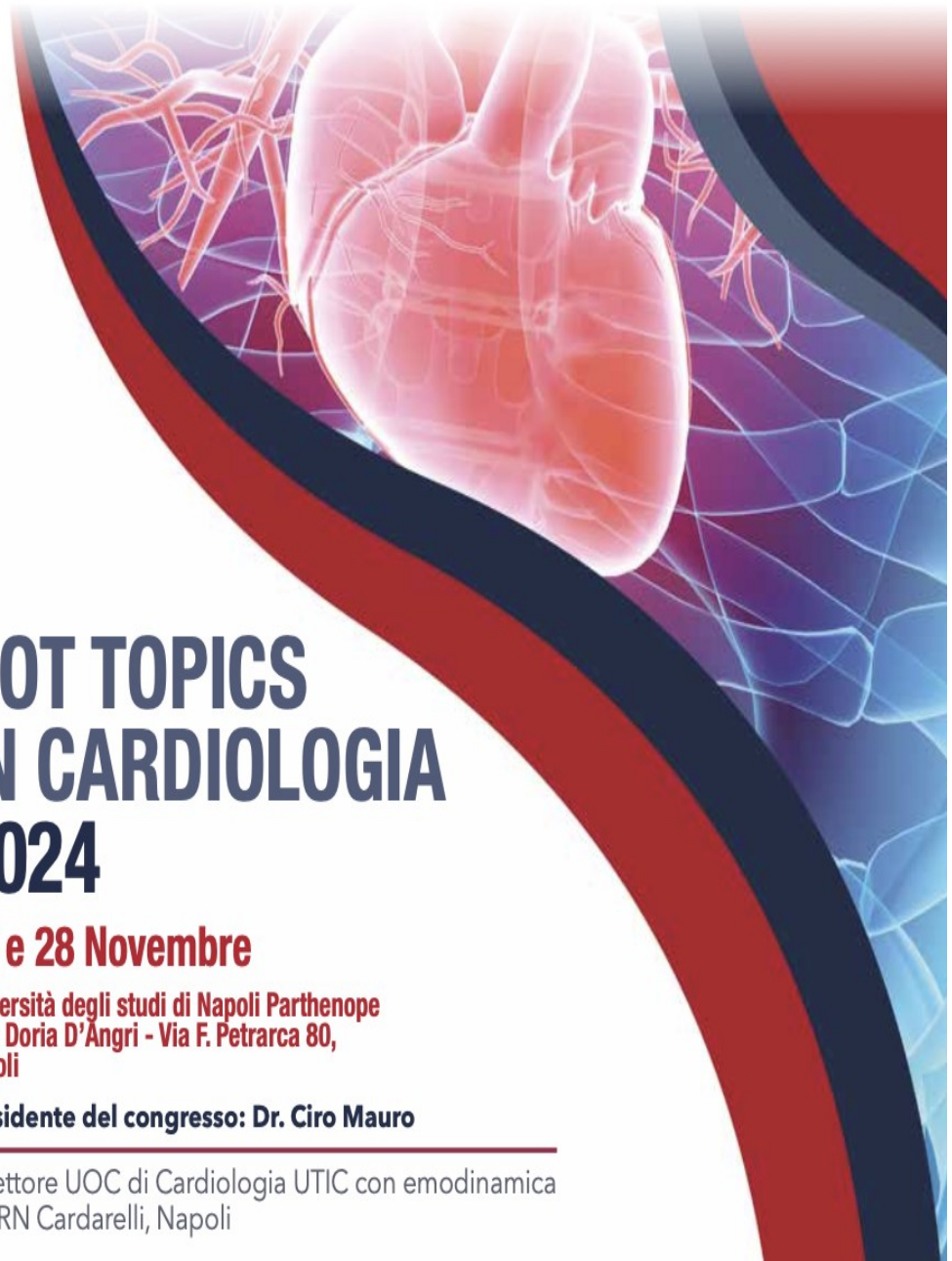


Il rischio emorragico nel paziente candidato a terapia anti-trombotica in Stroke Unit

Paolo Candelaresi
Responsabile UOS Stroke Unit
AORN Cardarelli, Napoli
UOC Neurologia e Stroke Unit
Direttore: Dr V. Andreone

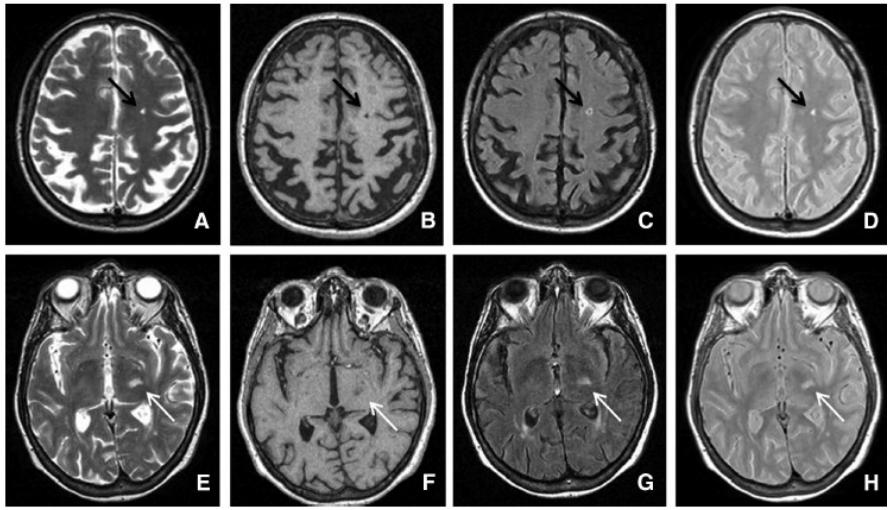
DISCLOSURES

- Member of the Cochrane Italian Neurological Field – Stroke
- Local Principal Investigator for the PRESTIGE-AF trial
- Member of the Italian Working Group on ICH guidelines

PRIMARY PREVENTION

Antiplatelet therapy

- Recent trials in important patient groups, including elderly and people with diabetes (i.e. ASPREE) have not shown benefit for primary stroke prevention with aspirin. Moreover, in patients ≥ 70 years of age, a small increase in intracranial bleeding was found.
- In adults with covert small vessel disease, the benefit of antiplatelet therapy to reduce the risk of ischemic stroke is uncertain.



Zhu YC et al. Stroke. 2011

AHA/ASA GUIDELINE

Recommendations for Antiplatelet Use for Primary Prevention

COR	LOE	Recommendations
2b	A	1. In patients with diabetes or other common vascular risk factors and no prior stroke, the use of aspirin to prevent a first stroke is not well established.[727–731]
2b	B-R	2. In patients with established, stable coronary artery disease and a low bleeding risk, the addition of ticagrelor to aspirin beyond 12 months for a period up to 3 years may be beneficial to reduce the rate of ischemic stroke.[732]
3: No Benefit	A	3. In individuals ≥70 years of age with at least 1 additional cardiovascular risk factor, the use of aspirin is not beneficial to prevent a first stroke.[360,733]
3: No Benefit	B-NR	4. In patients with chronic kidney disease, the use of aspirin is not effective to prevent a first stroke.[734]

Guideline

ESO Guideline on covert cerebral small vessel disease

EUROPEAN STROKE JOURNAL

Evidence-based Recommendation

We suggest against antiplatelet treatment in patients with ccSVD as a means to reduce the clinical outcome events of ischaemic or haemorrhagic strokes, cognitive decline or dementia, dependency, death, MACE, mobility, or mood disorders.
Quality of evidence: Very low⊕
Strength of recommendation: Weak against intervention ↓?

Expert Consensus Statement

Most group members agreed that:
- We advise against use of antiplatelet drugs to prevent clinical outcomes in subjects with ccSVD when no other indication for this treatment exists.
- With current available knowledge, the use of antiplatelet drugs to prevent progression of cerebral SVD may be harmful in older patients (from around ≥70 years of age) if no other indication for this treatment exists.

TIMING OF ANTICOAGULATION AFTER ISCHEMIC STROKE

Preliminary considerations

- About 20–30% of all ischaemic strokes are related to atrial fibrillation.
- The risk of recurrence in the first 14 days after cardioembolic stroke is 0.5-1.3% per day without anticoagulation.
- Anticoagulation has been thought to increase the risk of haemorrhagic transformation on the basis of RCT focused on heparin treatment vs aspirin and/or placebo (IST, TOAST, HAEST) and observational studies (RAF, RAF-NOACs).
- Risk factors could be used to estimate the risk of ischemic recurrence, including ALESSA score.

ESC European Society of Cardiology

American Heart Association.

ESO EUROPEAN STROKE ORGANISATION

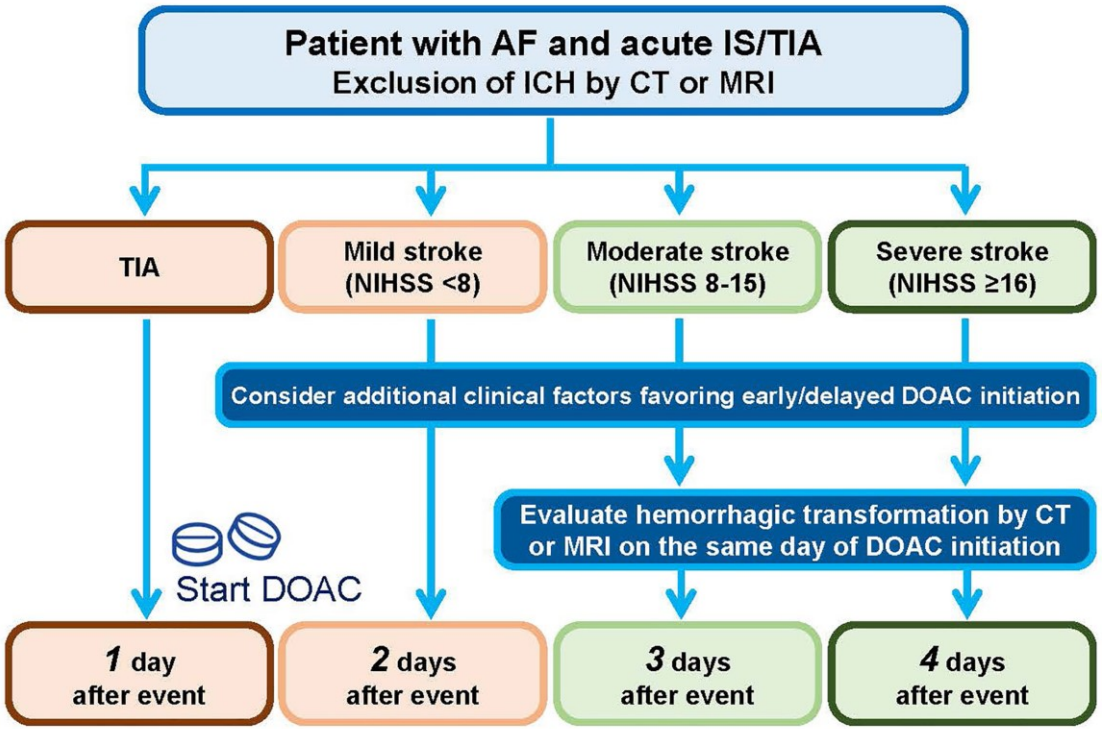
Reference		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 12	Day 14	
Guidelines	ESC 2016[9]	TIA		Mild AIS			Moderate AIS		Severe AIS		
	AHA/ASA 2019[11]				All AIS						
	ESO 2019[40]			Mild AIS and small infarct size				Moderate AIS and medium infarct size		Severe AIS and large infarct size	

Seiffge DJ et al. Lancet Neurol 2019
Seiffge DJ et al. Lancet Neurol 2024
Paciaroni M et al. Stroke 2007
Paciaroni M et al. J Am Heart Assoc 2017

TIMING OF ANTICOAGULATION AFTER ISCHEMIC STROKE

Prospective observational studies

SAMURAI NVAF RELAXED



	Early group N (%)	Late group N (%)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)	*P* value
Derivation cohort	N=785	N=1012			
Stroke/systemic embolism	15 (1.9)	39 (3.9)	0.49 (0.26–0.87)	0.50 (0.27–0.89)	0.019
Ischemic stroke	13 (1.7)	32 (3.2)	0.52 (0.26–0.96)	0.54 (0.27–0.999)	0.0497
Death	15 (1.9)	15 (1.5)	1.30 (0.63–2.67)	1.40 (0.68–2.89)	0.362
Major bleeding	6 (0.8)	10 (1.0)	0.77 (0.26–2.08)	0.81 (0.28–2.19)	0.687
Intracranial hemorrhage	2 (0.3)	4 (0.4)	0.64 (0.09–3.30)	0.66 (0.09–3.39)	0.623
Validation cohort	N=547	N=1489			
Ischemic stroke	13 (2.4)	33 (2.2)	1.07 (0.55–1.99)	1.07 (0.54–2.00)	0.828
Death	12 (2.2)	32 (2.2)	1.01 (0.50–1.92)	1.07 (0.53–2.03)	0.847
Intracranial hemorrhage	1 (0.2)	9 (0.6)	0.30 (0.02–1.61)	0.31 (0.02–1.65)	0.195

- Combined data from two registries in Japan (SAMURAI-NVAF and RELAXED). External validation using known European registries.
- DOAC initiation within 1 day after TIA, 2 days after mild stroke (NIHSS <8), 3 days after moderate stroke (NIHSS 8–15), and 4 days after severe stroke (NIHSS >15) was associated with better efficacy and similar safety compared with later initiation.

Yoshimura S. Circ J 2018
Yasaka M. Plos One 2019

TIMING OF ANTICOAGULATION AFTER ISCHEMIC STROKE

RCTs on early anticoagulation

TIMING

ELAN EARLY LATE

OPTIMAS OPTIMAL TIMING OF ANTICOAGULATION AFTER STROKE

START

	TIMING (NCT		(NCT03021928)
Status	Completed		tment completed, results presented International Stroke Conference (Feb 7, 2024, Phoenix, AZ, USA), t published
Sample size	888 participa		f 1500 planned participants patients with mild or moderate and 500 with severe stroke)
Early start group	≤4 days after stroke		to-treatment delay of 3, 6, 10, days for mild or moderate stroke; 14, or 21 days for severe stroke
Late start group	5–10 days aft stroke		to-treatment delay of 3, 6, 10, days for mild or moderate stroke; 14, or 21 days for severe stroke
Primary outcome	Composite ou ischaemic str intracerebral or all-cause m		osite of any CNS haemorrhagic or major haemorrhagic events and the mic events of stroke or systemic lism within 30 days of the index
Time of assessment	90 days		ys
Inclusion of patients with haemorrhagic transformation	Not reported		investigator's judgement
Inclusion of patients with severe stroke	Yes (79 [9%]		ion of patients with >50% infarct e in the middle cerebral artery ory
Inclusion of patients on anticoagulation	Yes, if stoppe index stroke for VKA		

Optimal timing of anticoagulation after acute ischaemic stroke with atrial fibrillation (OPTIMAS): a multicentre, blinded-endpoint, phase 4, randomised controlled trial

David J Werring, Hakim-Moulay Dehbi, Norin Ahmed, Liz Arram, Jonathan G Best, Maryam Balogun, Kate Bennett, Ekaterina Bordea, Emilia Caverly, Marisa Chau, Hannah Cohen, Mairead Cullen, Caroline J Doré, Stefan T Engelter, Robert Fenner, Gary A Ford, Aneet Gill, Rachael Hunter, Martin James, Archana Jayanthi, Gregory Y H Lip, Sue Massingham, Macey L Murray, Iwona Mazurczak, Philip S Nash, Amalia Ndoutoumou, Bo Norrving, Hannah Sims, Nikola Sprigg, Tishok Vanniyasingam, Nick Freemantle, on behalf of the OPTIMAS investigators*

	Early initiation (n=1814)	Delayed initiation (n=1807)	Adjusted risk difference (95% CI)	p value
Primary outcome*	59 (3·3%)	59 (3·3%)	0·000 (–0·011 to 0·012)	0·96
Recurrent ischaemic stroke	44 (2·4%)	42 (2·3%)	–0·001 (–0·011 to 0·009)	0·84
Symptomatic intracranial haemorrhage	11 (0·6%)	12 (0·7%)	0·001 (–0·004 to 0·006)	0·78
Systemic embolism	2 (0·1%)	4 (0·2%)	0·001 (–0·002 to 0·004)	0·40
Unclassifiable stroke	3 (0·2%)	2 (0·1%)	–0·001 (–0·003 to 0·002)	0·66
All-cause mortality	159 (8·8%)	160 (8·9%)	0·002 (–0·015 to 0·019)	0·83
Primary outcome and mortality	196 (10·8%)	190 (10·5%)	–0·001 (–0·021 to 0·018)	0·88
Major extracranial bleeding	7 (0·4%)	13 (0·7%)	0·004 (–0·001 to 0·009)	0·16
Non-major extracranial bleeding	45 (2·5%)	37 (2·0%)	–0·004 (–0·014 to 0·006)	0·42
All major bleeding (extracranial and intracranial)	18 (1·0%)	25 (1·4%)	0·004 (–0·003 to 0·011)	0·24
Venous thromboembolism	7 (0·4%)	10 (0·6%)	0·002 (–0·003 to 0·006)	0·46

Data are n (%) unless otherwise specified. Risk difference estimates and p values are adjusted for stroke severity (assessed with National Institutes of Health Stroke Scale score) at randomisation. *Composite of recurrent ischaemic stroke, unclassifiable stroke, symptomatic intracranial haemorrhage, and systemic embolism at 90 days.

Table 2: **First occurrence of outcome events during follow-up in the modified intention-to-treat population**

Seiffge DJ et al. Lancet Neurol 2024
Werring DJ et. Lancet Neurol 2024

TIMING OF ANTICOAGULATION AFTER ISCHEMIC STROKE

RCTs on early anticoagulation

World Stroke Organization

CATALYST
CollAboration on the optimal Timing of anticoagulation after ischaemic stroke and Atrial fibrillation: prospective individuaL participant data meta-analYsiS (IPDMA) of randomized controlled Trials

- The design of these trials varies, but similar outcomes will allow meta-analysis of RCTs (CATALYST).
- Preliminary results have been recently presented at the 16th World Stroke Congress.

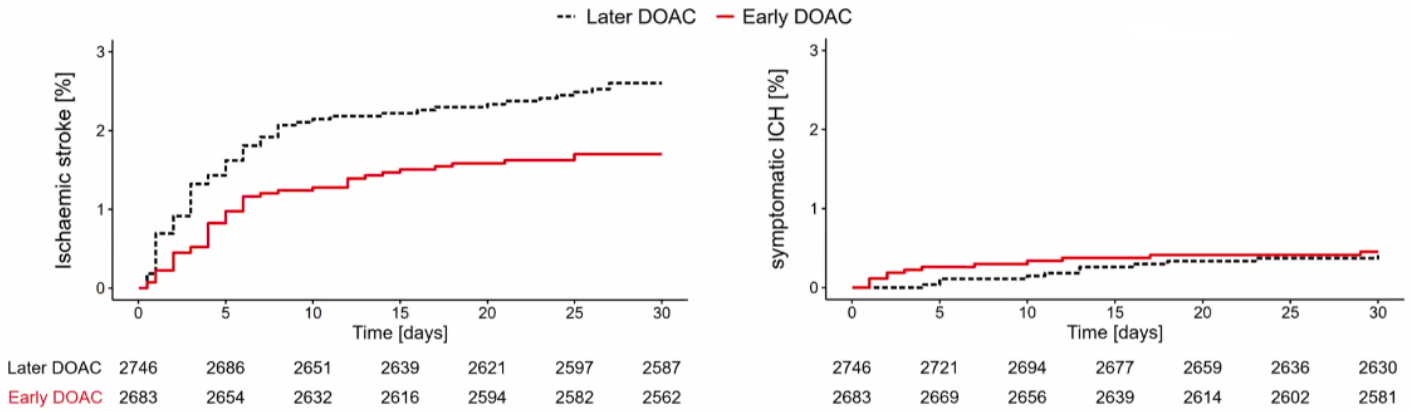
Timing of DOAC initiation
- Early: within 4 days
- Later: 5 days or more

Primary outcome at 30 days

Composite of:
- recurrent ischaemic stroke,
- symptomatic intracerebral haemorrhage, or
- unclassified stroke

→
- TIMING n=886 patients: ≤ 4 days vs 5-10 days
- ELAN n=754 patients with moderate strokes: ≤ 2 days vs 6-7 days
- OPTIMAS n=3621 patients: ≤ 4 days vs 7-14 days
- START n=180 patients: day 3 vs 6-14 day

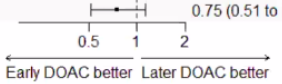
Primary outcome at 30 days



Primary outcome	Early DOAC	Later DOAC	OR (95% CI)	P-value
Ischaemic stroke, symptomatic ICH, unclassified stroke	57 (2.12%)	83 (3.02%)	0.70 (0.50 – 0.98)	0.04
Ischaemic stroke	45 (1.68%)	70 (2.55%)	0.66 (0.45 – 0.96)	0.03
Symptomatic ICH	12 (0.45%)	11 (0.40%)	1.12 (0.49 – 2.54)	0.79

Subgroups

Subgroup	Early DOAC sample size	Early DOAC # outcomes	Later DOAC sample size	Later DOAC # outcomes	OR (95% CI)	Interaction p-value
All patients	2683	57	2746	83	0.70 (0.50 to 0.98)	
NIHSS score						0.54
0-4	1129	24	1194	31	0.82 (0.48 to 1.40)	
5-10	861	17	885	29	0.60 (0.33 to 1.09)	
11-15	342	11	306	13	0.75 (0.33 to 1.70)	
16+	335	5	337	9	0.55 (0.18 to 1.67)	
Reperfusion treatment						0.36
No	1800	43	548	57	0.77 (0.52 to 1.15)	
Yes	879	14	884	26	0.54 (0.28 to 1.04)	
Prior anticoagulation						0.89
No	1762	33	1714	44	0.72 (0.46 to 1.14)	
Yes	872	23	901	31	0.76 (0.44 to 1.31)	
Sex						0.75
Female	1223	32	1244	44	0.73 (0.46 to 1.16)	
Male	1460	25	1502	39	0.66 (0.39 to 1.09)	
Age						0.46
≤ 75	971	13	1008	24	0.56 (0.28 to 1.10)	
> 75	1712	44	1738	59	0.75 (0.51 to 1.12)	



STROKE PREVENTION

2024 ESC Guidelines

ESC European Society of Cardiology
European Heart Journal (2024) 45, 3314–3414
https://doi.org/10.1093/eurheartj/ehae176

2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS)

Stroke risk

Initiating oral anticoagulation—*Section 6.1*		
Oral anticoagulation is recommended in patients with clinical AF at elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism.	I	A
A CHA_2DS_2-VA score of 2 or more is recommended as an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	I	C
A CHA_2DS_2-VA score of 1 should be considered an indicator of elevated thromboembolic risk for decisions on initiating oral anticoagulation.	IIa	C
Oral anticoagulation is recommended in all patients with AF and hypertrophic cardiomyopathy or cardiac amyloidosis, regardless of CHA_2DS_2-VA score, to prevent ischaemic stroke and thromboembolism.	I	B
Individualized reassessment of thromboembolic risk is recommended at periodic intervals in patients with AF to ensure anticoagulation is started in appropriate patients.	I	B
Direct oral anticoagulant therapy may be considered in patients with asymptomatic device-detected subclinical AF and elevated thromboembolic risk to prevent ischaemic stroke and thromboembolism, excluding patients at high risk of bleeding.	IIb	B

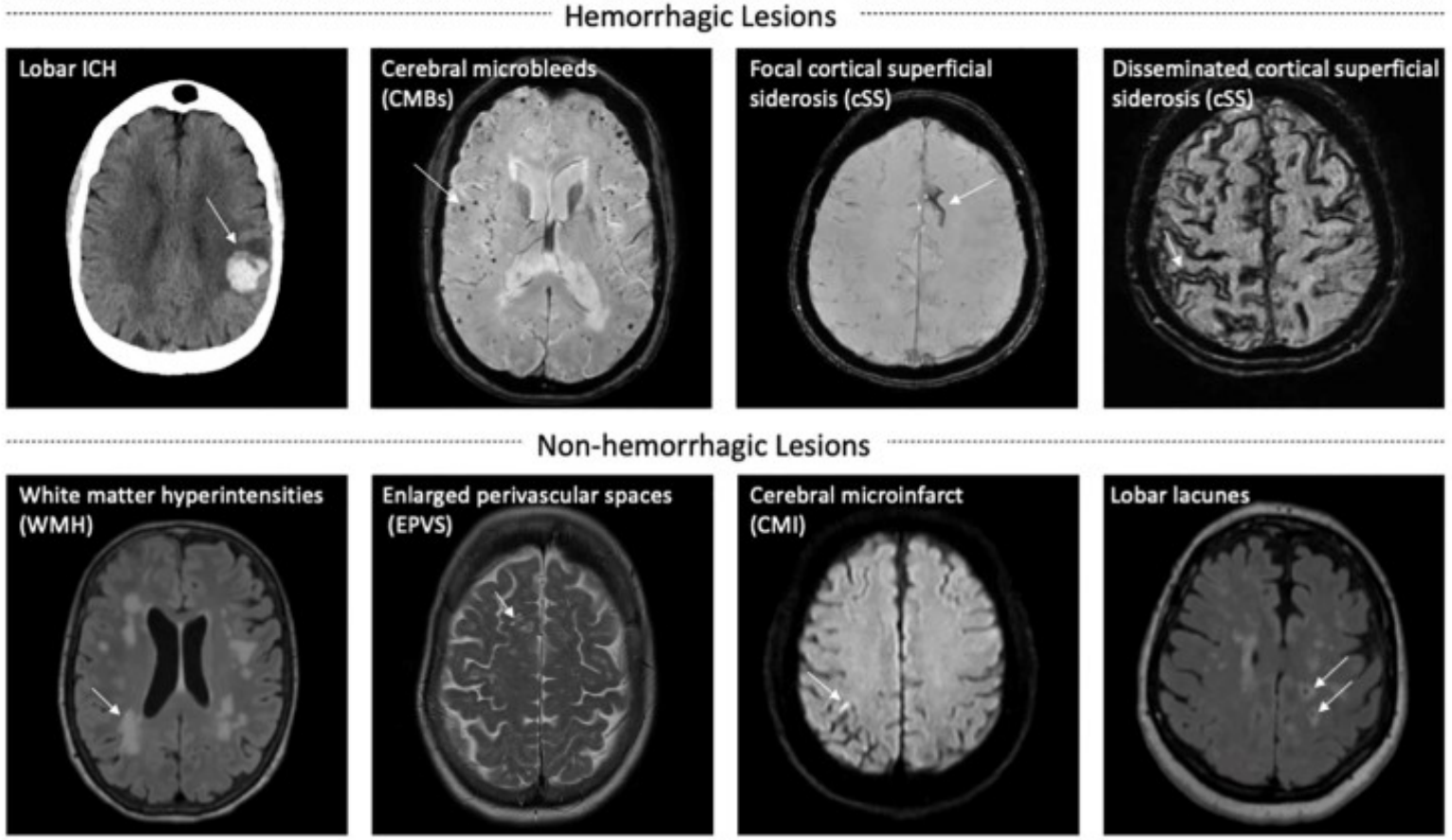
Bleeding risk

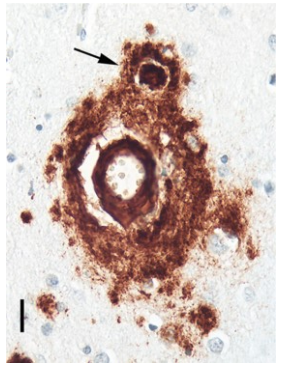
Recommendations	Class[a]	Level[b]
Assessment and management of modifiable bleeding risk factors is recommended in all patients eligible for oral anticoagulation, as part of shared decision-making to ensure safety and prevent bleeding.[439–444]	I	B
Use of bleeding risk scores to decide on starting or withdrawing oral anticoagulation is not recommended in patients with AF to avoid under-use of anticoagulation.[431,445,446]	III	B

STROKE PREVENTION

Bleeding Risk

- CAA is the second most common cause of cerebral small vessel disease
- CMBs are usually a sign of cerebral small vessel disease such as hypertensive microangiopathy or CAA
- People with CAA are at risk for future ICH as well as ischemic stroke, TFNS and dementia
- The risk of primary ICH in CAA is not uniform:
  - Incidental CAA up to 1%/year
  - Cognitive decline up to 3%/year
  - cSS up to 10%/year
- The totality of current evidence does not justify withholding anticoagulation based on CMB's presence on MRI alone
- Reasonable options for people with cSS may be either a low dose DOAC (ie, Dabi 110 bid) or non-pharmacological treatment strategy (although no RCTs tested this option)





Charidimou A et al. Stroke. 2024

SECONDARY PREVENTION

Antiplatelets in ICH survivors

Ongoing RCTs:
ASPIRING, STATICH

THE LANCET
Neurology

Antiplatelets after intracerebral haemorrhage: treat the patient, not the brain imaging

Hanne Christensen

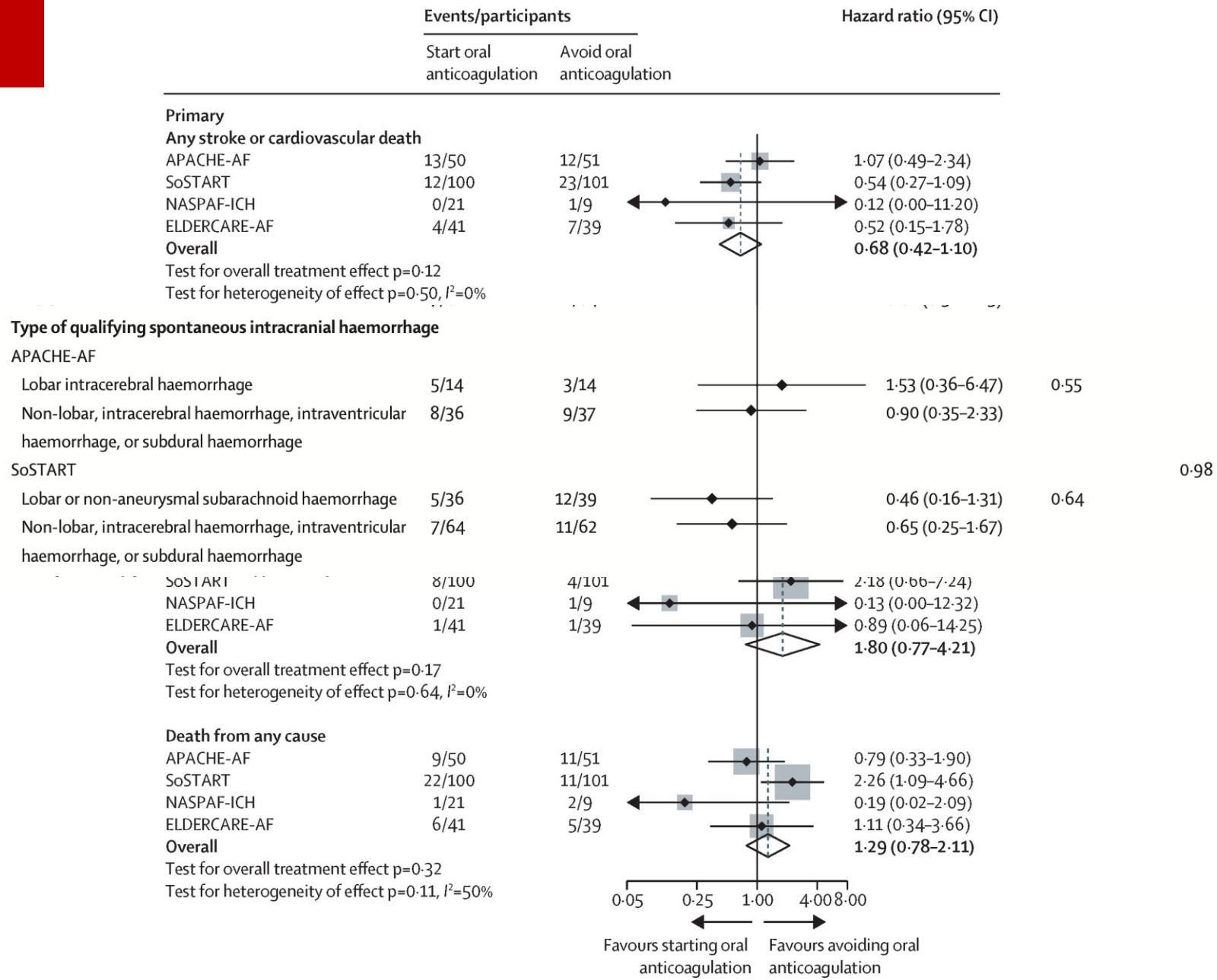
Clinicians underestimate harms and overestimate benefits from medical interventions.[1] However, according to a report by Rustam Al-Shahi Salman and colleagues[2] published in *The Lancet Neurology*, the perceived risk from restarting antiplatelet therapy after intracerebral haemorrhage in patients with cerebral microbleeds has been substantially overestimated on the basis of observational data. Use of antiplatelet therapy in patients with intracerebral haemorrhage is common,[3] a conservative estimate is one in four patients, so more certainty in making decisions regarding restarting such therapy is highly relevant.

The RESTART trial,[4] which is published in *The Lancet*, randomly assigned 537 survivors of intracerebral haemorrhage that occurred while taking antithrombotic therapy to start or avoid antiplatelet therapy. The investigators reported no significant differences in risk of recurrent intracerebral haemorrhage but a reduced risk, albeit not reaching statistical significance, of both haemorrhagic and ischaemic stroke was observed consistently in subgroups in patients allocated to start antiplatelet therapy.[4] The neuroimaging substudy[2] of the RESTART trial, published in *The Lancet Neurology*, focused on the 254 patients with MRI performed before randomisation. By contrast with previous observational data, there were no indications that starting antiplatelet therapy increased risk of recurrent intracerebral haemorrhage in patients with cerebral microbleeds or superficial siderosis. The number of microbleeds did not seem to affect risk of recurrent intracerebral haemorrhage.

RESTART is the first randomised trial to address this subject; until now, data were based on observational hospital cohorts that suggested excess risk of recurrent intracerebral haemorrhage from reintroduction of antiplatelets, with the highest risk

SECONDARY PREVENTION

Anticoagulation in ICH survivors

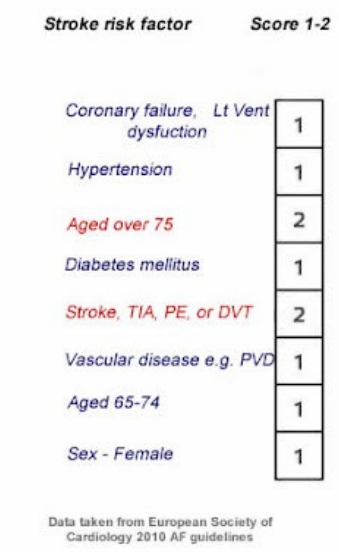


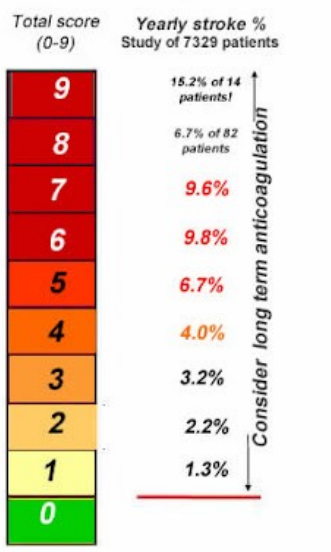
Ongoing trials: PRESTIGE-AF, ENRICH-AF, ASPIRE, A3ICH, STATICH

The Lancet Neurology, Volume 22, Issue 12, 1140 - 1149

SECONDARY PREVENTION

Anticoagulation in ICH survivors





THE LANCET

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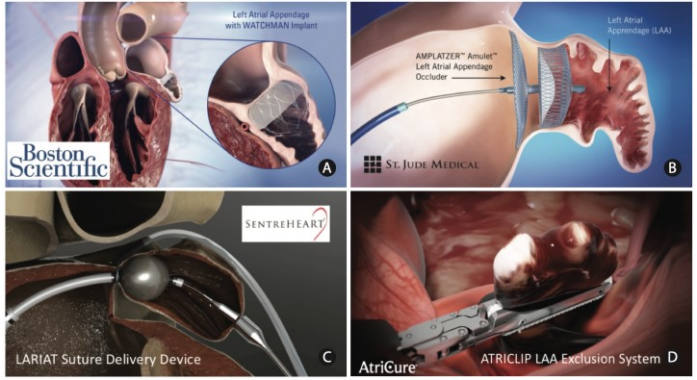
ndomised trials comparing anticoagulation with no anticoagulation in survivors of intracranial
orillation are ongoing (appendix). The Edoxaban for Intracranial Haemorrhage Survivors with
ICH-AF; NCT03950076) is assessing standard-dose edoxaban (60 mg daily dose reduced to 30
oderate renal impairment, bodyweight of ≤60 kg, or concomitant use of potent P-glycoprotein
non-anticoagulant medical treatment for stroke prevention in survivors of intracranial
orillation. ENRICH-AF is currently enrolling patients at 339 hospitals in 9 countries. Following
9 patients (174 [25%] of 699 with lobar intracranial haemorrhage and 34 [5%] of 699 with
emorrhage), the ENRICH-AF data safety monitoring board (DSMB) recommended that
acranial haemorrhage and convexity subarachnoid haemorrhage stop receiving the drug. Soon
ther patients with these intracranial haemorrhage subtypes be enrolled. The DSMB indicated that
ere based on observations of unacceptably high risks of recurrent haemorrhagic stroke among
rebral haemorrhage and convexity subarachnoid haemorrhage assigned to the edoxaban arm.
mmittee has accepted the DSMB recommendations and remains masked to these results (two members who were unmasked to interact with the DSMB are recused from further participation). The ENRICH-AF trial is continuing to recruit the remainder of the eligible population, and the results for the participants with lobar intracerebral haemorrhage and convexity subarachnoid haemorrhage will not be available until after study completion. In the interim, we write to make physicians aware of these ENRICH-AF DSMB recommendations as survey data indicate that 30–70% of specialists are currently resuming anticoagulation in survivors of lobar and cerebral amyloid angiopathy-related intracerebral haemorrhage with atrial fibrillation.[5] On the basis of emerging information from the ENRICH-AF trial, caution is warranted regarding the use of standard-dose anticoagulation in survivors of lobar intracerebral haemorrhage and 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.

- The risk of secondary ICH in CAA is higher than hypertensive microangiopathy (7.39%/year versus 1.11%/year) but again not uniform:
  - CMBs (deep or lobar) up to 5%/year
  - cSS up to 20%/year

SECONDARY PREVENTION

LAAO

"Quis custodiet ipsos custodes?"



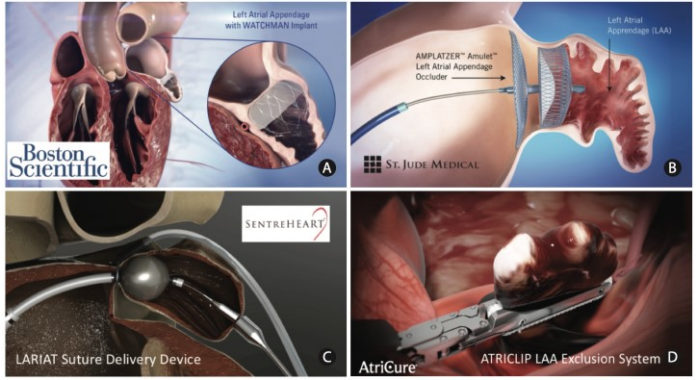
- PROTECT-AF: WATCHMAN vs WARFARIN
  - CHADS2 score 1 in about 30%, previous history of ischemic stroke/TIA < 20%: THIS IS A PRIMARY PREVENTION TRIAL
  - Ischemic stroke: 2.2 per 100 patient/years vs 1.6 per 100 patient/years NON-INFERIORITY MISSED
  - Hemorrhagic stroke: 0.1 per 100 patient/years vs 1.6 per 100 patient/years NON-INFERIORITY MET
  - Crude Hemorrhagic stroke rate associated with VKA was however 2.5%
  - Long term follow up: MISSED NON-INFERIORITY FOR ISCHEMIC STROKE PREVENTION
- PREVAIL: WATCHMAN vs WARFARIN
  - About 400 patients enrolled: QUITE A SMALL TRIAL
  - Previous history of ischemic stroke/TIA up to 28%: AGAIN A PRIMARY PREVENTION TRIAL
  - The efficacy coprimary endpoints were (1) composite of stroke, systemic embolism, and cardiovascular/unexplained death THIS WAS MISSED, and (2) stroke or systemic embolism >7 days postrandomization: THIS IS A NEGATIVE TRIAL
  - Crude ischemic stroke rate: WATCHMAN 1.9% vs WARFARIN 0.7%
  - Crude hemorrhagic stroke rate: WATCHMAN 0.4% vs WARFARIN 0%

Holmes DR 2009, Lancet; Reddy VY, JAMA 2014; Holmes DR, 2019

SECONDARY PREVENTION

LAAO

"Quis custodiet ipsos custodes?"



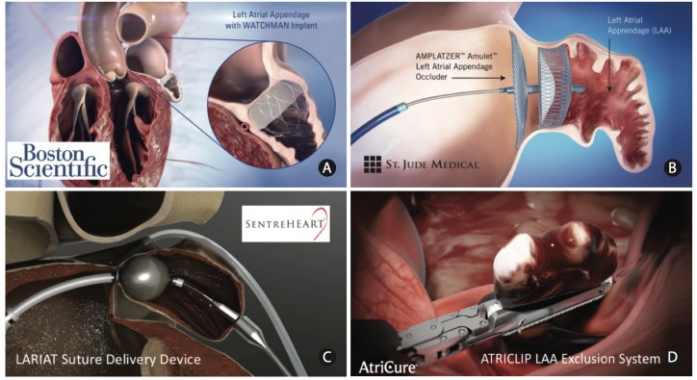
- PRAGUE 17: LAAO (Amulet, Watchman, Watchman FLX) versus DOAC (Apixaban 97%)
  - High-risk population with mean CHA2DS2-VASc score 4.7 and mean HAS-BLED score 3
  - History of cardioembolic event: up to 36% (mainly stroke)
  - About 400 patients enrolled, procedural complication rate around 5% and cross-over to DOAC around 10%
  - Primary endpoint was a composite of 1) stroke (ischemic or hemorrhagic) or TIA; 2) systemic embolism; 3) clinically significant bleeding; 4) cardiovascular death; or 5) a significant peri-procedural or device-related complications
  - Non-inferiority margin set at 5%
  - Primary endpoint: LAAO 10.99% per 100 patient-years vs 13.42% per 100 patient-years (P=0.004 for non-inferiority)
  - PRAGUE-17 is underpowered to evaluate the relative differences in the individual components of the primary endpoint

Osmanik P, JACC2020; Jun 30, 75: 3122-3135

SECONDARY PREVENTION

LAAO

"Quis custodiet ipsos custodes?"



- OPTION: Watchman FLX versus DOAC (Api 59.3%, Riva 27.2%, Edo 4.3%, Dabi 3.9%)
  - 1600 patients; Mean CHA2DS2-VASc score 3.5 and mean HAS-BLED score 1.2
  - The primary safety endpoint of non-procedural (FROM DAY 3) major bleeding or clinically relevant non-major bleeding (*P*<0.001 for superiority): Can safety of a surgical procedure be established with a non-procedural bleeding endpoint?
  - The secondary safety endpoint of major bleeding, which includes procedure-related bleeding, occurred in 3.9% of patients in the device arm and 5.0% of patients in the anticoagulation arm (HR, 0.77; 95% CI, 0.48-1.24): SUPERIORITY NOT SHOWN; NON-INFERIORITY (probability criterion of 85% ... statistically higher than 95%)
  - Primary safety endpoint diverge almost immediately in favor of the device arm…but LAAO patients were initially taking an anticoagulant and aspirin
  - Based on the observed low rates of stroke/systemic embolism (1.2% vs 1.3%) the trial would have required nearly five times more patients to properly establish non-inferiority: NON-INFERIORITY CANNOT BE INFERED
  - Missing data for 144 patients (8.8% overall), with most of those patients in the anticoagulation arm (10.5% vs 7.4% missing in the LAAC arm): CONSIDERING THE LOW EVENT RATES, MISSING DATA ADDS EVEN MORE UNCERTAINTY

4% jump in Boston Scientific's stock price

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CONCLUSIONS

- In adults with silent white matter hyperintensities, the benefit of antiplatelet therapy to reduce the risk of ischemic stroke is uncertain and it may even be harmful
- Early (within 4 days) start of anticoagulation after ischemic stroke is safe and effective
- Bleeding risk scores cannot be reliably used to decide on start/withdrawal of anticoagulation
- In patients with previous vascular disease, restart of single antiplatelet regimen after ICH was proved to be safe
- The safety and efficacy of anticoagulation after ICH is under investigation
- CAA confers different bleeding risk according to its various subtypes
- LAAO is a valuable therapeutic option for stroke prevention, but low-quality evidence prevents firm conclusions