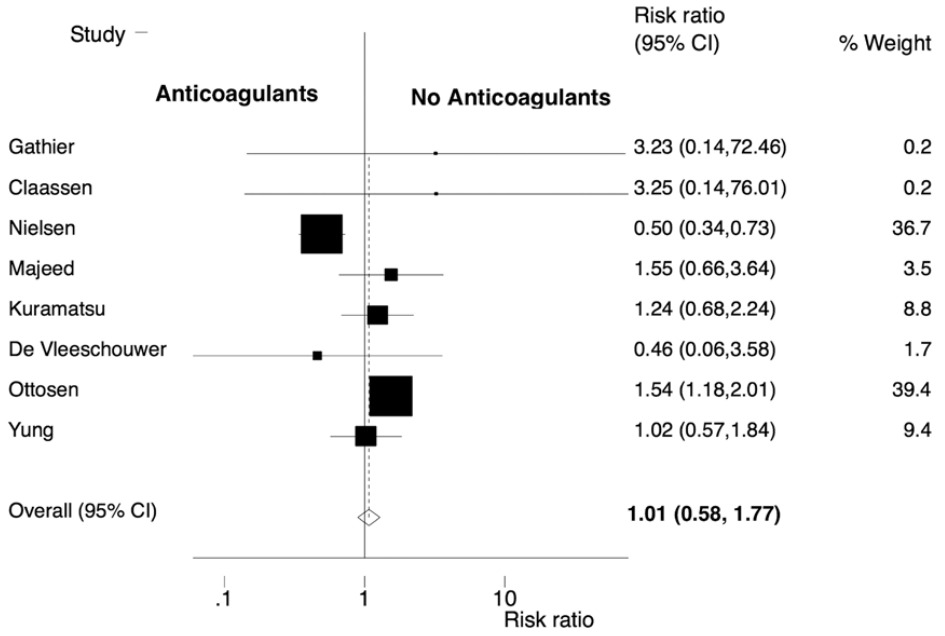


Restarting Anticoagulant Therapy After Intracranial Hemorrhage

A Systematic Review and Meta-Analysis

Santosh B. Murthy, MD, MPH; Ajay Gupta, MD; Alexander E. Merkler, MD; Babak B. Navi, MD, MS; Pitchaiah Mandava, MD, PhD, MSEE; Costantino Iadecola, MD; Kevin N. Sheth, MD; Daniel F. Hanley, MD; Wendy C. Ziai, MD, MPH; Hooman Kamel, MD





Stroke. 2017 Jun;48(6):1594-1600.

Effects of antiplatelet therapy after stroke due to intracerebral haemorrhage (RESTART): a randomised, open-label trial

*RESTART Collaboration**

Published online May 22, 2019 http://dx.doi.org/10.1016/S0140-6736(19)30840-2

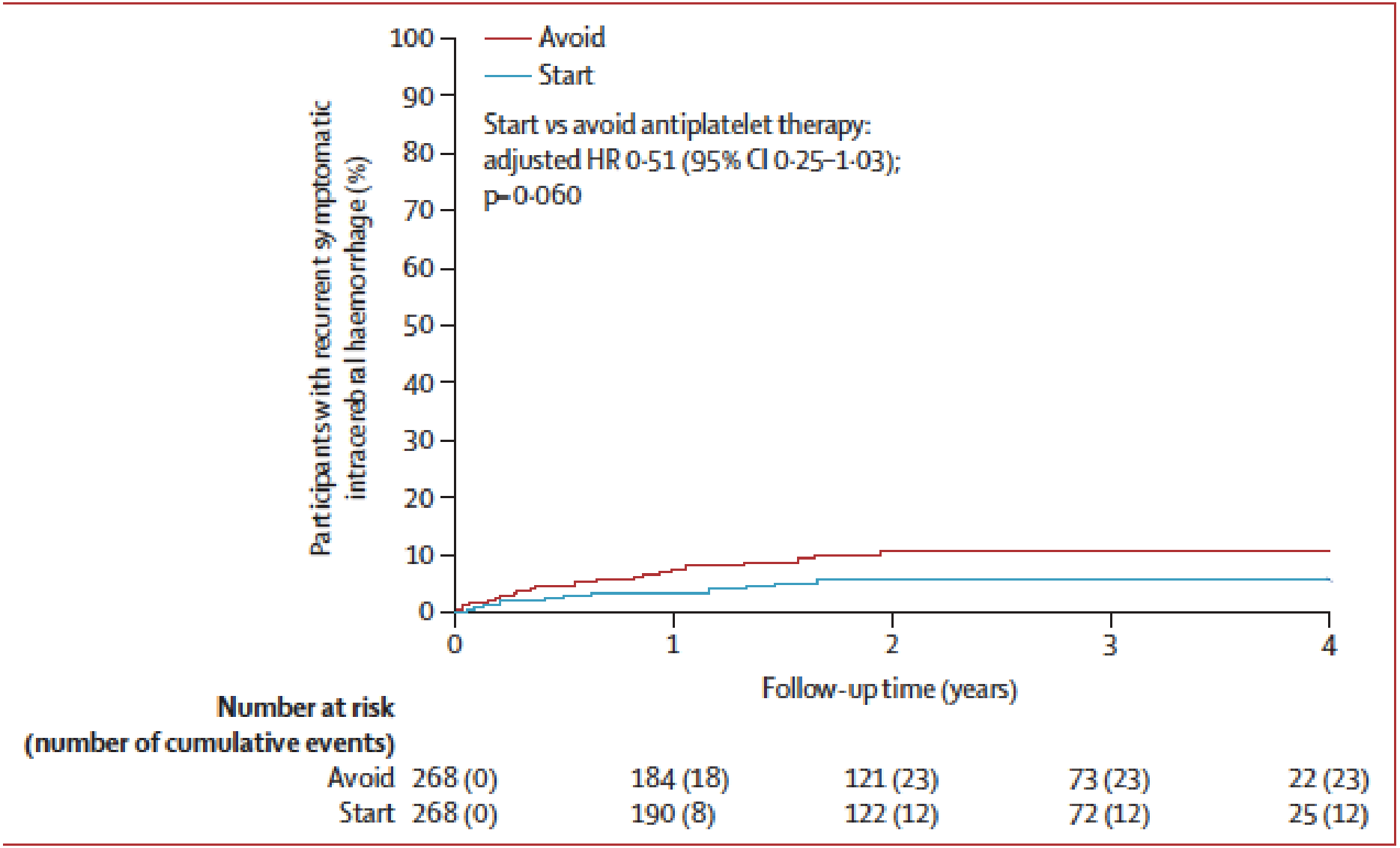


Figure 2: Kaplan-Meier plot of the first occurrence of recurrent symptomatic intracerebral haemorrhage
Numbers at risk refer to survivors under follow-up at the start of each year according to treatment allocation. Cumulative events indicate the participants in follow-up with a first event. HR=hazard ratio.

	Start antiplatelet therapy (n=268)	Avoid antiplatelet therapy (n=268)	Log-rank test p value	Unadjusted analysis		Adjusted analysis	
				HR (95% CI)	p value	HR (95% CI)	p value
Primary outcome							
Recurrent symptomatic spontaneous intracerebral haemorrhage	12 4 %	23 9 %	0·057	0·51 (0·26–1·03)	0·062	0·51 (0·25–1·03)	0·060
Sensitivity analyses of the primary outcome							
Recurrent symptomatic spontaneous intracerebral haemorrhage or symptomatic stroke of uncertain subtype	12	24	0·041	0·49 (0·25–0·99)	0·046	0·49 (0·24–0·98)	0·044
Recurrent symptomatic spontaneous intracerebral haemorrhage or death of undetermined cause	13	25	0·047	0·51 (0·26–1·00)	0·051	0·51 (0·26–0·99)	0·048
Secondary outcomes							
All major haemorrhagic events (all types of symptomatic spontaneous or traumatic intracranial haemorrhage, or symptomatic major extracranial haemorrhage)	18	25	0·27	0·71 (0·39–1·30)	0·27	0·71 (0·39–1·30)	0·27
All major occlusive vascular events (ischaemic stroke; myocardial infarction; mesenteric ischaemia; peripheral arterial occlusion; deep vein thrombosis; pulmonary embolism; or carotid, coronary, or peripheral arterial revascularisation procedures)	39	38	0·97	1·01 (0·65–1·58)	0·97	1·02 (0·65–1·60)	0·92
All major haemorrhagic or occlusive vascular events	54	61	0·42	0·86 (0·60–1·24)	0·42	0·86 (0·60–1·24)	0·43
Major occlusive vascular events*	45	52	0·39	0·84 (0·56–1·25)	0·39	0·84 (0·56–1·25)	0·39
Major vascular events (as defined by the Antithrombotic Trialists' Collaboration)	45	65	0·026	0·65 (0·45–0·95)	0·027	0·65 (0·44–0·95)	0·025

HR=hazard ratio. *As defined in the trial protocol.

***Table 3*: Risks of first occurrence of primary and secondary outcome events during follow-up**

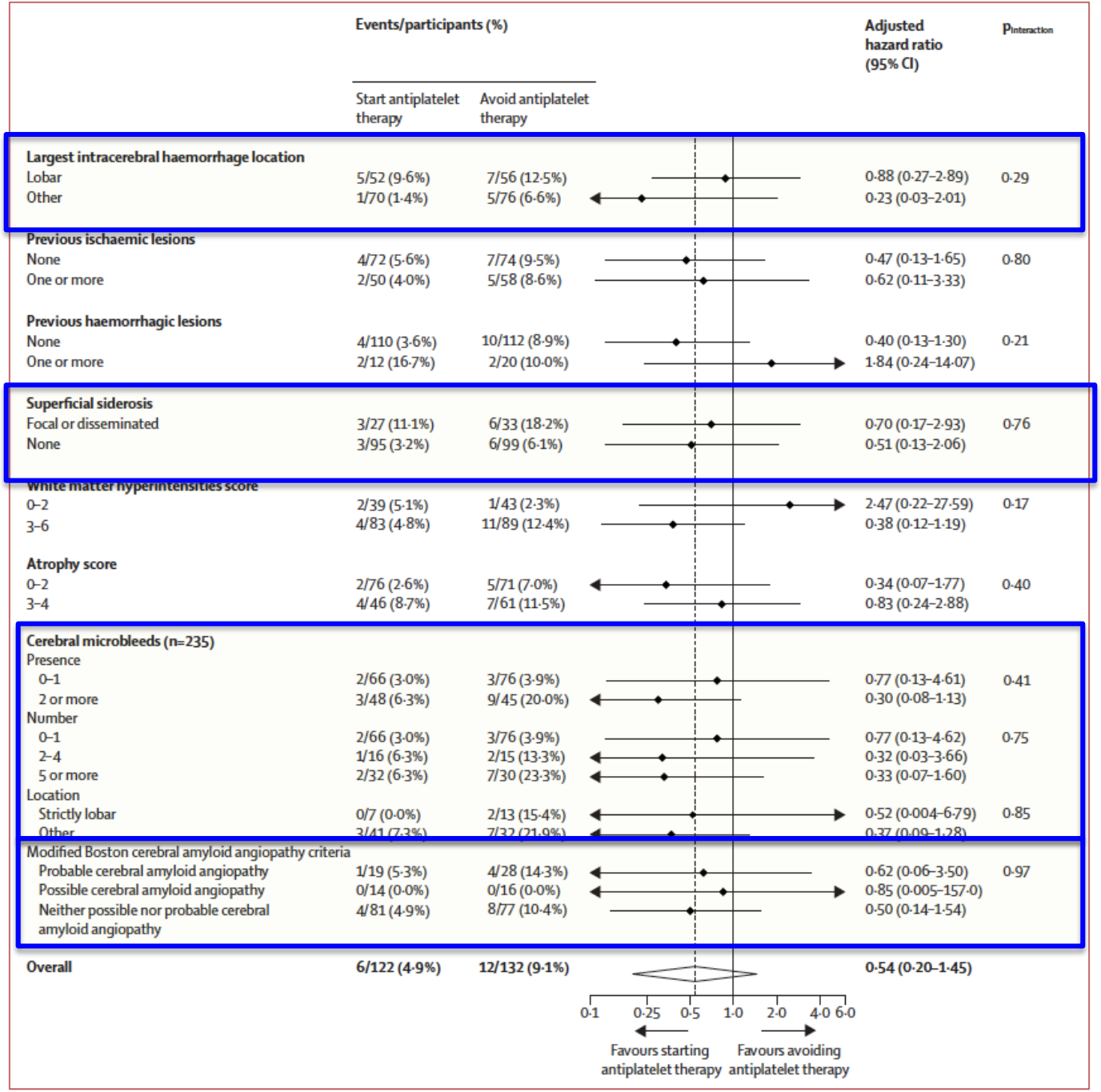


Figure 3: **Prespecified primary and exploratory subgroup analyses of the risk of first recurrent symptomatic intracerebral haemorrhage (the primary outcome) by brain MRI features**

Table 1. *Ongoing randomized controlled trials investigating optimal stroke prevention in AF patients following intracranial hemorrhage*

Trial; principal investigator	Population	Intervention	Target sample	Status
Antithrombotic therapy				
APACHE-AF; Karin Klijn NCT02565693	Atrial fibrillation and ICH	Apixaban vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	100	Recruiting
NASPAF-ICH; Ashkan Shoamanesh NCT02998905	Atrial fibrillation and ICH	Any DOAC vs. aspirin (open-label)	100	Enrollment completed/ stopped at 30 participants
SoSTART; Rustam Al-Shahi Salman NCT03153150	Atrial fibrillation and intracranial hemorrhage	Any anticoagulant vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	190	Recruiting
STATICH; Eivind Berge NCT03186729	Thrombo-occlusive disease indicating antithrombotic therapy and ICH	Any antithrombotic therapy vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	500	Recruiting
PRESTIGE AF; Roland Veltkamp NCT03996772	Atrial fibrillation and ICH	Any DOAC vs. no antithrombotic therapy/antiplatelet monotherapy (open-label)	654	Recruiting
ASPIRE; Kevin Sheth NCT03907046	Atrial fibrillation and ICH	Apixaban vs. aspirin (double-blind)	700	Activating
ENRICH-AF; Ashkan Shoamanesh NCT03950076	Atrial fibrillation and intracranial hemorrhage	Edoxaban vs. standard of care (no antithrombotic therapy/ antiplatelet monotherapy; open-label)	1200	Activating
LAAO				
A3ICH; Charlotte Cordonnier NCT03243175	Atrial fibrillation and ICH	Apixaban vs. no antithrombotic therapy/antiplatelet monotherapy vs. LAAO (open-label)	300	Recruiting
STROKECLOSE; Mårten Rosenqvist NCT02830152	Atrial fibrillation and ICH	LAAO vs. medical therapy (open-label)	750	Recruiting

Abbreviations: AF, atrial fibrillation; DOAC, direct oral anticoagulant; ICH, intracerebral hemorrhage; LAAO, left atrial appendage occlusion.

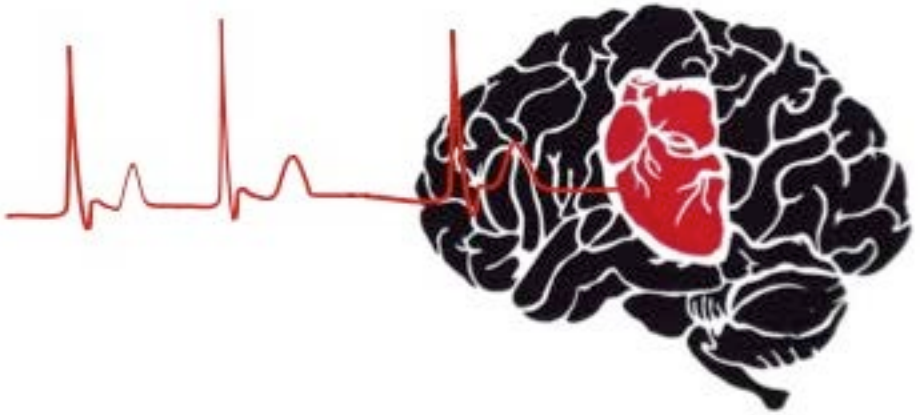
NASPAF-ICH

	Overall	
	n	Percent
Randomized	30	100%
Primary outcome: Ischemic stroke/Recurrent ICH	1	3.3%
Ischemic stroke	1	3.3%
Recurrent ICH	0	0.0%
Fatal stroke	0	0.0%
Intracranial hemorrhage	0	0.0%
MI	0	0.0%
All mortality	3	10%
Stroke, MI, systemic thromboembolism, death	2	6.7%
Systemic thromboembolism	0	0.0%

NASPAF-ICH

	Overall	
	n	Percent
Randomized	30	100%
Major bleed	1	3.3%
- Intraocular	0	0.0%
- Oral	0	0.0%
- Genitourinary	1	3.3%
- Gastrointestinal	0	0.0%
- Symptomatic intracranial hemorrhage	0	0.0%

ENRICH-AF



EdoxabaN foR IntraCranial Hemorrhage survivors with Atrial Fibrillation

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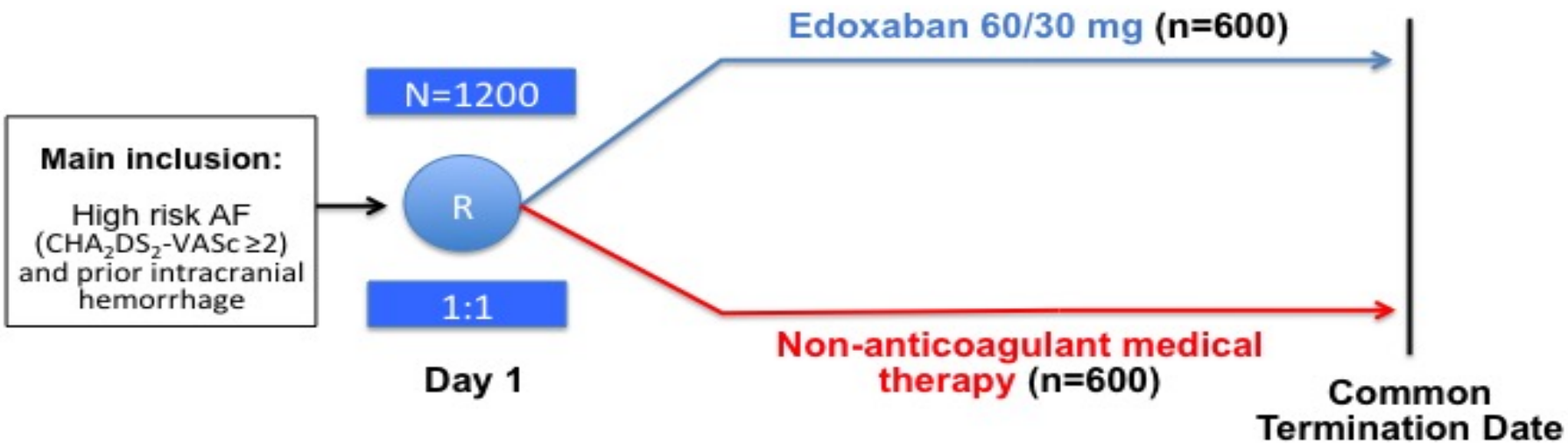
ENRICH-AF: Objective

- To assess whether edoxaban (60/30 mg daily) compared to standard of care (either no antithrombotic therapy or antiplatelet monotherapy) reduces the risk of stroke (composite of ischemic, hemorrhagic and undetermined stroke) in high-risk atrial fibrillation (CHA_2DS_2-VASc ≥2) patients with previous intracranial hemorrhage.

Hypothesis

- Treatment with edoxaban will reduce the risk of stroke (composite of ischemic, hemorrhagic and undetermined) compared with standard of care.

Design



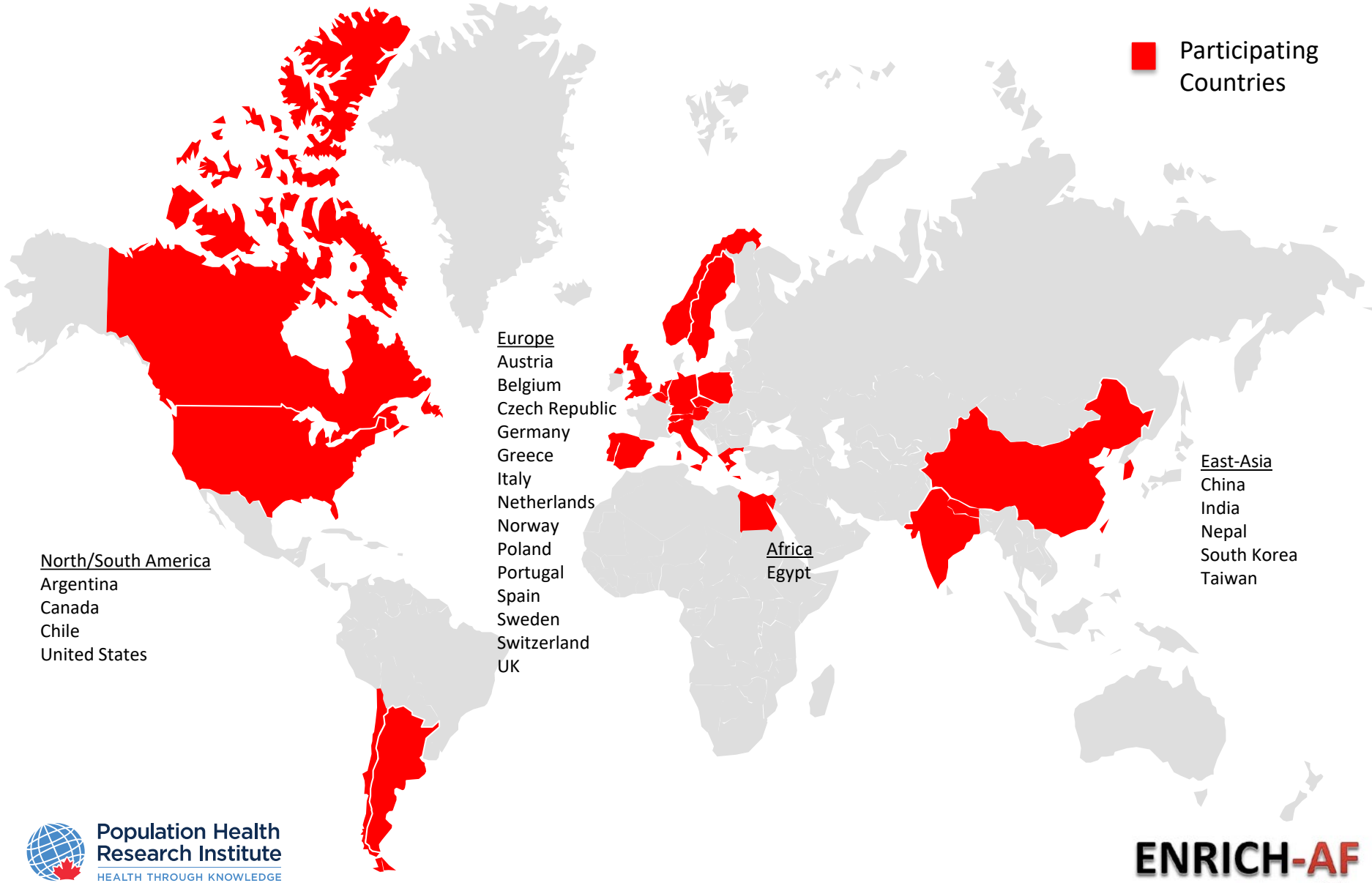
Recruitment period: 24 months

Last participant followed: common study termination once 123 primary events have accrued; estimated to occur 12 months following end of recruitment

Total study duration: ~ 36 months

Mean follow-up per participant: 24 months (range 12 – 36 months)

ENRICH-AF Countries



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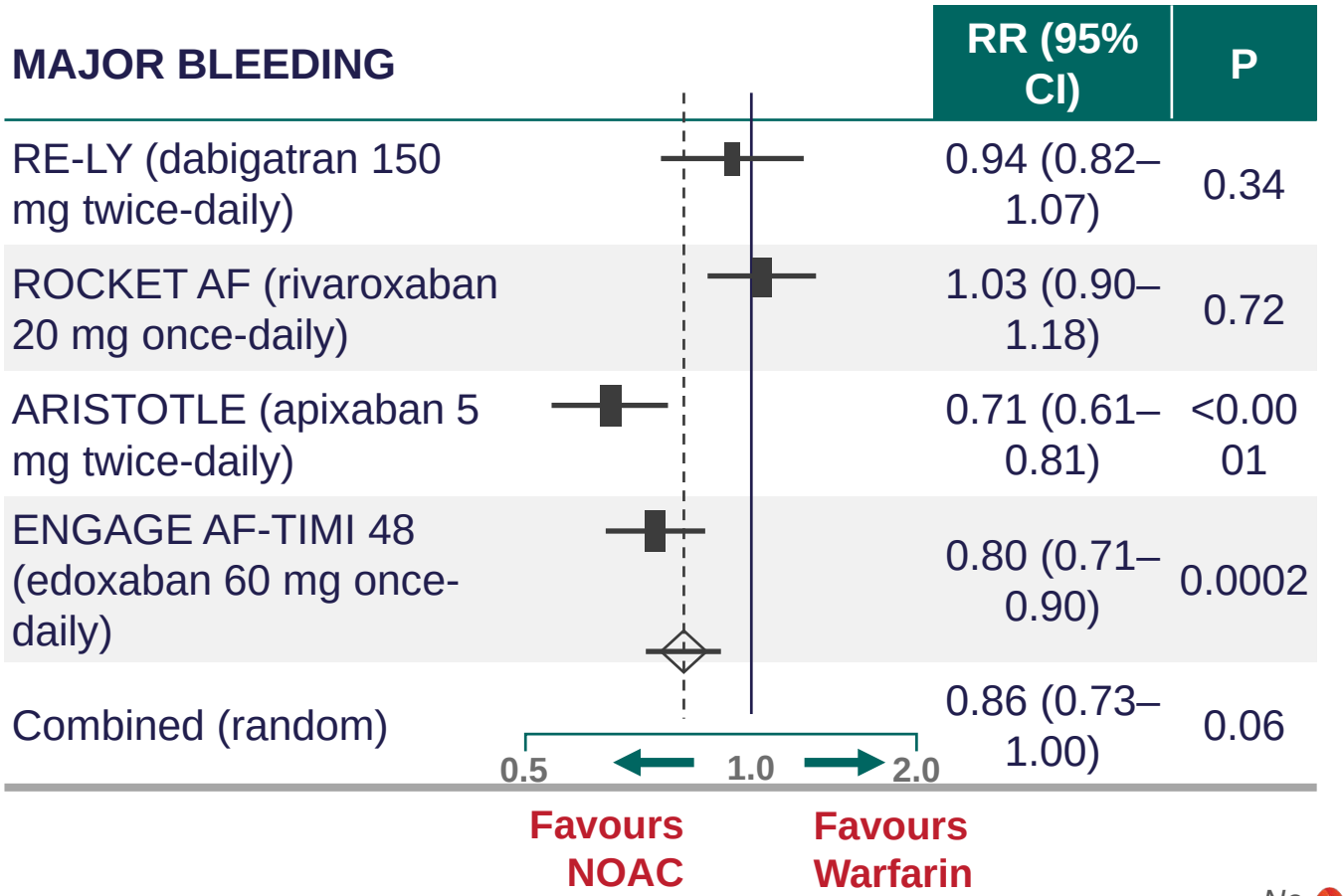
ENRICH-AF

Comparison of Major Bleeding of NOACs vs. Warfarin in Patients with AF: a Meta-analysis of Randomized Trials

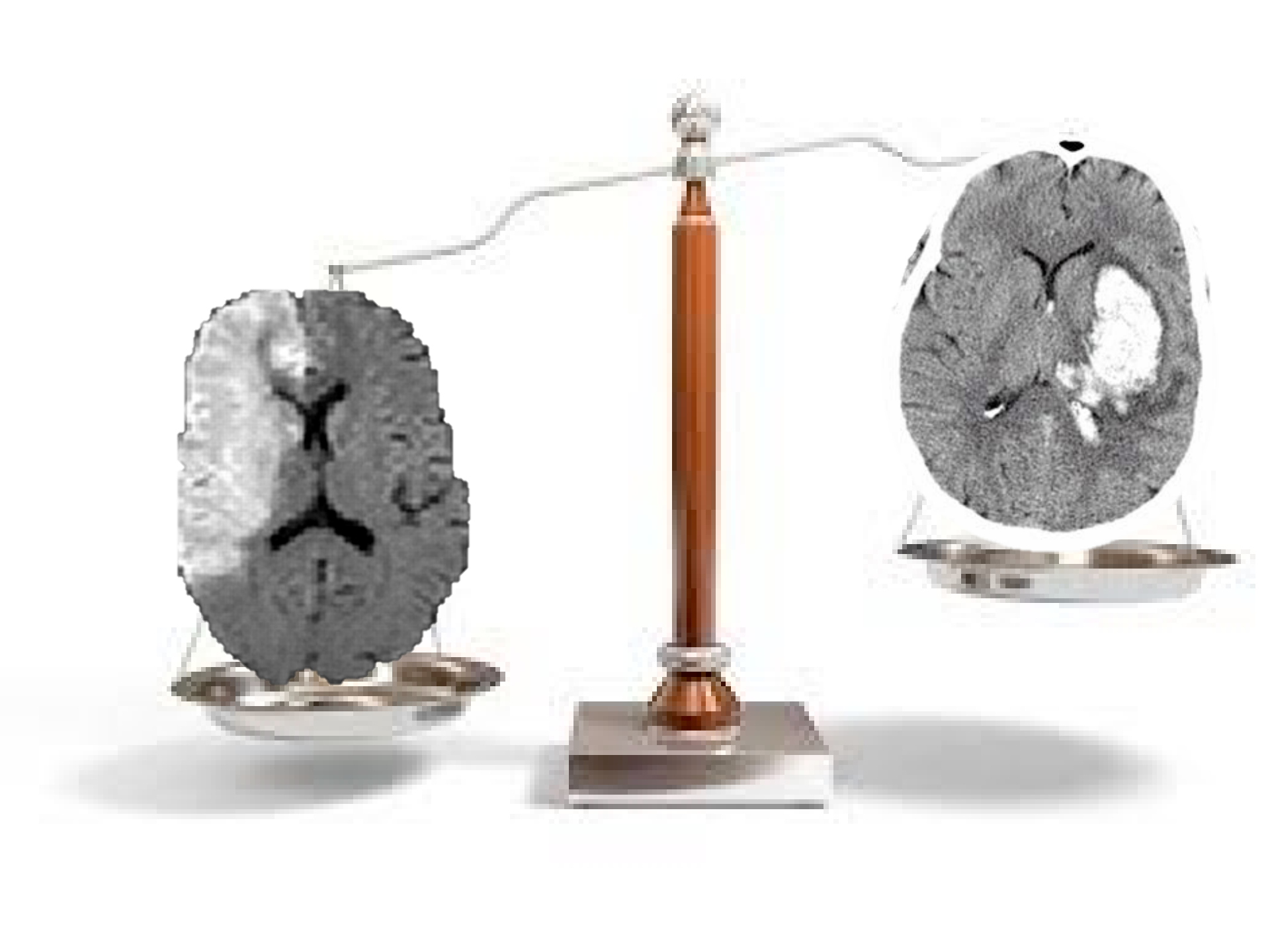


Next

 Ruff CT, *et al. Lancet* 2014;383(9921):955-62.

Edoxaban

- **Advantages**
  - Superior efficacy for stroke prevention compared to warfarin (mITT)
  - Cardiovascular mortality benefit
  - Reduction in Major Bleeding
  - Once daily
  - Bioavailability independent of food
  - Can be crushed for NG or PEG tube.
  - Large number of patients tested at lower dose (n=1784) in 60/30 mg arm of ENRICH-AF.
- **Disadvantage**
  - Increase in GI bleeding



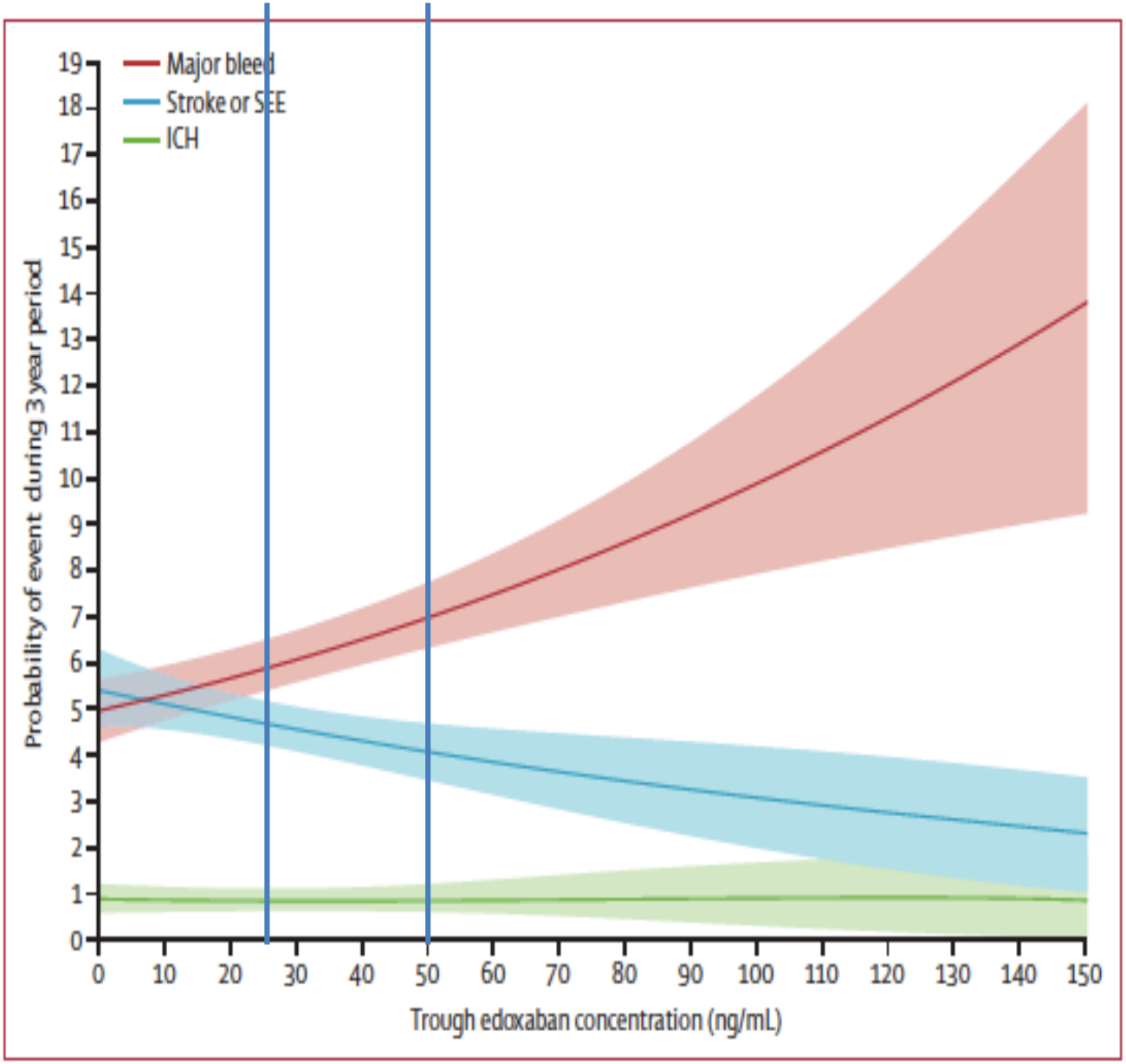


***Figure 2*: Probability of clinical outcomes versus edoxaban concentration**

Trough edoxaban plasma concentration at 1 month after randomisation versus probability of efficacy and safety outcomes (median follow-up 2·8 years). ICH=intracranial haemorrhage. SEE=systemic embolic event.

Observed event rates in pivotal trials

Event	Aspirin (AVERROES)	Apixaban 5/2.5 (ARISTOTLE)	Edoxaban 60/30 (ENGAGE-AF TIMI 48)
Hemorrhagic stroke	0.30%/yr	0.24%/yr	0.26%/yr
Intracranial hemorrhage	0.4%/yr	0.33%/yr	0.39%/yr
$CHADS_2$	Mean 2.1	Mean 2.1	Mean 2.8

Estimated Outcomes in ENRICH-AF

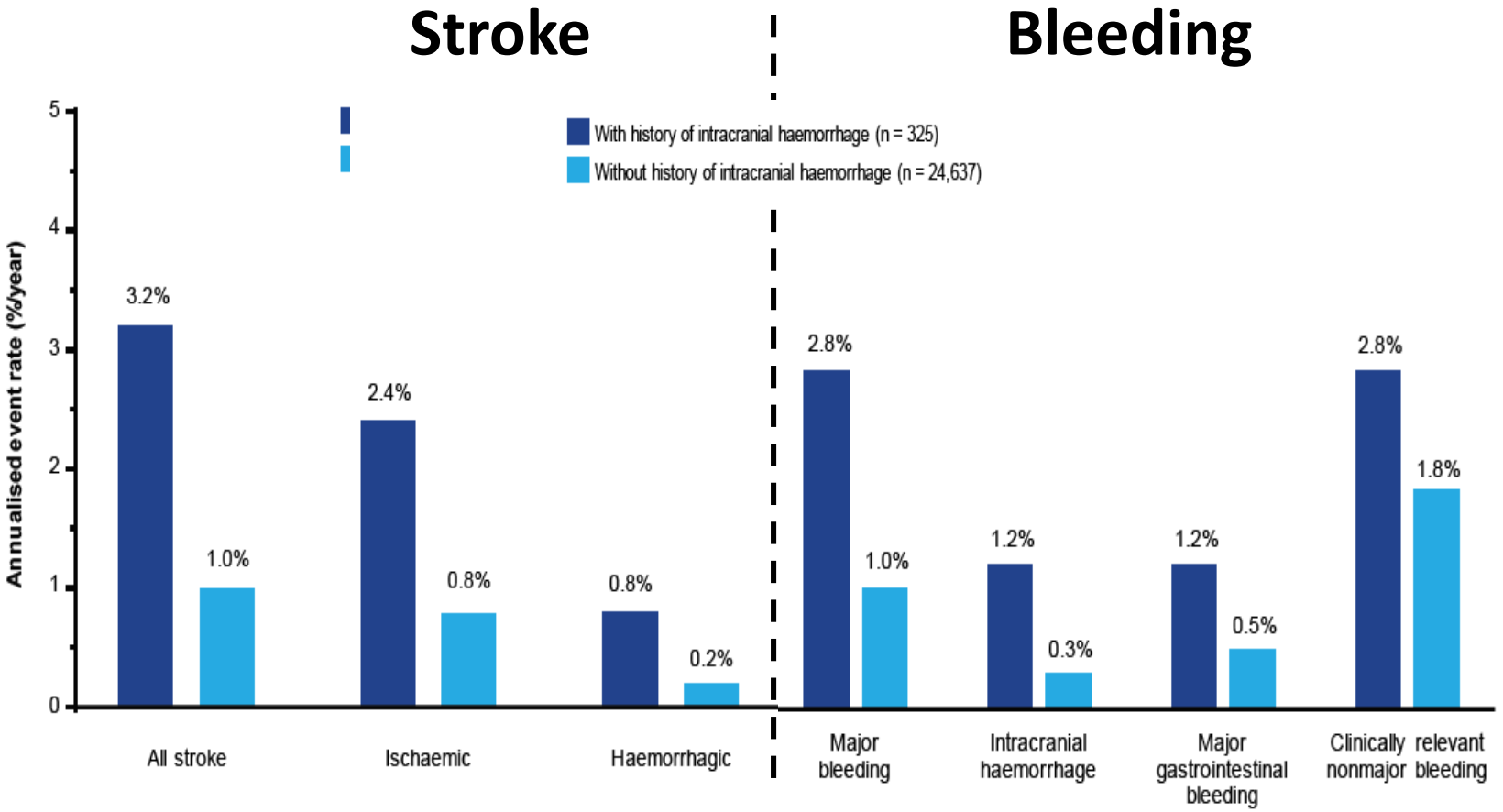
	Ischemic stroke	Hemorrhagic Stroke	All stroke
No anticoagualtion*	6%/yr	1.5%/yr	7.5%/yr
Edoxaban 60/30	2%/yr	2.5%/yr	4.5%/yr

aHR: 0.60

*antiplatelet monotherapy or no antithrombotic therapy

Event Rates in Patients Taking Edoxaban With or Without History of ICH

Data from the Global ETNA-AF Programme (N=24,962)



Kirchhof P, *et al.* Presented at ESC 2019; Poster #P4785.

Inclusion Criteria

- Intracranial hemorrhage; occurring on or not on anticoagulation/antiplatelet therapy.
- Documented atrial fibrillation
- CHA_2DS_2-VASc ≥2

Intracranial Hemorrhage Eligibility

Clinical Scenario	Intraventricular hemorrhages	Intraparenchymal hemorrhages	Convexal subarachnoid hemorrhages	Subdural hemorrhages
Spontaneous	Yes	Yes	Yes	Yes
Asymptomatic	No	No	No	No
Traumatic	No	No	No	Yes
Macrovascular, infectious, neoplasm, bleeding diathesis, etc.	No	No	No	No
On antiplatelet or anticoagulant therapy	Yes	Yes	Yes	Yes
Off antiplatelet or anticoagulant therapy	Yes	Yes	Yes	Yes
Due to thrombolysis	No	No	No	No
Underlying cerebral amyloid angiopathy	Yes	Yes	Yes	Yes

Exclusion Criteria

- Recent intracranial hemorrhage (<14 days)
- Need for ongoing oral anticoagulant therapy for indication other than AF (e.g.mechanical heart valve, venous thromboembolic disease)
- Need for ongoing antiplatelet therapy for indication where edoxaban would not be a suitable substitute
- Plans for left atrial appendage occlusion
- Estimated creatinine clearance (CrCl) < 15 mL/min or other creatinine clearance following local product monograph (Canada < 30 mL/min)
- Platelet count less than 100,000 at enrollment or other bleeding diathesis
- Persistent, uncontrolled hypertension (systolic BP averaging >150 mmHg)
- Known hypersensitivity to edoxaban
- Estimated inability to adhere to study procedures
- Pregnancy or breastfeeding
- Estimated life expectancy < 6 months at the time of enrollment

Outcomes

- Primary efficacy parameter: **Stroke (composite of ischemic, hemorrhagic and undetermined stroke)**

- Secondary outcomes:
  - Ischemic stroke
  - cardiovascular death
  - hemorrhagic stroke
  - disabling/fatal stroke
  - composite of all stroke, myocardial infarct, systemic thromboembolism or all-cause death

- Safety outcomes:
  - Major hemorrhage (ISTH criteria)
  - Intracranial hemorrhage
  - subdural hemorrhage
  - Fatal intracranial hemorrhage
  - Hospitalization (for any cause)