Antithrombotic treatment after stroke due to intracerebral haemorrhage (ICH): harmful or beneficial?

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THE UNIVERSITY *of* EDINBURGH

NHS Lothian

UKCRC Registered Clinical Trials Units

My disclosures

Research to Understand Stroke due to Haemorrhage

Salary (paid to me)

THE UNIVERSITY of EDINBURGH

NHS Lothian

UKCRC Registered Clinical Trials Units

Grants (paid to employer)

British Heart Foundation

CHIEF SCIENTIST OFFICE

Consultancies (paid to employer)

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Recursion

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www.whopaysthisdoctor.org/doctor/276/active

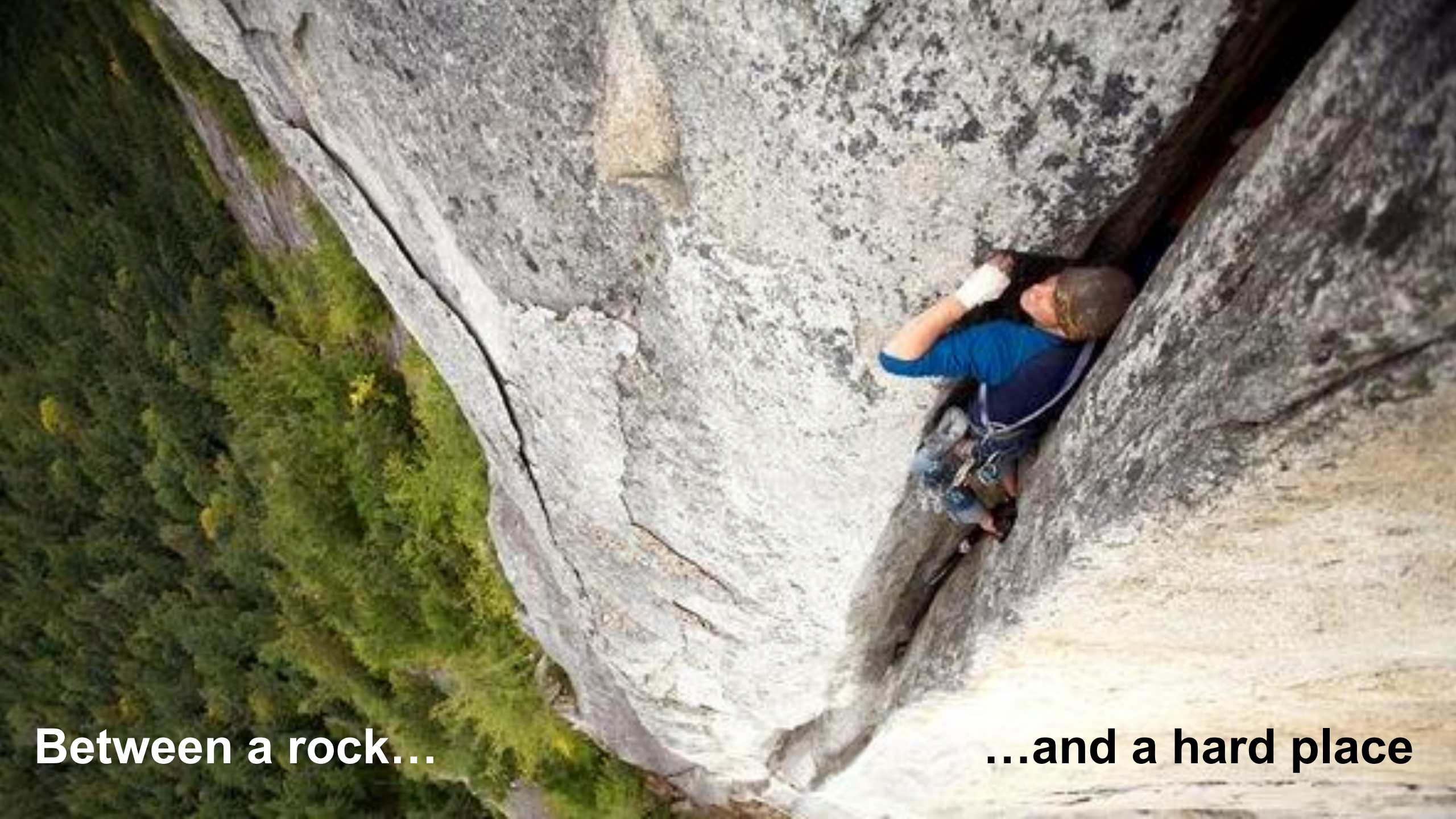
My disclosures

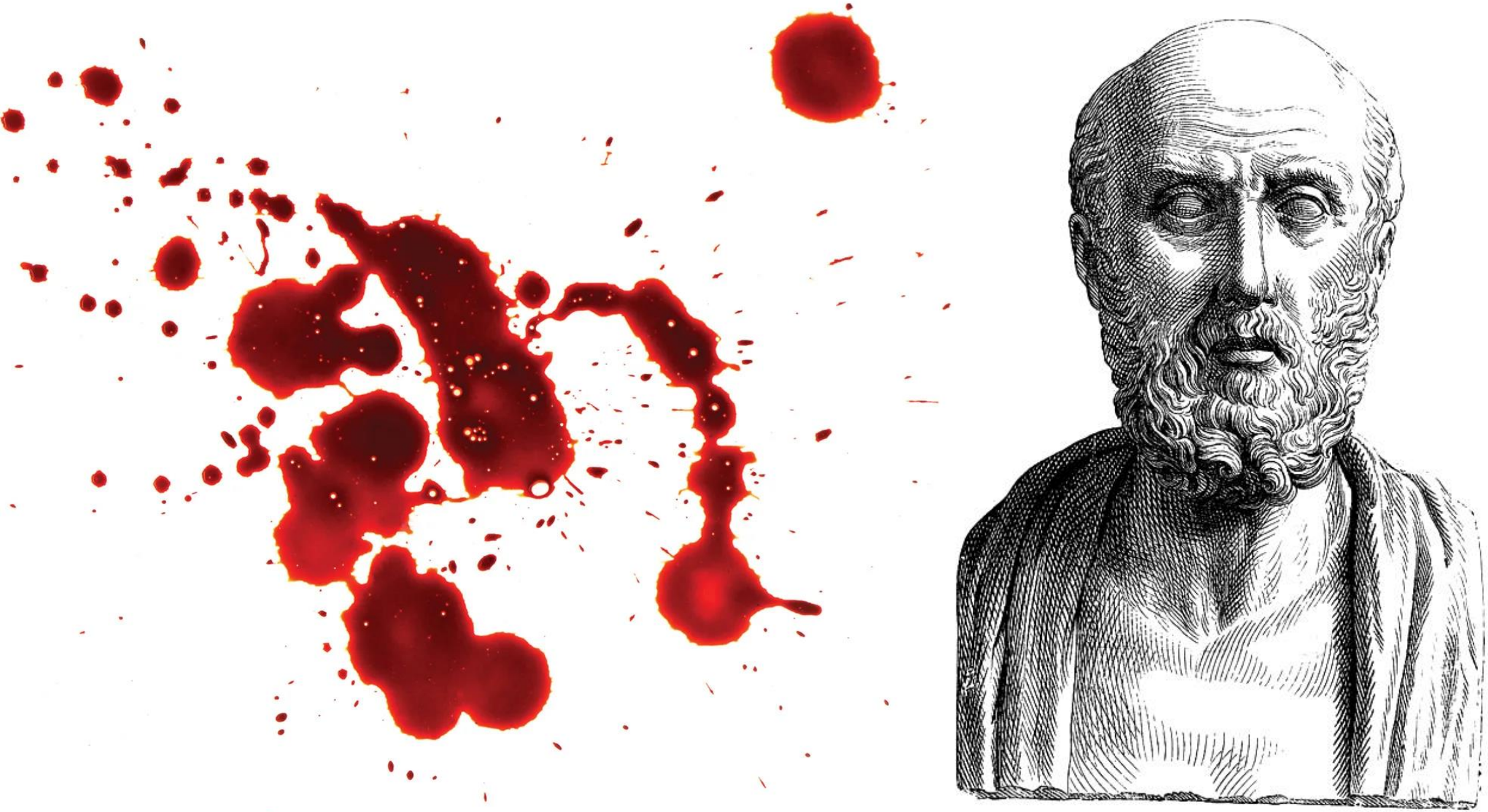
Research to Understand Stroke due to Haemorrhage

REWARD

REduce research Waste And Reward Diligence

Sustainable Healthcare Coalition

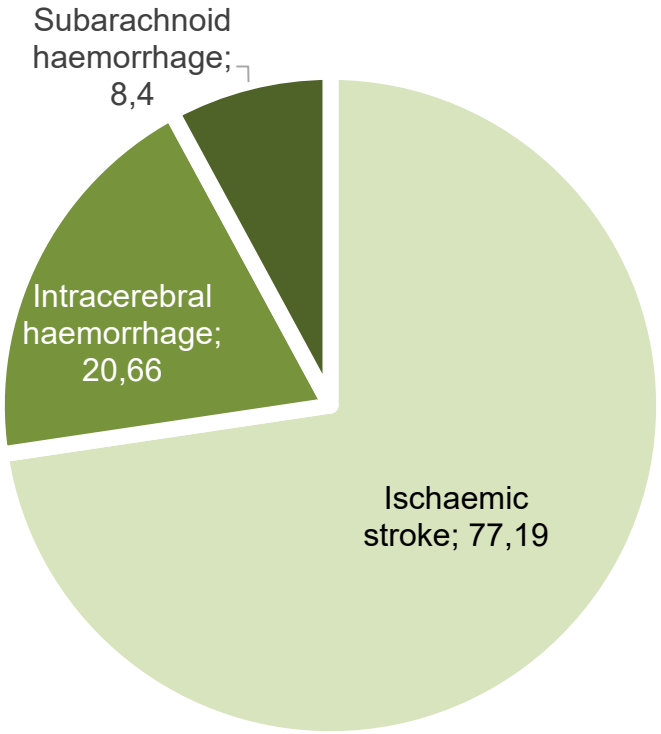

Between a rock…
…and a hard place



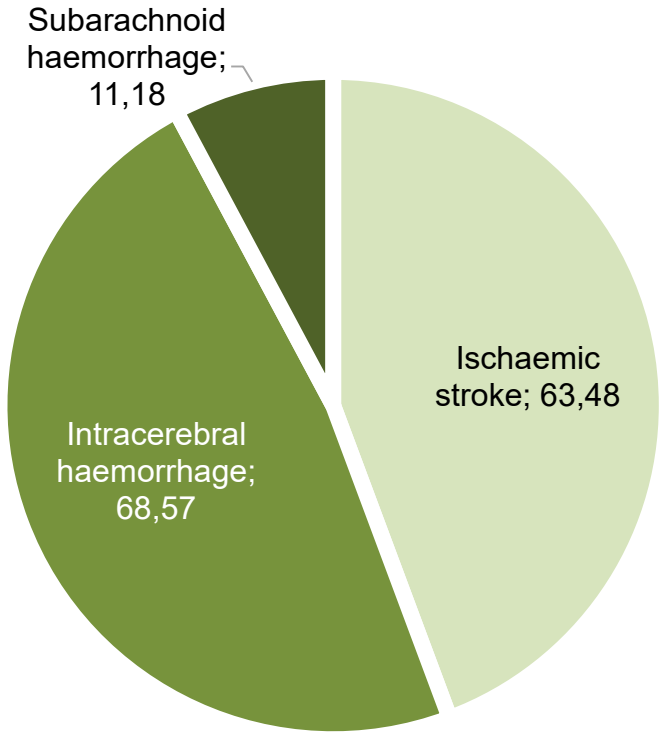
Reality check: global burden of stroke

GBD 20
CELEBRATING 20 YEARS
OF COLLABORATION AND INNOVATION

Prevalence (millions) in 2019

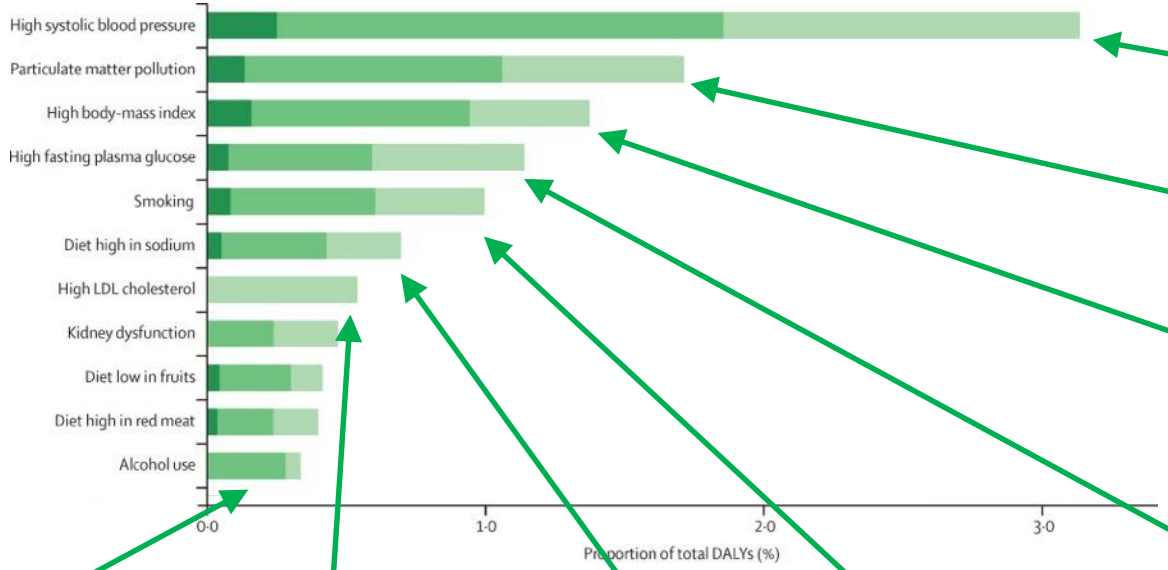


DALYs (millions) in 2019



Lancet Neurology 2021;20:795-820

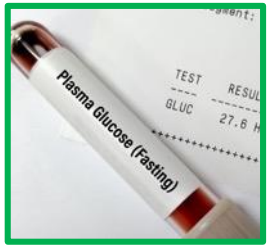
What are the main risk factor contributions to DALYs due to ICH?



High systolic BP

Particulate matter pollution

High body mass index



High fasting plasma glucose

Smoking

Diet (salt etc)

High HDL cholesterol

Alcohol use

Lancet Neurology 2021;20:795-820


Risks


Risk factors


Treatment effects

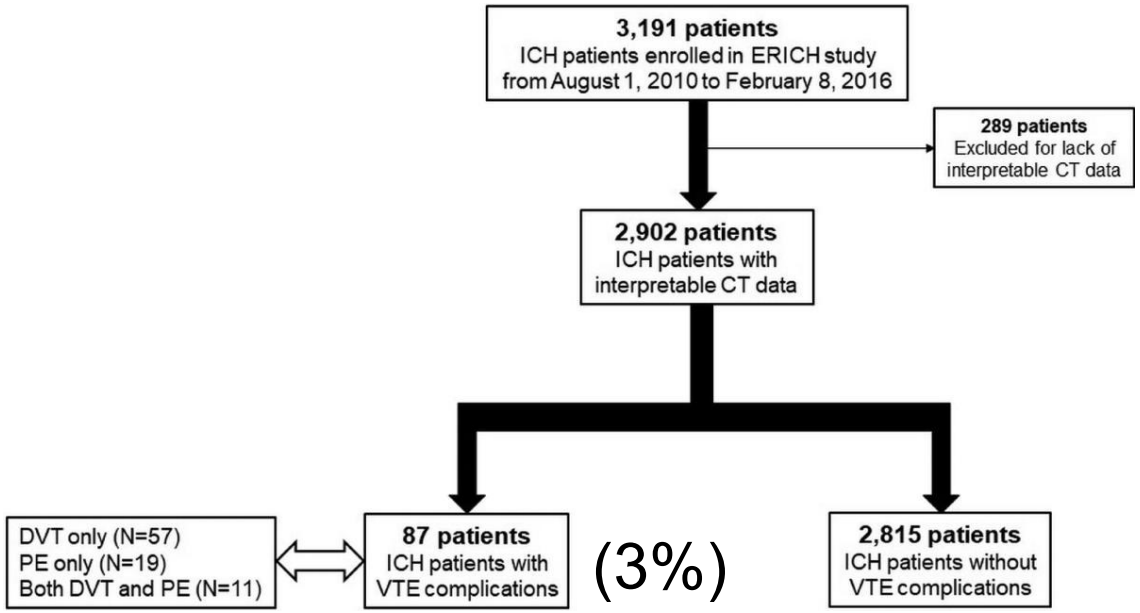

Heterogeneity
of treatment effect


Risks
Risk factors
Treatment effects
Heterogeneity
of treatment effect

Risk of venous thromboembolism (VTE) after ICH

Ethnic/Racial Variations of Intracerebral Hemorrhage study

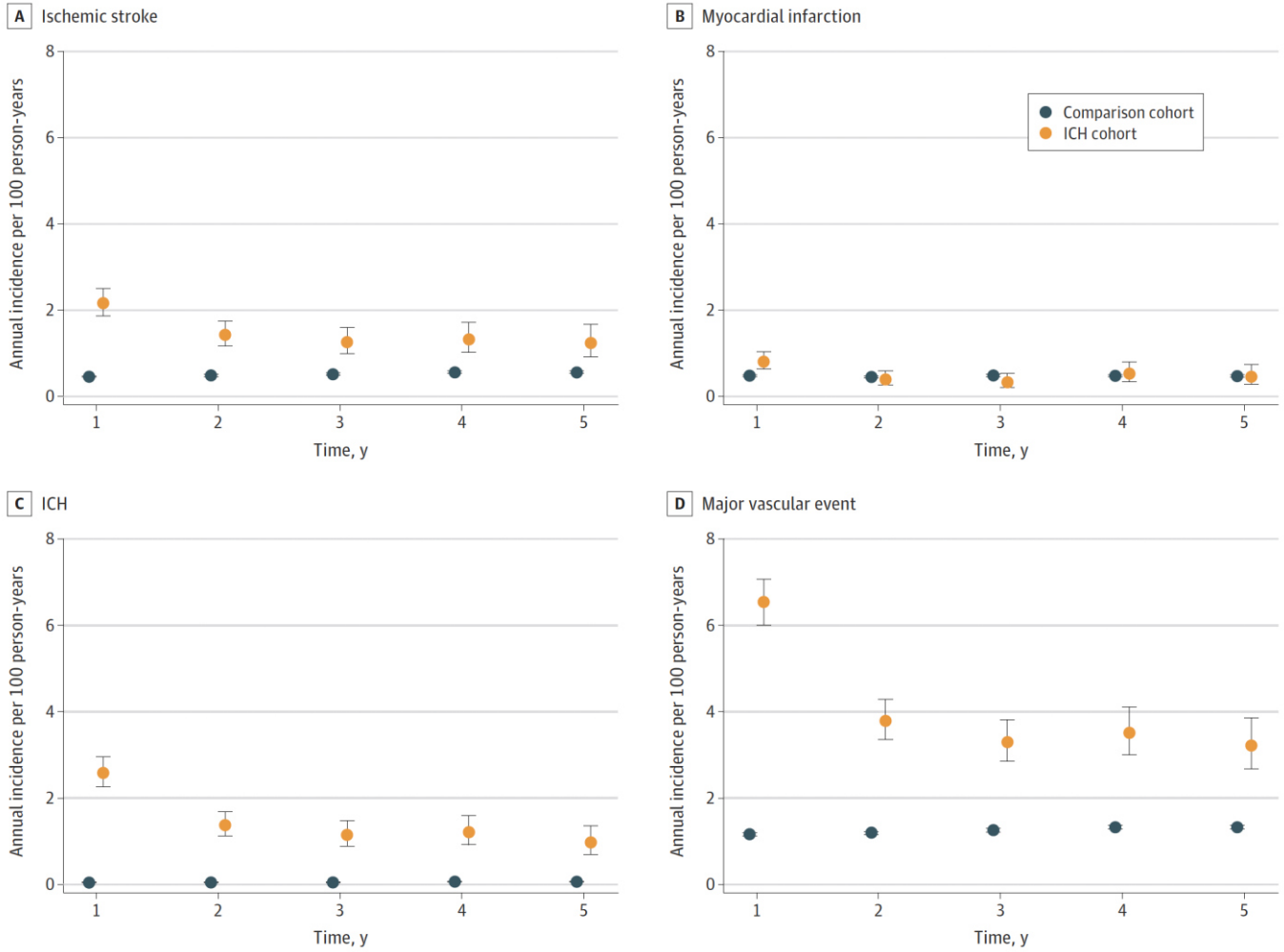
Multicentre cohort study



Neurosurgery 2019;84:e304-e310

Risks of major adverse cardiovascular and cerebrovascular events (MACE) after ICH

Region of Southern Denmark
OUH
Odense University Hospital
Svendborg Hospital



JAMA Network Open 2022;5(10):e2234215 (Denmark 2005-2018)


Risks


Risk factors

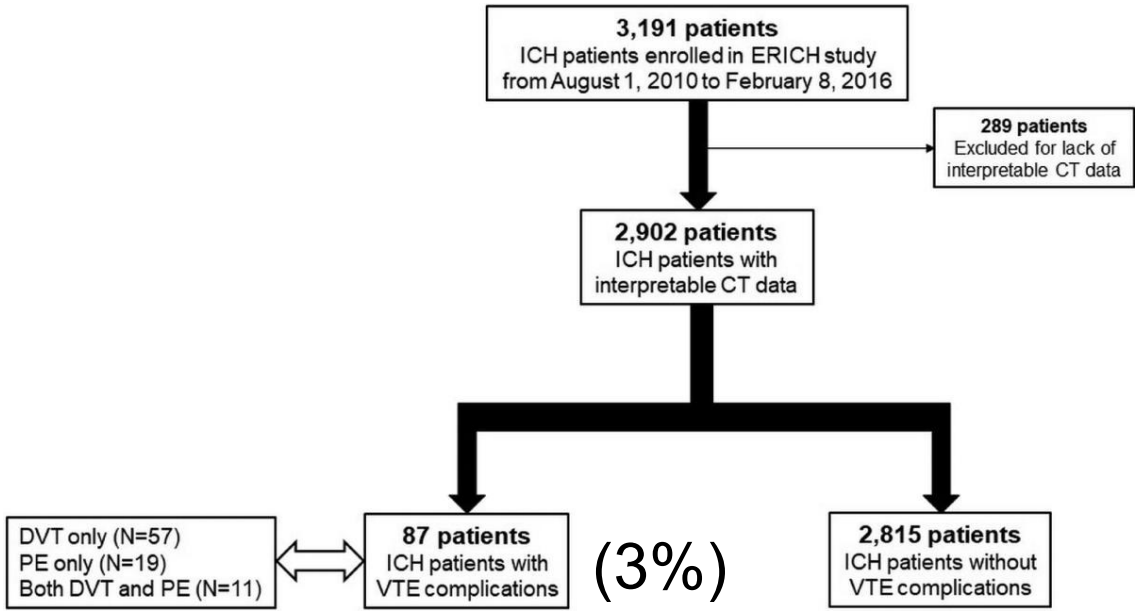

Treatment effects


Heterogeneity
of treatment effect

Risk factors for VTE after ICH

Ethnic/Racial Variations of Intracerebral Hemorrhage study

Multicentre cohort study



Independent risk factors

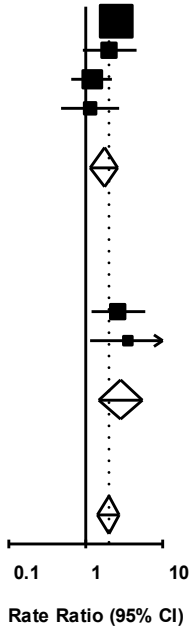
Predictor	OR (95%CI)	p
Prior VTE	6.8 (3.4-13.4)	<0.0001
Intubation	4.0 (2.4-6.5)	<0.0001
IVH	1.8 (1.1-2.9)	0.0157

Neurosurgery 2019;84:e304-e310

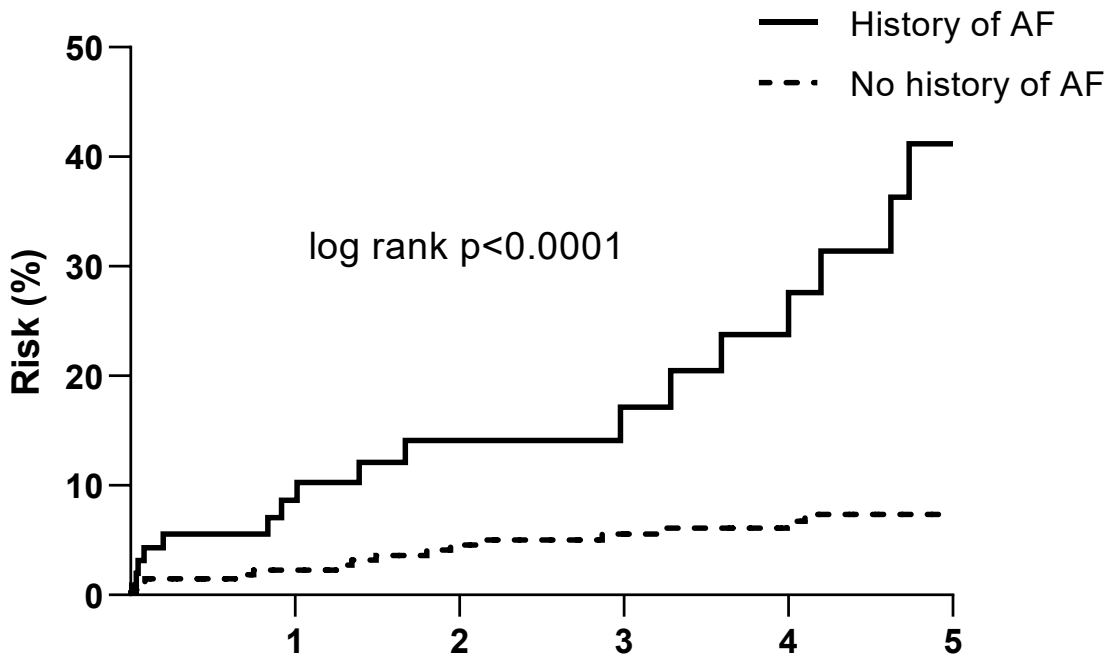
Risk factors for recurrent ICH and ischaemic stroke, after ICH

Recurrent ICH: lobar vs. non-lobar

Study	Events / Patient-years		RR	95% CI
	Lobar	Non-lobar		
Hospital-based studies				
Biffi	102 / 1308	44 / 1375	2.4	1.7-3.5
Casolla	13 / 690	11 / 1170	2.0	0.9-4.5
Chong	17 / 776	25 / 1374	1.2	0.7-2.2
Zia	9 / 360	11 / 500	1.1	0.5-2.8
Total	141 / 3134	91 / 4419	1.7	1.2-2.6
Significance: p =0.008				
Heterogeneity: p = 0.15				
Population-based studies				
LATCH	22 / 384	9 / 404	2.6	1.2-5.9
OXVASC	11 / 275	4 / 351	3.5	1.1-11.0
Total	33 / 659	13 / 755	2.8	1.5-5.5
Significance: p =0.002				
Heterogeneity: p = 0.66				
TOTAL	174 / 3793	104 / 5174	2.0	1.4-2.7
Significance: p <0.0001				
Heterogeneity: p = 0.25				



Ischaemic stroke: atrial fibrillation (AF) vs. no AF



Lancet Neurology 2021;20:437-47

High risks of MACE in all sub-groups

Pooled community-based studies in Oxford and Edinburgh, stratified by two risk factors	Annual outcome event rate, % per year (95% CI)		
	Recurrent ICH	Ischaemic stroke	MACE
AF and lobar ICH	4.4 (1.6-11.6)	7.3 (3.5-15.4)	14.6 (8.6-24.6)
AF and non-lobar ICH	3.6 (1.3-10.3)	5.6 (2.5-12.4)	14.9 (5.8-38.2)
No AF and lobar ICH	5.2 (3.6-7.5)	0.9 (0.2-4.8)	9.1 (6.6-12.6)
No AF and non-lobar ICH	1.6 (0.9-2.9)	0.9 (0.2-4.8)	5.0 (1.9-13.1)

Lancet Neurology 2021;20:437-47 (Oxford 2002-2018, Edinburgh 2010-2013)


Risks


Risk factors


Treatment effects


Heterogeneity
of treatment effect

Effect of short-term prophylactic dose anticoagulation after ICH on VTE

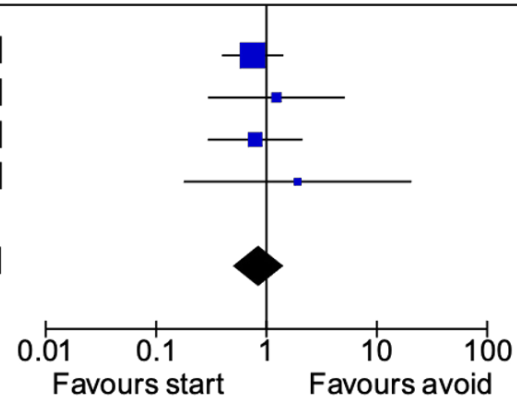
Uncertain effects in small randomised controlled trials (RCTs)

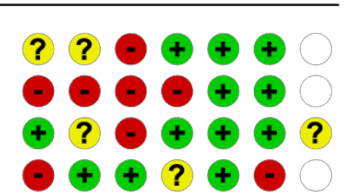
Study or Subgroup	Start anticoagulation Events	Total	Avoid anticoagulation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dickmann 1988	9	23	12	23	58.9%	0.75 [0.39 , 1.43]
Orken 2009	4	39	3	36	11.9%	1.23 [0.30 , 5.13]
PREVENTIHS 2020	6	38	7	35	24.9%	0.79 [0.29 , 2.12]
Qian 2021	2	71	1	68	4.3%	1.92 [0.18 , 20.64]
Total (95% CI)		**171**		**162**	**100.0%**	**0.84 [0.51 , 1.37]**
Total events:	21		23			

Heterogeneity: Tau² = 0.00; Chi² = 0.90, df = 3 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.70 (P = 0.49)

Test for subgroup differences: Not applicable

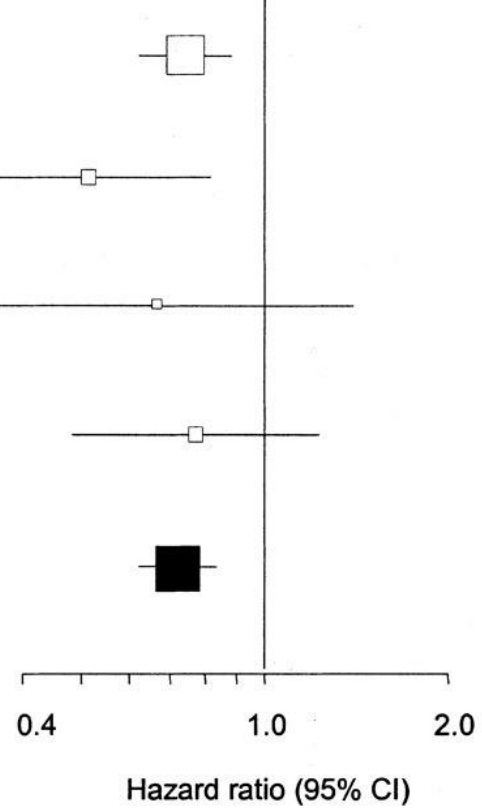




Secondary prevention: BP lowering reduced recurrent stroke after ICH in PROGRESS

The George Institute for Global Health

Qualifying event	Number of events/ total participants active	placebo	Favours perindopril ± indapamide	Favours placebo	Risk Reduction (95%CI)
All Ischemic	229/2135	302/2127			26% (12 to 38%)
Hemorrhagic	32/306	54/305			49% (18 to 68%)
Stroke of Unknown Type	13/119	21/132			33% (-36 to 67%)
TIA	33/491	43/490			23% (-23 to 52%)
OVERALL	**307/3051**	**420/3054**			**28% (17 to 38%)**

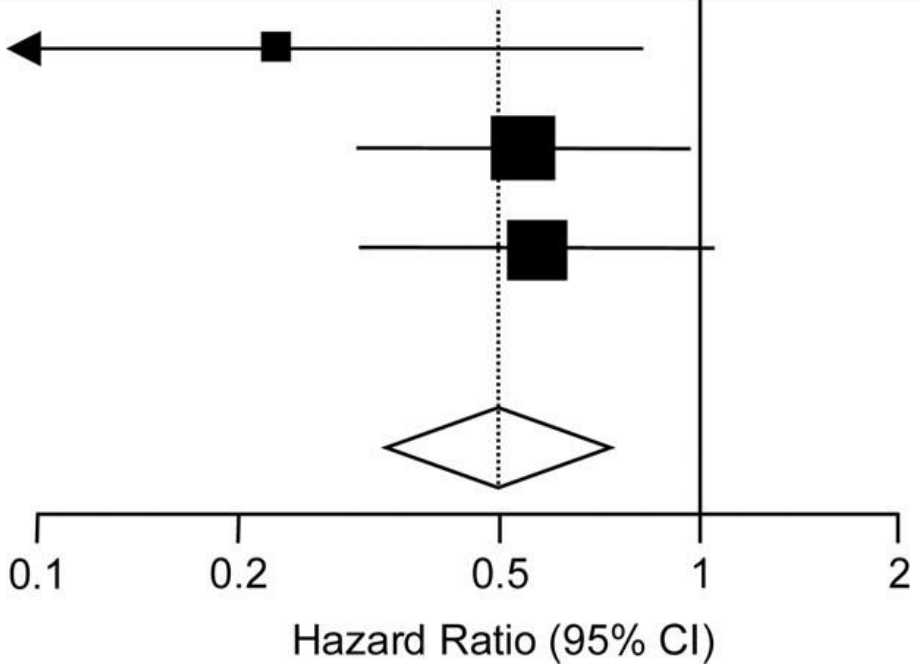


Lancet 2001;358:1033, *Stroke* 2004;35:116

Secondary prevention: BP lowering reduced recurrent stroke, regardless of ICH sub-type

The George Institute for Global Health

	Number of Events		Risk Reduction
	Active	Placebo	(95% CI)
Probable CAA-related ICH	3	13	77% (19 to 93%)
Probable HT-related ICH	18	33	46% (4 to 69%)
Unclassified ICH	16	28	43% (-5 to 69%)
$p_{heterogeneity}$=0.4			
Overall	37	74	50% (26 to 67%)



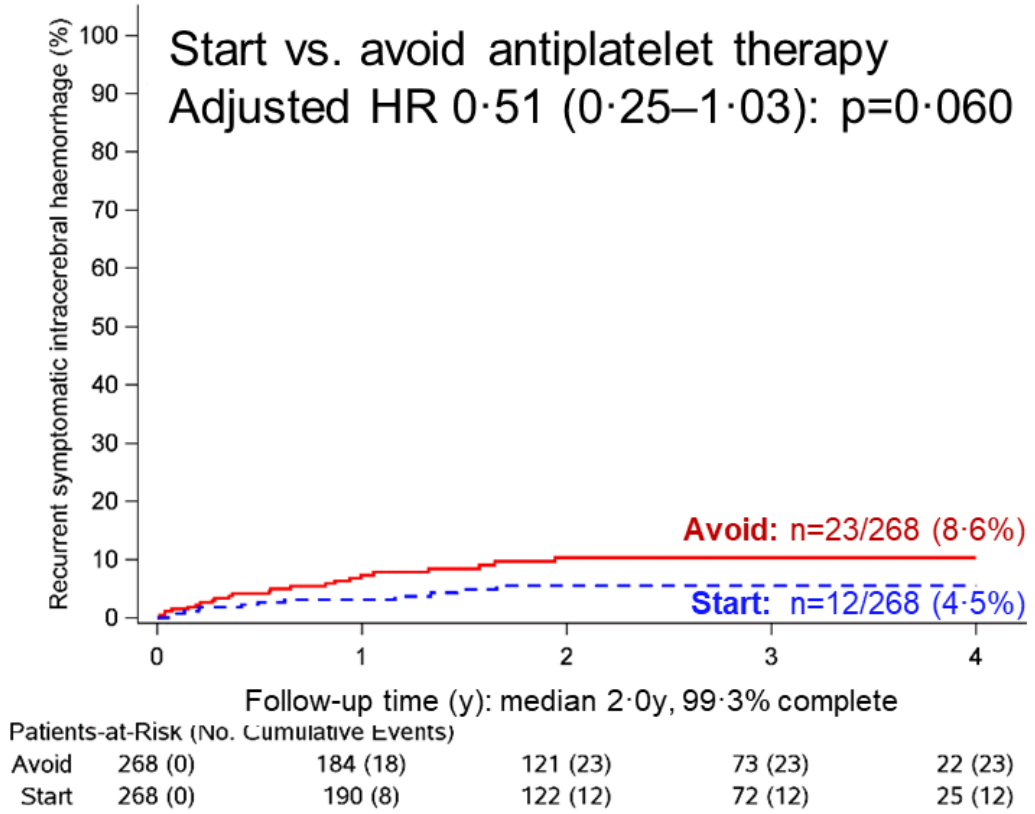
Stroke 2010;41:394-6

Start vs. avoid antiplatelet agents after ICH

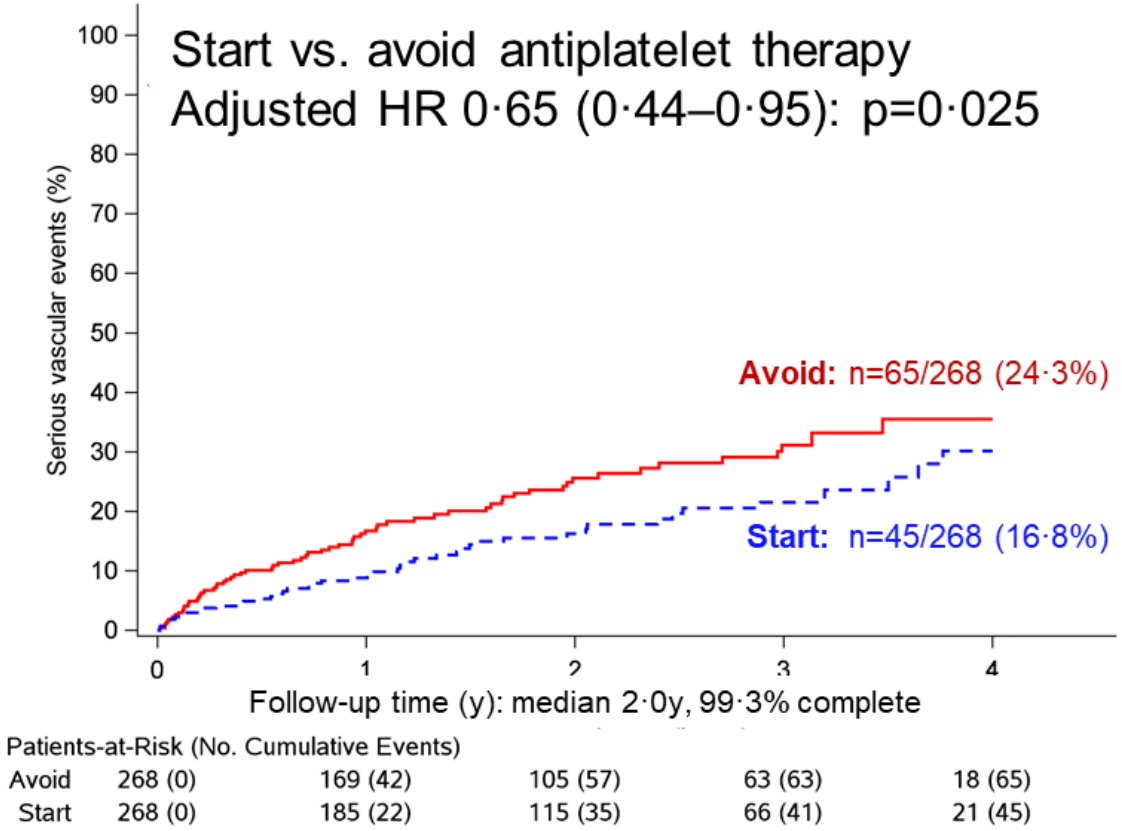
REstart or STop Antithrombotics Randomised Trial

Research to Understand Stroke due to Haemorrhage

Primary outcome: recurrent ICH

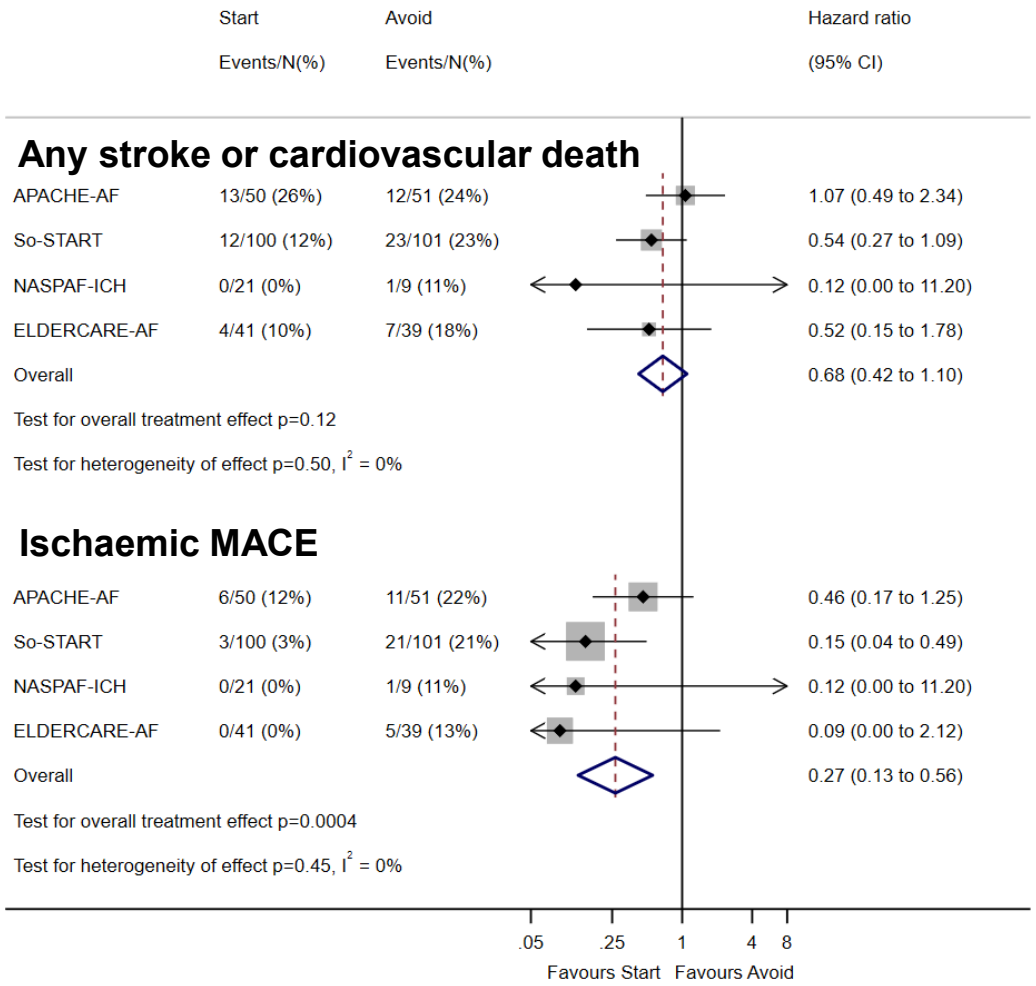


MACE



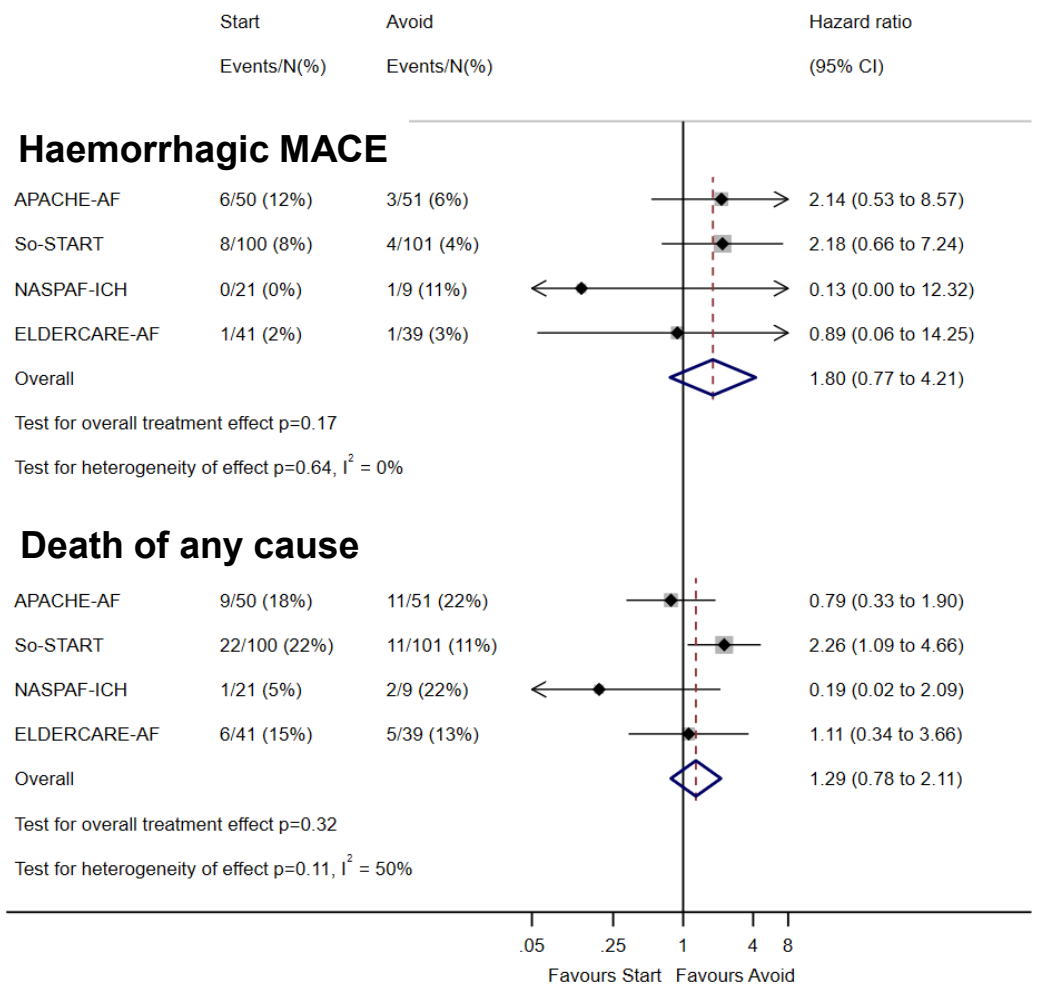
Lancet 2019;393:2613-23

Start vs avoid oral anticoagulation (OAC) for AF after ICrH



Lancet Neurol 2023;22:1140-49

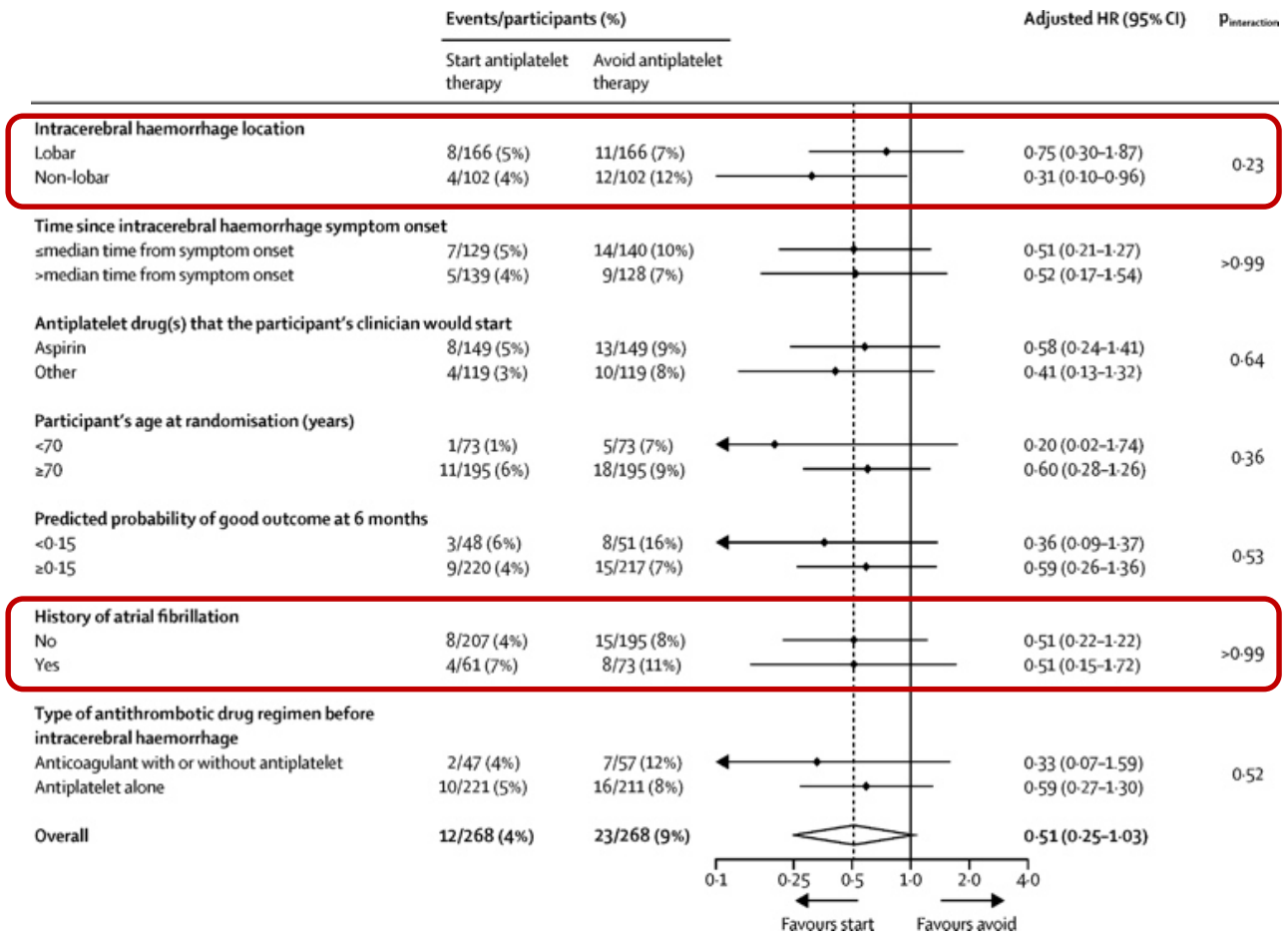
Start vs avoid OAC for AF after ICrH



Lancet Neurol 2023;22:1140-49


Risks
Risk factors
Treatment effects
Heterogeneity
of treatment effect

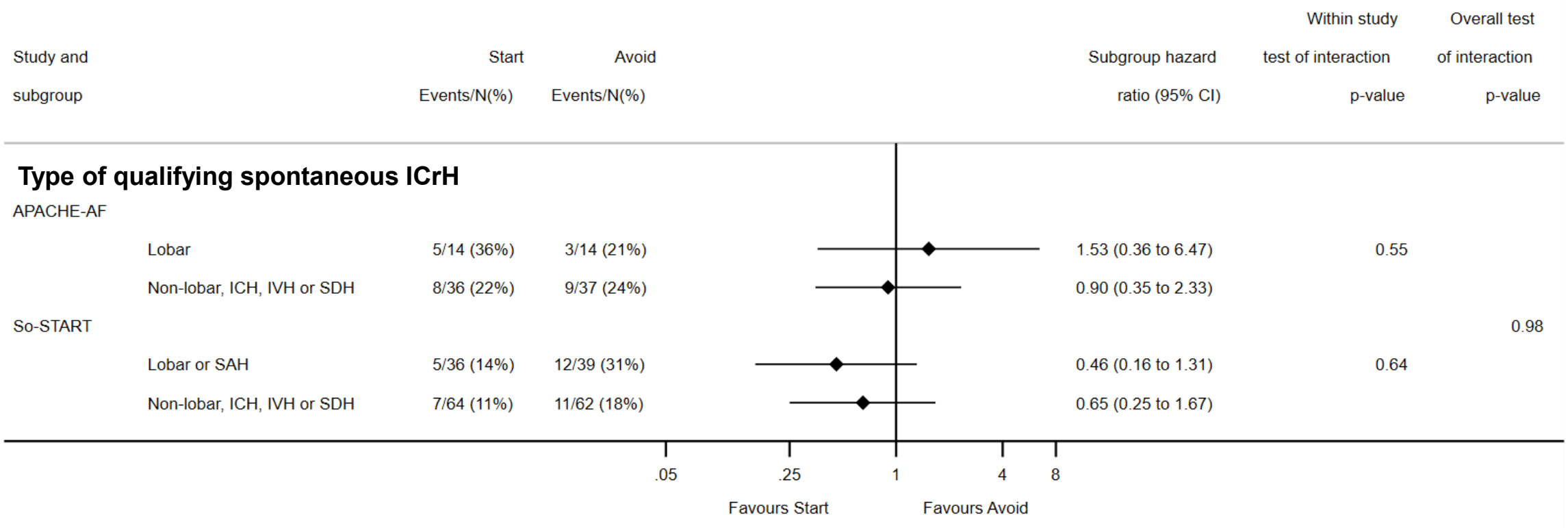
Antiplatelet agent effects on recurrent ICH in sub-groups



Lancet 2019;393:2613-23

OAC for AF after ICrH effects on stroke / cardiovascular death in sub-groups

Research to Understand Stroke due to Haemorrhage



Lancet Neurol 2023;22:1140-49

OAC for AF after lobar ICH / convexity SAH in the ongoing ENRICH-AF trial

Anticoagulation in patients with cerebral amyloid angiopathy

Survivors of intracranial haemorrhage with atrial fibrillation are a population that have a heightened risk of future ischaemic stroke and recurrent intracranial haemorrhage.[1] In the absence of definitive randomised evidence to guide antithrombotic prophylaxis in these patients, current guidelines recommend individualised decisions that weigh a patient's absolute risks of thromboembolism and recurrent haemorrhage.[2] Intracranial haemorrhage can occur from different underlying causes, with different rates of disease progression

with non-anticoagulant medical treatment for stroke prevention in survivors of intracranial haemorrhage with atrial fibrillation. ENRICH-AF is currently enrolling patients at 239 hospitals in 20 countries. Following a safety review of the first 699 patients (174 [25%] of 699 with lobar intracranial haemorrhage and 34 [5%] of 699 with convexity subarachnoid haemorrhage), the ENRICH-AF data safety monitoring board (DSMB) recommended that participants with lobar intracranial haemorrhage and convexity subarachnoid haemorrhage stop receiving the drug as soon as possible and that no further patients with these intracranial haemorrhage subtypes be enrolled. The DSMB indicated that

convexity subarachnoid haemorrhage with atrial fibrillation outside of ongoing randomised trials until more data become available on the net benefit of anticoagulation in these high-risk subgroups of patients.

AS reports research funding from the National Institutes of Health, Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Brain Canada, British Heart Foundation, Medical Research Future Fund, Marta and Owen Boris Foundation, Daiichi Sankyo, Bayer, Servier Canada, and Octapharma; and reports consultancy honoraria from AstraZeneca, Bayer AG, Bioxodes, Daiichi Sankyo, Servier Canada, and Takeda Pharmaceuticals. The ENRICH-AF trial is an investigator initiated study that is supported by an unrestricted grant-in-aid from Daiichi Sankyo Company. *Members of the ENRICH-AF Steering Committee are listed in the appendix.

*Ashkan Shoamanesh, on behalf of the *ENRICH-AF Steering Committee*
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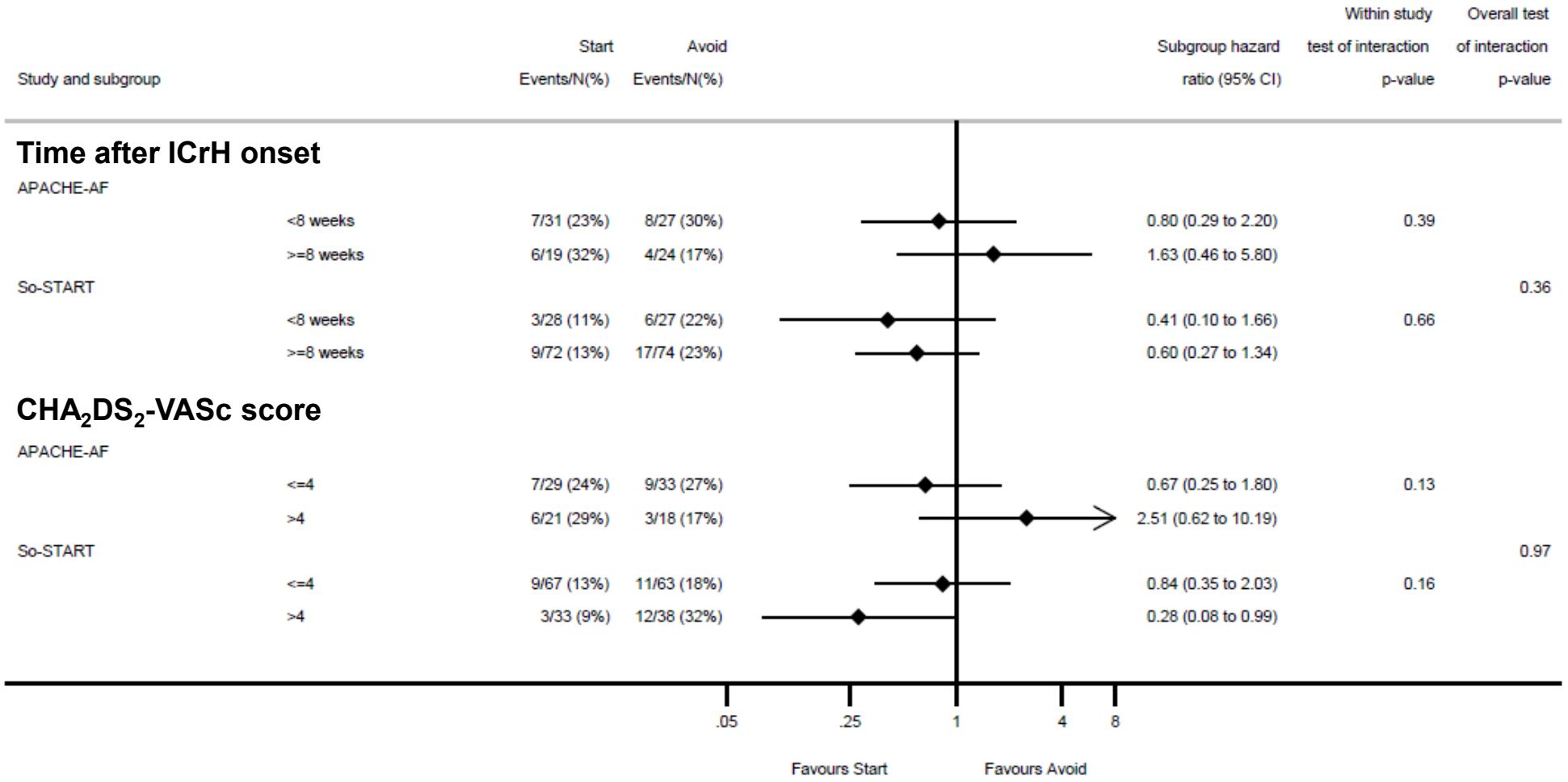
OAC for AF after ICrH effects on stroke / cardiovascular death in sub-groups

Research to Understand Stroke due to Haemorrhage



Lancet Neurol 2023;22:1140-49

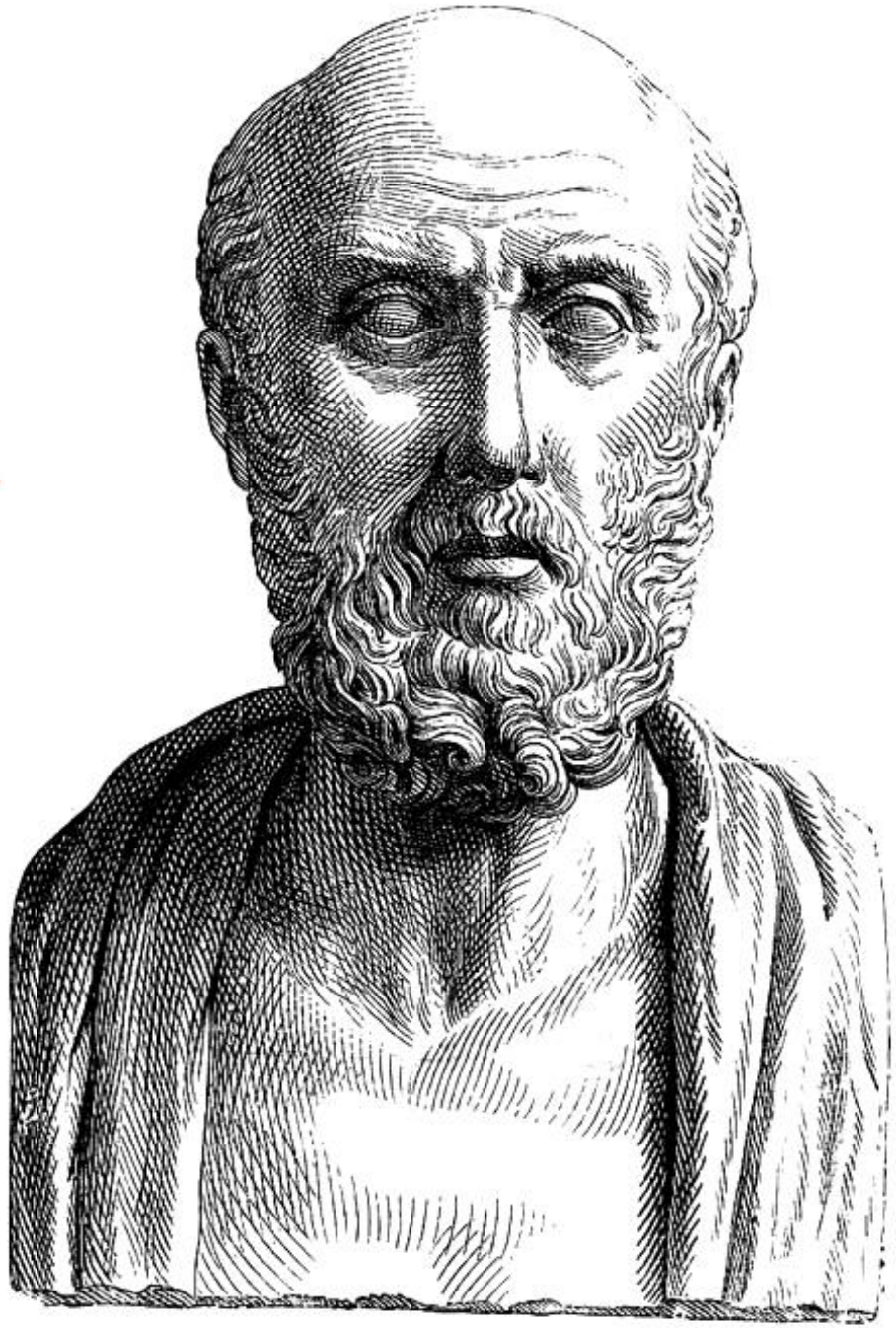

Risks


Risk factors


Treatment effects


Heterogeneity
of treatment effect

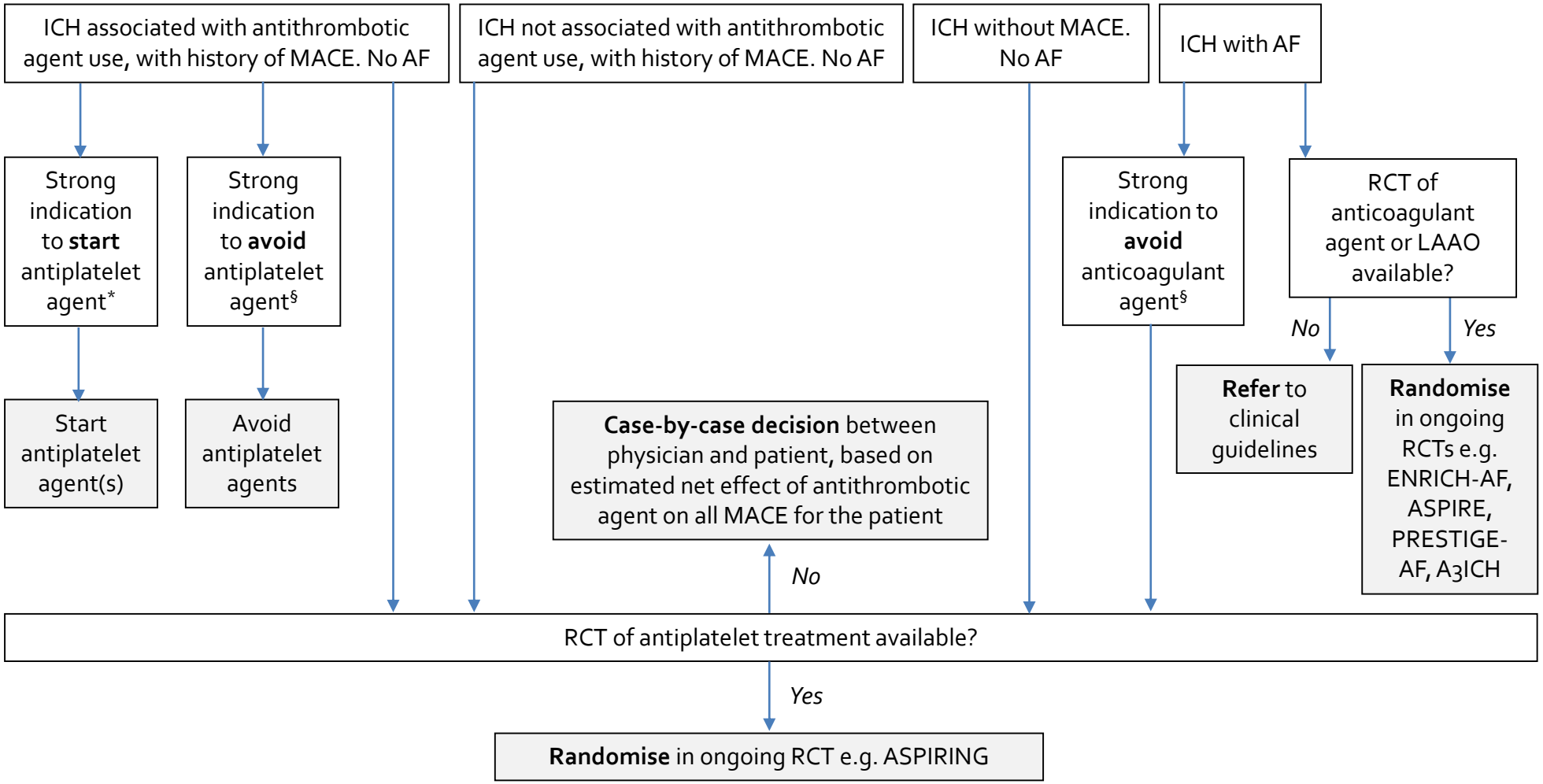
Let’s be definitive…



…not defensive

What should you do about antiplatelet drugs after ICH in your clinical practice today?

Research to Understand Stroke due to Haemorrhage

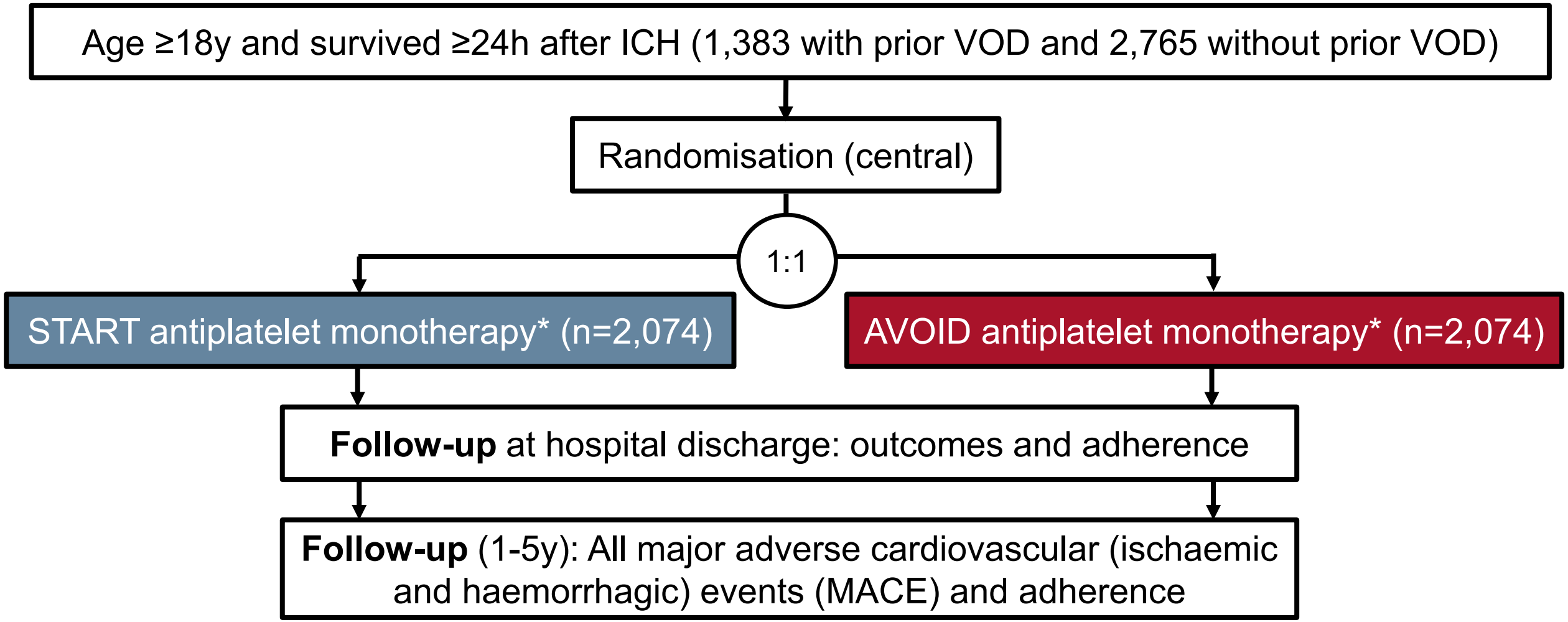


Stroke 2023;54:3173-81

Definitive ICH trial of antiplatelet agents

ASPIRING
Antiplatelet Secondary Prevention International Randomised study after INtracerebral haemorrhaGe

Research to Understand Stroke due to Haemorrhage



www.isrctn.com/ISRCTN16705062

What should you do about OAC for AF after ICH in your clinical practice today?

American Heart Association | American Stroke Association

2b	B-NR	3. In patients with nonvalvular atrial fibrillation (AF) and spontaneous ICH, the resumption of anticoagulation to prevent thromboembolic events and reduce all-cause mortality may be considered based on weighing benefit and risk.[590–595]
2b	C-LD	4. In patients with AF and spontaneous ICH in whom the decision is made to restart anticoagulation, initiation of anticoagulation ≈7 to 8 weeks after ICH may be considered after weighing specific patient characteristics to optimize the balance of risks and benefits.[596,597]
2b	C-LD	5. In patients with AF and spontaneous ICH deemed ineligible for anticoagulation, left atrial appendage closure may be considered to reduce the risk of thromboembolic events.[598–602]

National Clinical Guideline for Stroke for the UK & Ireland

- Patients with lobar ICH associated with probable CAA and AF may be considered for OAC for stroke prevention, but wherever possible patients should be offered participation in a randomised trial. If participation in a randomised trial is not possible then clinicians should make an individualised decision based on estimates of the future risks of recurrent ICH and vaso-occlusive events.
- Patients with lobar ICH associated with probable CAA and AF may be considered for a left atrial appendage occlusion (LAAO) device, but wherever possible patients should be offered participation in a randomised trial. If participation in a randomised trial is not possible then LAAO may be considered based on an estimation of the future risks of recurrent ICH and vaso-occlusive events.

Stroke 2022;53:e282–e361

www.strokeguideline.org, 2023

RCTs of OAC for AF after ICrH

Research to Understand Stroke due to Haemorrhage

RCT	Stroke type(s)	Intervention vs. comparator	Recruited / target	Contact
A_3ICH	ICH	Apixaban *vs* LAAO *vs* no antithrombotic therapy	117/300 (39%)	Cordonnier
PRESTIGE-AF	ICH	DOAC *vs* no OAC	319/350 (81%)	Veltkamp
ASPIRE	ICH	Apixaban *vs* aspirin	331/700 (47%)	Sheth/Kamel
ENRICH-AF	ICrH	Edoxaban *vs* no OAC	919/950 (97%)	Shoamanesh

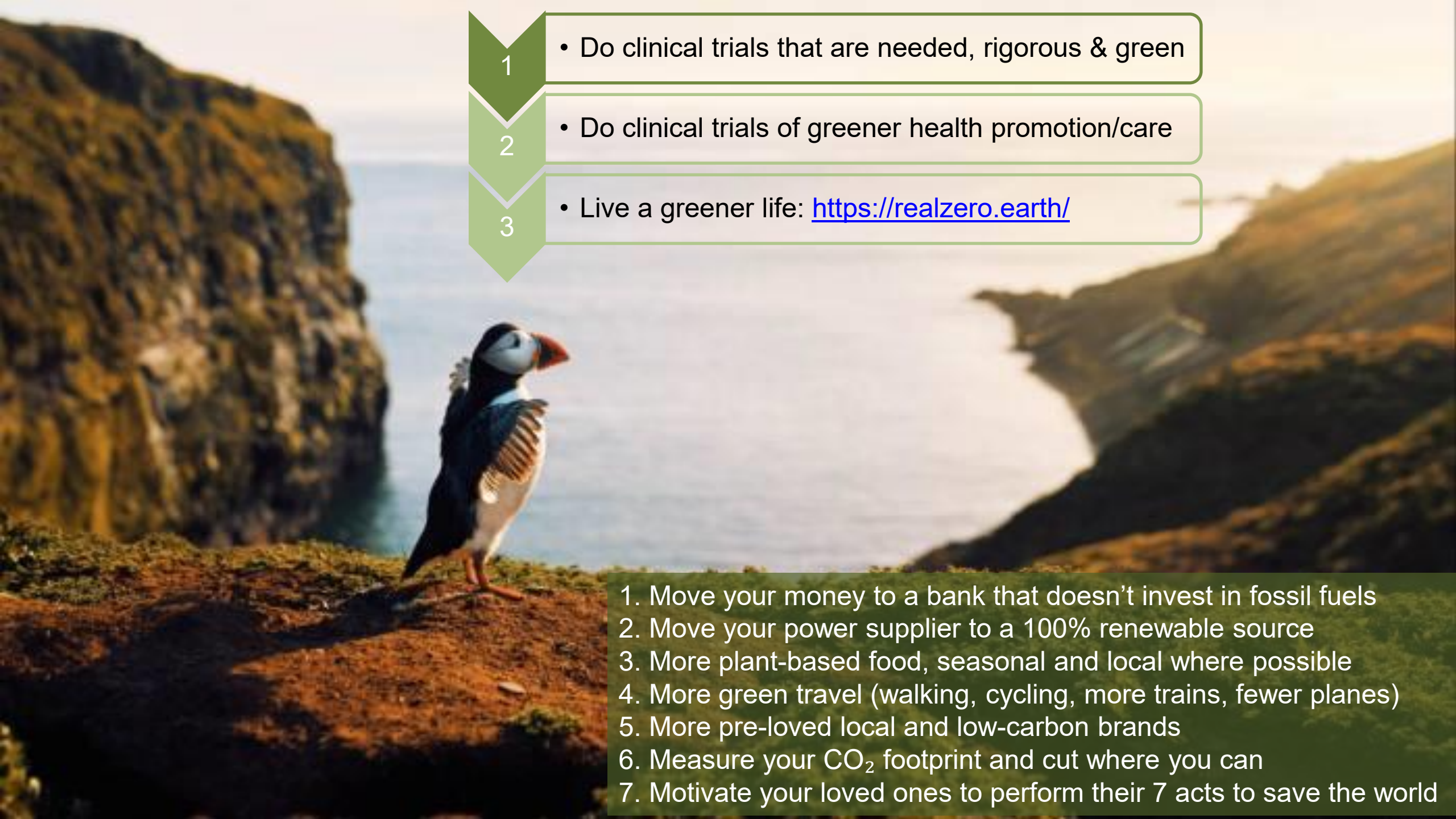
Recruitment as of October 2024


Risks


Risk factors


Treatment effects


Heterogeneity
of treatment effect



1. • Do clinical trials that are needed, rigorous & green
2. • Do clinical trials of greener health promotion/care
3. • Live a greener life: https://realzero.earth/

1. Move your money to a bank that doesn't invest in fossil fuels
2. Move your power supplier to a 100% renewable source
3. More plant-based food, seasonal and local where possible
4. More green travel (walking, cycling, more trains, fewer planes)
5. More pre-loved local and low-carbon brands
6. Measure your CO_2 footprint and cut where you can
7. Motivate your loved ones to perform their 7 acts to save the world

Contact/follow us

Research to Understand Stroke due to Haemorrhage

Clinical care and audit

NHS Lothian

Research

THE UNIVERSITY of EDINBURGH

Scottish Intracranial Vascular Malformation Study SIVMS

LINCHPIN

RESTART?

SoSTART?

CareTrial
CAVERNOMAS: A RANDOMISED EFFECTIVENESS TRIAL

PLINTH
PLATFORM STUDY FOR INTRACEREBRAL HAEMORRHAGE

ASPIRING
Antiplatelet Secondary Prevention International Randomised study after INtracerebral haemorrhaGe

Education & teaching

Neurology Statistics Nursing Radiology Neurosurgery

Public engagement

www.RUSH.ed.ac.uk

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