

MASTER CLASS Symposium
**Recent advance in the treatment of
stroke patients with AF**



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박광열

Patients with atrial fibrillation

Case studies

Hyperacute ischemic stroke

ICH

Summary

Cardioembolic stroke

- ▶ 비판막성 심방세동
- ▶ 인공판막
- ▶ 좌심실 혈전증
- ▶ 점액종
- ▶ 감염성 심뇌막염

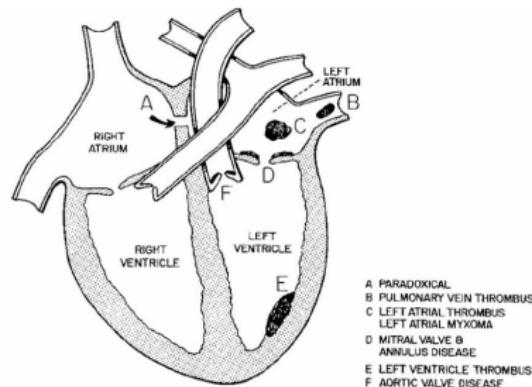
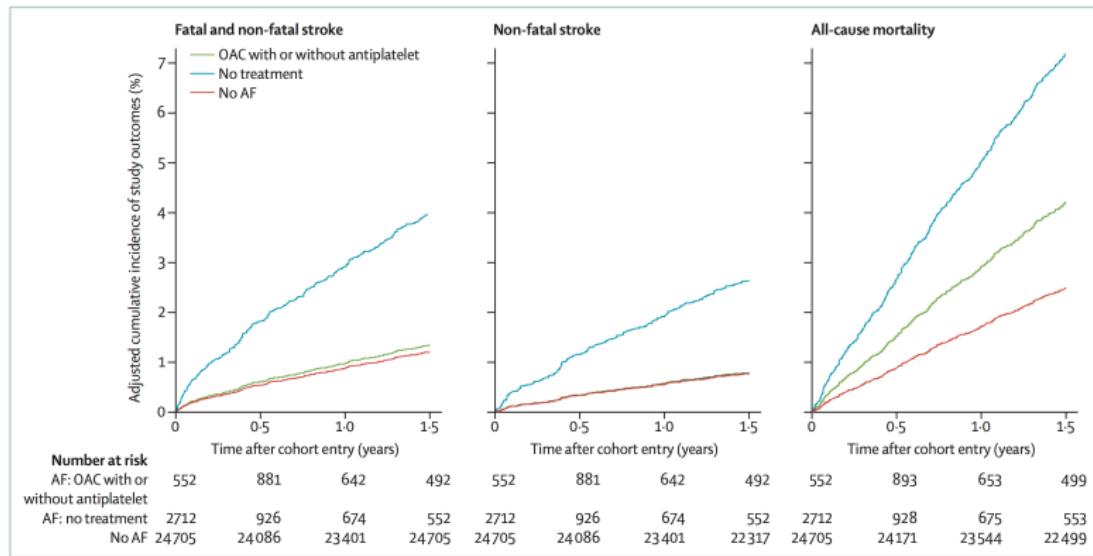
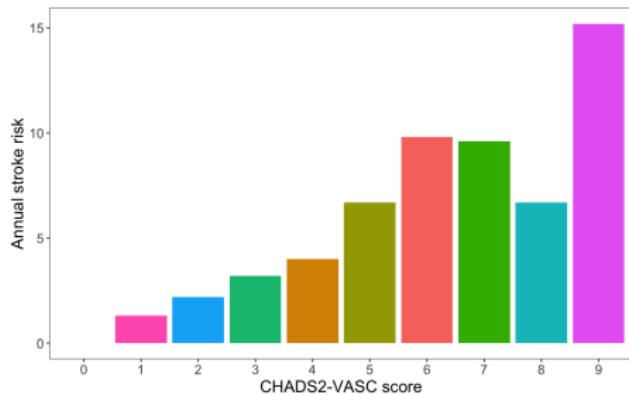


Figure 1. Cardiac causes of stroke (Adapted from Barnett et al)

**Figure 2: Effect of treatment on incidentally detected atrial fibrillation**AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.²¹

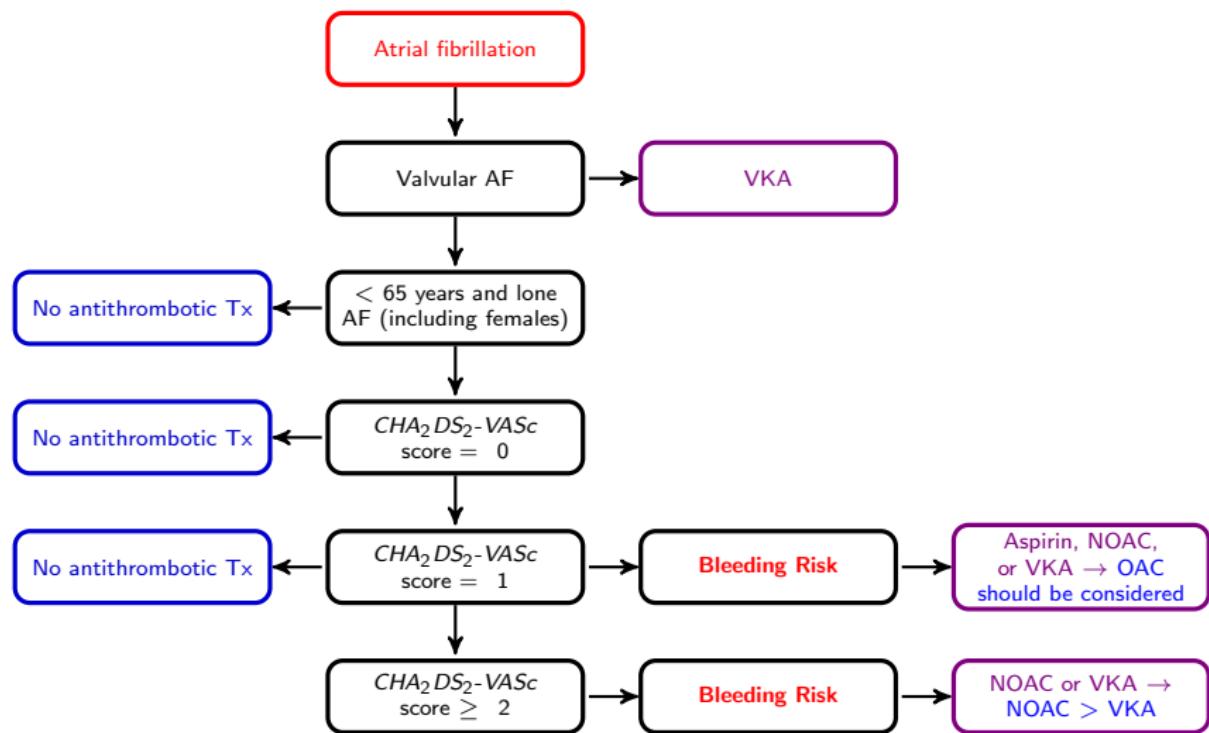
Thromboembolic risk of AF

<i>CHA₂DS₂-VASc</i> criteria	Score
CHF	1
Hypertension	1
Age \geq 75 years	2
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease	1
Age 65-74 years	1
Sex category (female)	1



Anticoagulation after stroke

Patients with atrial fibrillation



Case 1, F/75

내원일 저녁 10시30분경 혼자서 TV 보던중 갑자기 말이 어둔해져서 좌측 팔다리에 힘이 빠져서 11시 5분 응급실 내원함.

NIHSS 10

Lt. central type facial palsy, dysarthria, neglect Lt. hemiparesis
(U/Ex I, L/Ex IV-)

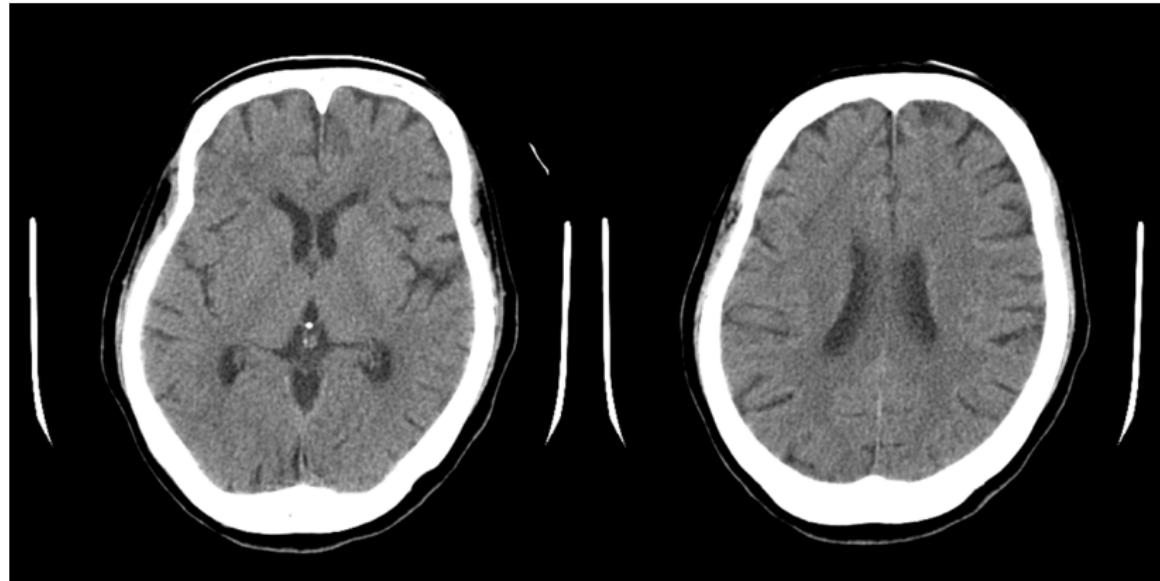
HTN, AF (NOAC - 금일 약을 드시지 않음)

Anticoagulation after stroke

└ Case studies

└ Hyperacute ischemic stroke

Brain CT, 51min

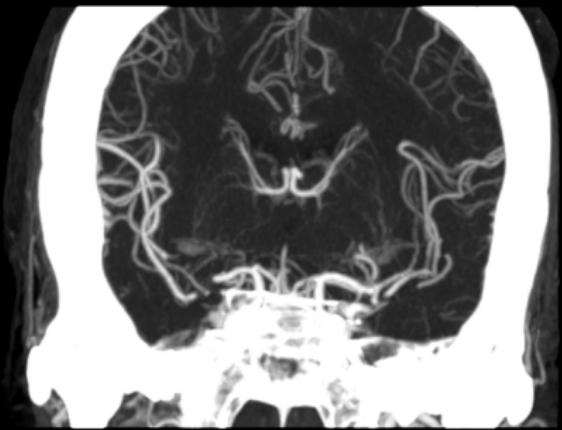
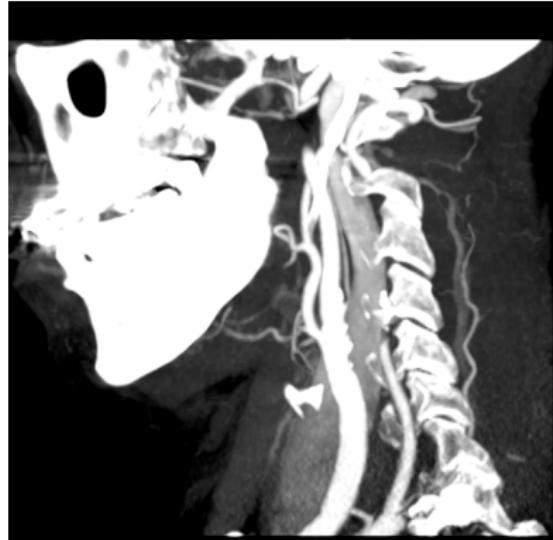


Anticoagulation after stroke

└ Case studies

└ Hyperacute ischemic stroke

Brain CTA



Anticoagulation after stroke

└ Case studies

└ Hyperacute ischemic stroke

How to treat this patient?

How to treat this patient?

1. Consider IV thrombolysis
2. Consider IA thrombectomy
3. No reperfusion therapy

Hyperacute ischemic stroke in patients on NOAC

- ▶ No prospective data exist!
- ▶ The use of rtPA is not recommended according to official labelling.
- ▶ If patients took the last dose of NOAC 48 hours ago and coagulation assay (e.g. aPTT for Dabigatran) is within normal range, the use of fibrinolytics can be considered.
- ▶ Mechanical thrombectomy may be considered as an alternative option.

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials



Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Diederik W J Dipper, Peter J Mitchell, Andrew M Demchuk, Antoni Dávalos, Charles B L M Majeski, Aad van der Loos, María Á de Miguel, Geoffrey A Donnan, Yeo B W E M Roos, Alain Bonafe, Reza Jahan, Hans-Christoph Diener, Lucie A van den Berg, Elad Levy, Olvert A Benkhader, Vitor M Pereira, Jeremy Rempel, Mónica Millán, Stephen M Davis, Daniel Roy, John Thornton, Luis San Roman, Marc Ribó, Débrie Beumer, Bruce Stouch, Scott Brown, Bruce C V Campbell, Robert J van Oestenbrugge, Jeffrey L Saver, Michael D Hill, Tudor G Jovin, for the HERMES collaborators

Summary

Background In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is efficacious across the diverse populations included.

Lancet 2016; 387: 1723–31

Published Online

February 18, 2016

<http://dx.doi.org/10.1016/j.laneurology.2016.01.016>

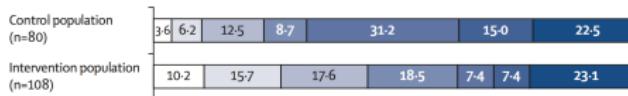
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A Overall

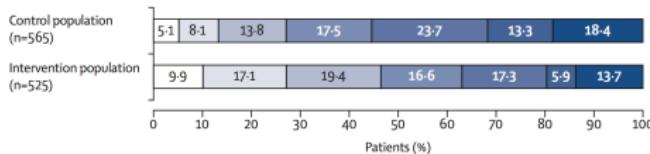


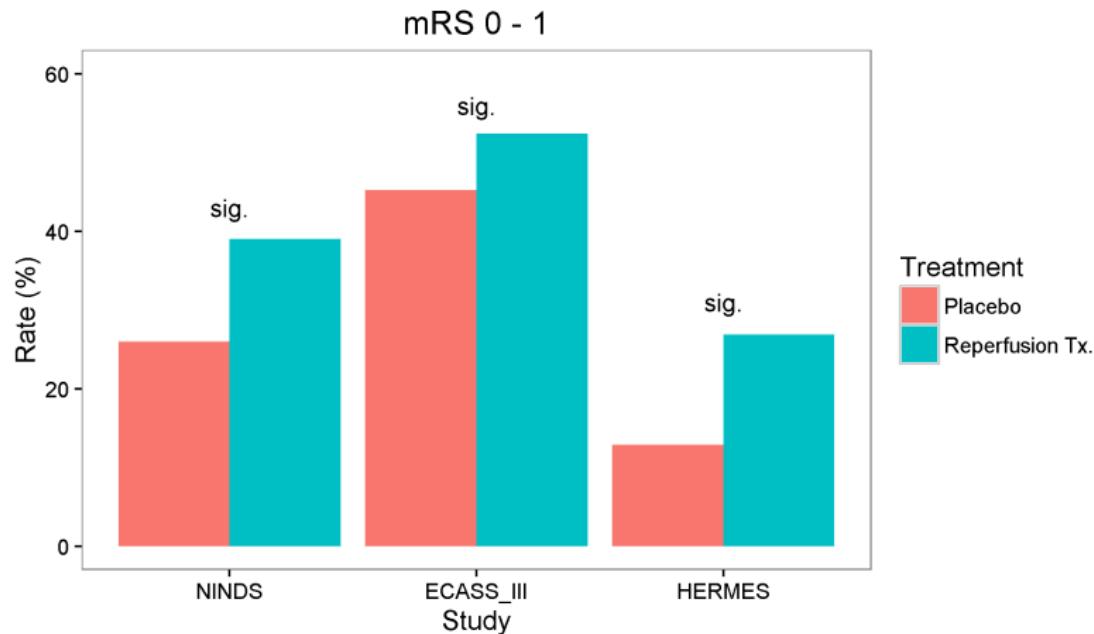
B

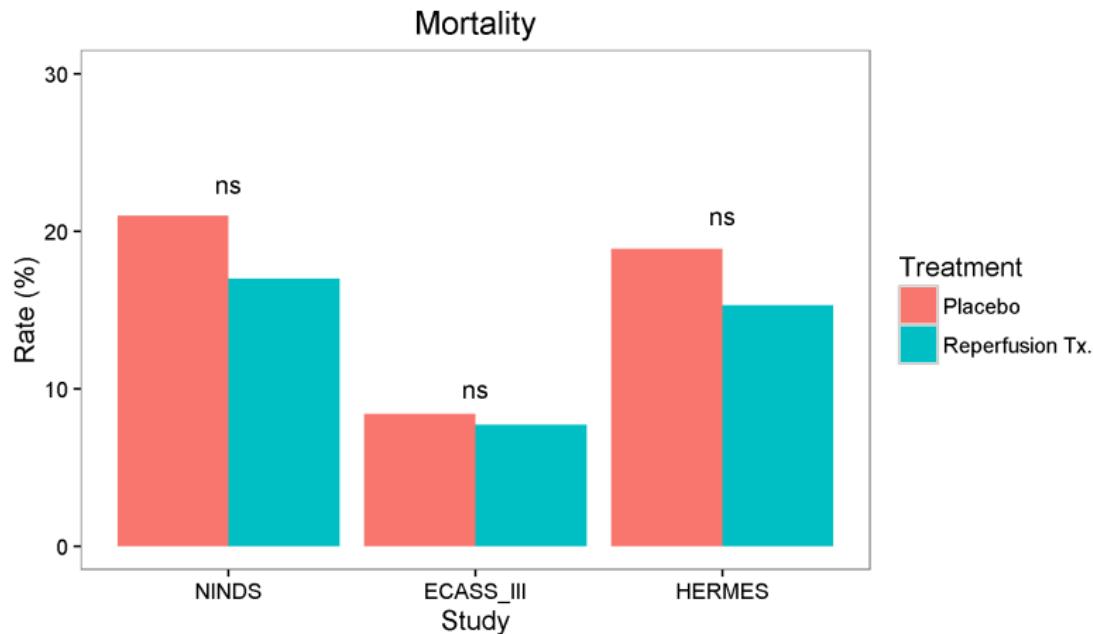
Ineligible for alteplase

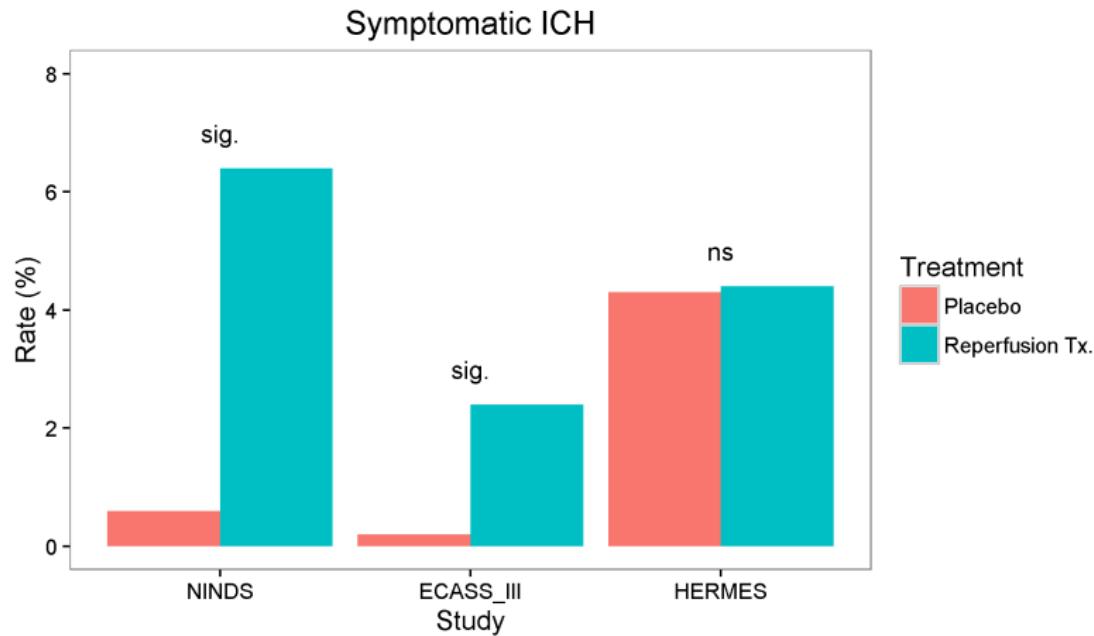


Received alteplase







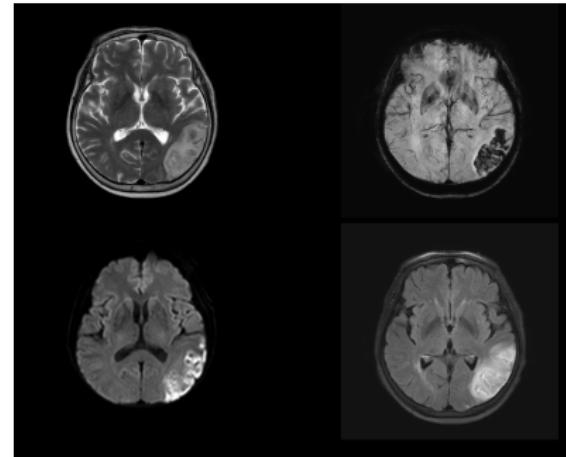


Anticoagulation after stroke

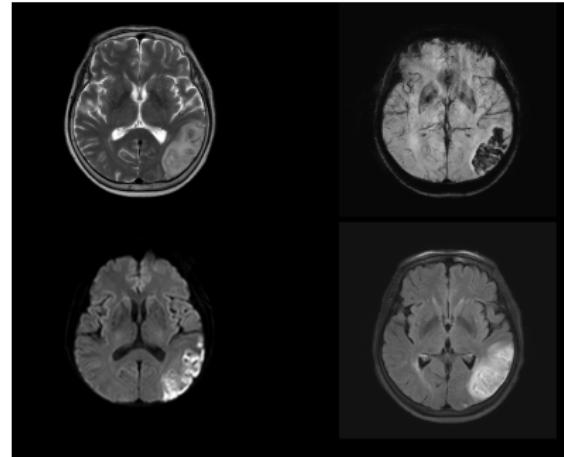
└ Case studies

└ Hyperacute ischemic stroke

When to resume NOAC ?



When to resume NOAC ?

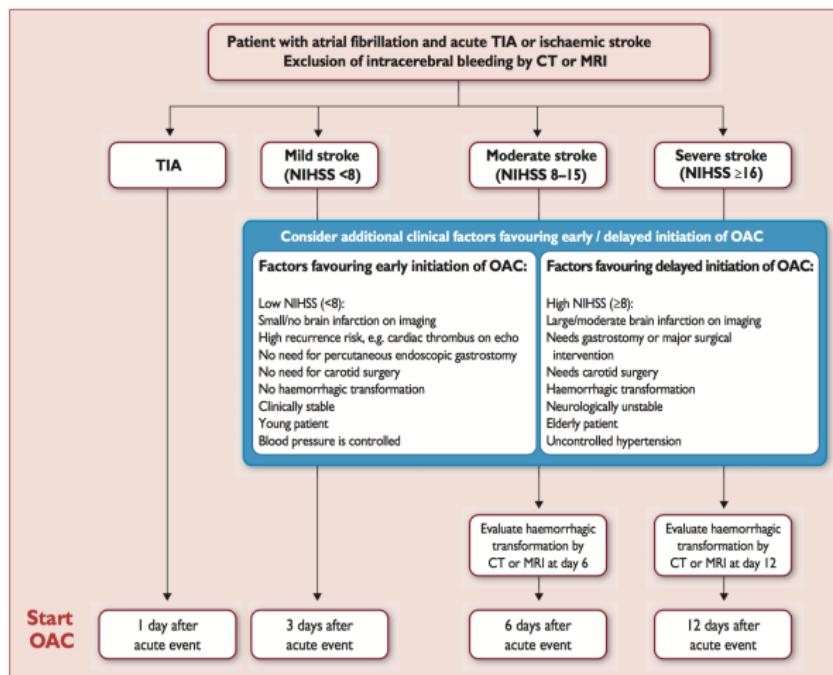


- ▶ Rule-of-thumb: 1-3-6-12 (TIA-small-moderate-large)

Anticoagulation after stroke

Case studies

Hyperacute ischemic stroke



AF = atrial fibrillation; CT = computed tomography; NIHSS = National Institutes of Health stroke severity scale (available at http://www.strokecenter.org/wp-content/uploads/2011/08/NIH_Stroke_Scale.pdf); OAC = oral anticoagulation; TIA = transient ischaemic attack

Anticoagulation after stroke

└ Case studies

└ Hyperacute ischemic stroke

Dosage adjustment ?

- ▶ 75/F

Dosage adjustment ?

- ▶ 75/F
- ▶ Body weight 53Kg
- ▶ Serum Cr 1.3

Dosage adjustment ?

- ▶ 75/F
- ▶ Body weight 53Kg
- ▶ Serum Cr 1.3

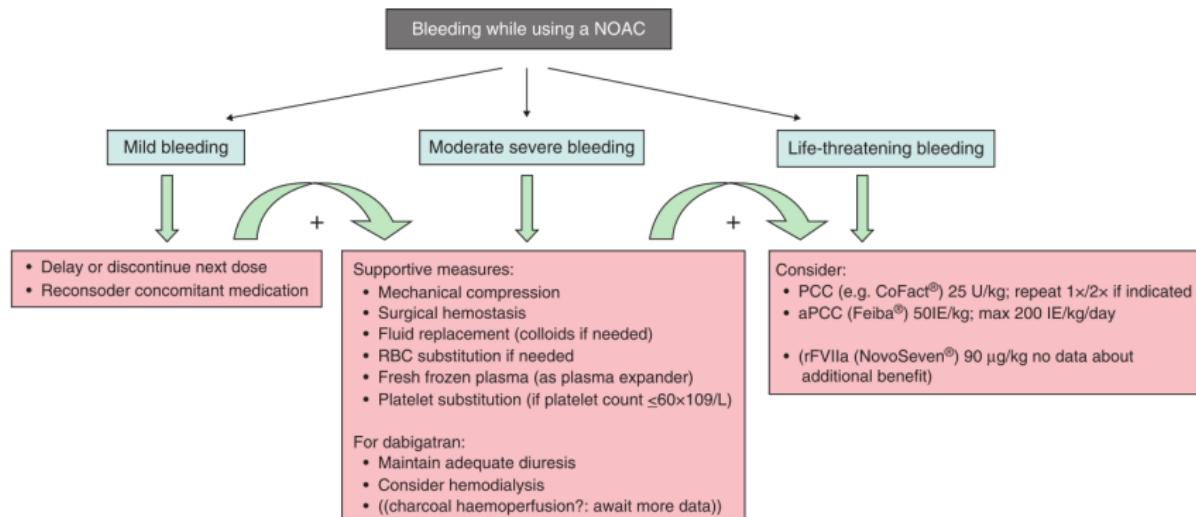
Apixaban 2.5 mg twice daily if at least 2 of

- ▶ age \geq 80 years
- ▶ body weight \leq 60 kg
- ▶ serum creatinine level \geq 1.5 mg/dL (133 μ mol/L)

Case 2 (M/63) and Case 3 (F/78)



Management of bleeding complication



ARTICLES

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Outcome of intracerebral hemorrhage associated with different oral anticoagulants

OPEN

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ABSTRACT

Objective: In an international collaborative multicenter pooled analysis, we compared mortality, functional outcome, intracerebral hemorrhage (ICH) volume, and hematoma expansion (HE) between non-vitamin K antagonist oral anticoagulation-related ICH (NOAC-ICH) and vitamin K antagonist-associated ICH (VKA-ICH).

Methods: We compared all-cause mortality within 90 days for NOAC-ICH and VKA-ICH using a Cox proportional hazards model adjusted for age; sex; baseline Glasgow Coma Scale score, ICH location, and log volume; intraventricular hemorrhage volume; and intracranial surgery. We addressed heterogeneity using a shared frailty term. Good functional outcome was defined as discharge modified Rankin Scale score ≤ 2 and investigated in multivariable logistic regression. ICH volume was measured by ABC/2 or a semiautomated planimetric method. HE was defined as an ICH volume increase $>33\%$ or >6 mL from baseline within 72 hours.

Results: We included 500 patients (97 NOAC-ICH and 403 VKA-ICH). Median baseline ICH volume was 14.4 mL (interquartile range [IQR] 3.6–38.4) for NOAC-ICH vs 10.6 mL (IQR 4.0–27.9) for VKA-ICH ($p = 0.78$). We did not find any difference between NOAC-ICH and VKA-ICH for all-cause mortality within 90 days (33% for NOAC-ICH vs 31% for VKA-ICH [$p = 0.64$]; adjusted Cox hazard ratio for NOAC-ICH vs VKA-ICH 0.93 [95% confidence interval (CI) 0.52–1.64] [$p = 0.79$]), the rate of HE (NOAC-ICH $n = 29/48$ [40%] vs VKA-ICH $n = 93/140$ [34%] [$p = 0.45$]), or functional outcome at hospital discharge (NOAC-ICH vs VKA-ICH odds ratio 0.47; 95% CI 0.18–1.19 [$p = 0.11$]).

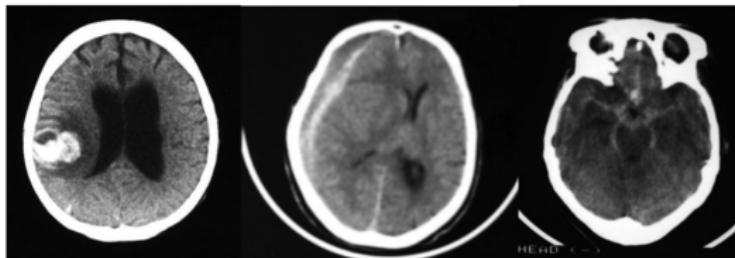
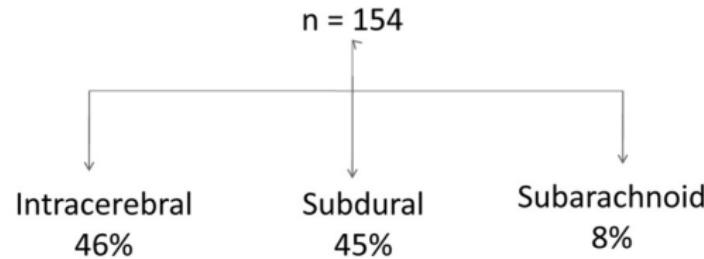
Conclusions: In our international collaborative multicenter pooled analysis, baseline ICH volume, hematoma expansion, 90-day mortality, and functional outcome were similar following NOAC-ICH and VKA-ICH. *Neurology®* 2017;88:1–8

	ICH during NOAC n=97	ICH during VKA n=403	p value
ICH volume	14.4mL	10.6mL	0.78
Hematoma expansion	40%	34%	0.45
All-cause mortality (< 30 d)	33%	31%	0.64

NOAC: apixaban(13), dabigatran(13), and rivaroxaban(69).

ICH during anticoagulation

Intracranial Hemorrhages in RE-LY



ICH during anticoagulation

	Warfarin	Dabigatran 150mg	Dabigatran 110mg
ICH, %/y	0.76	0.31	0.23
Mortality	36%	35%	41%
Fatal ICH	32	13	11

Independent predictors of ICH

- ▶ Assignment to warfarin (RR 2.9, $p<0.001$)
- ▶ Aspirin use (RR 1.6, $p=0.01$)
- ▶ Age (RR 1.1 per year, $p<0.001$)
- ▶ Previous stroke or TIA (RR 1.8, $p=0.001$)

Anticoagulation after stroke

└ Case studies

└ ICH

Anticoagulation in patients with Af and ICH

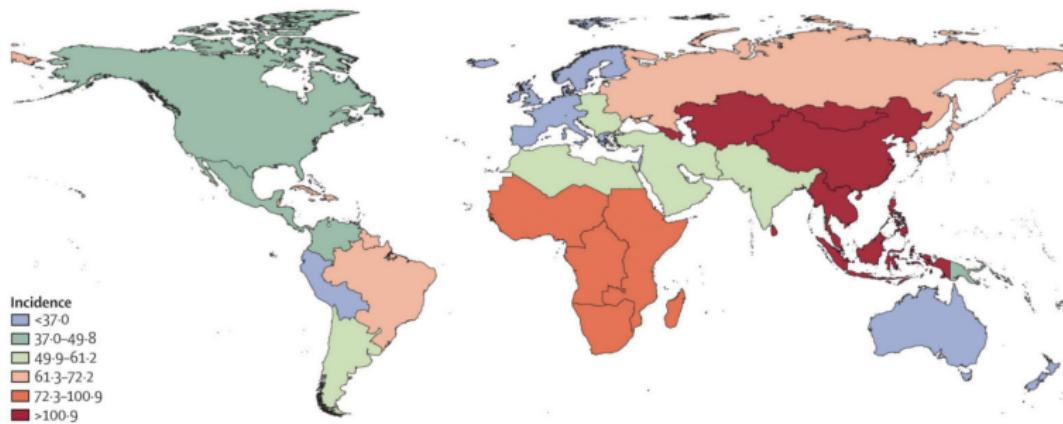
To resume or Not to resume

Asian

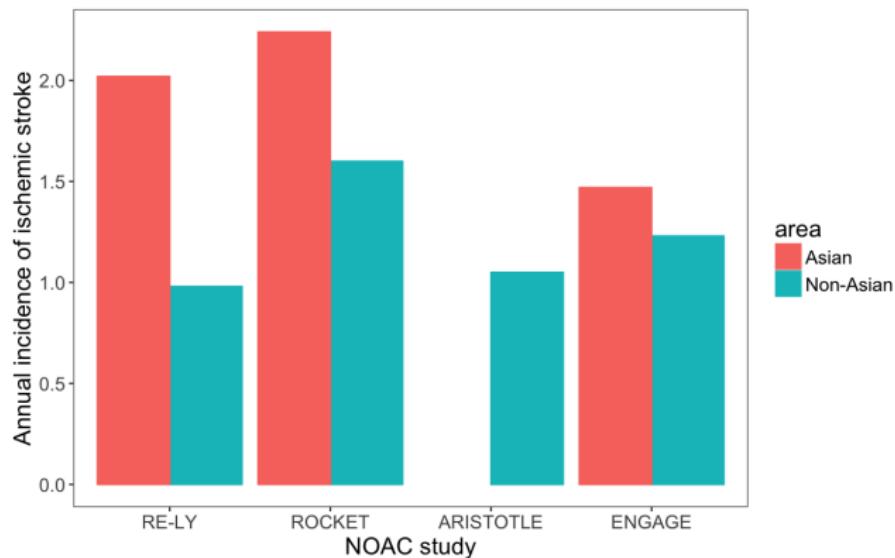


Knowing the characteristics of race is important !

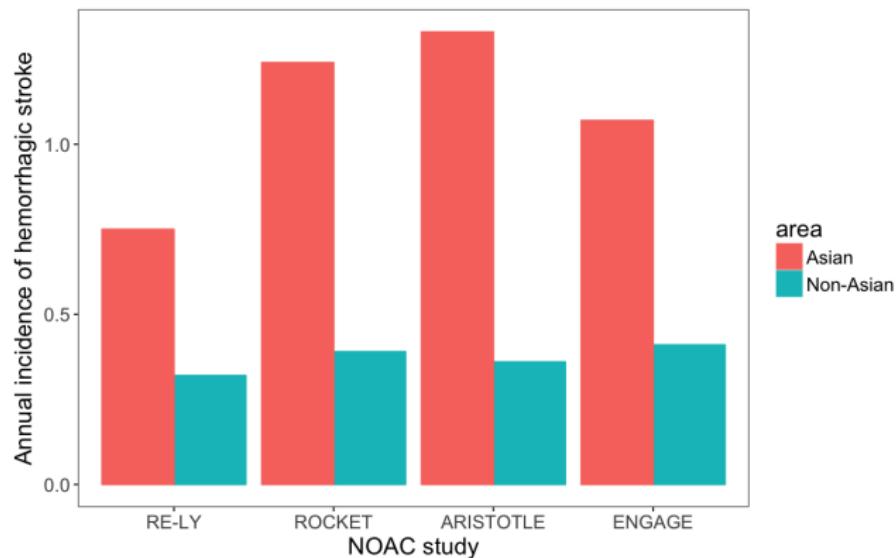
Age-standardised incidence of haemorrhagic stroke per 100 000 person-years for 2010



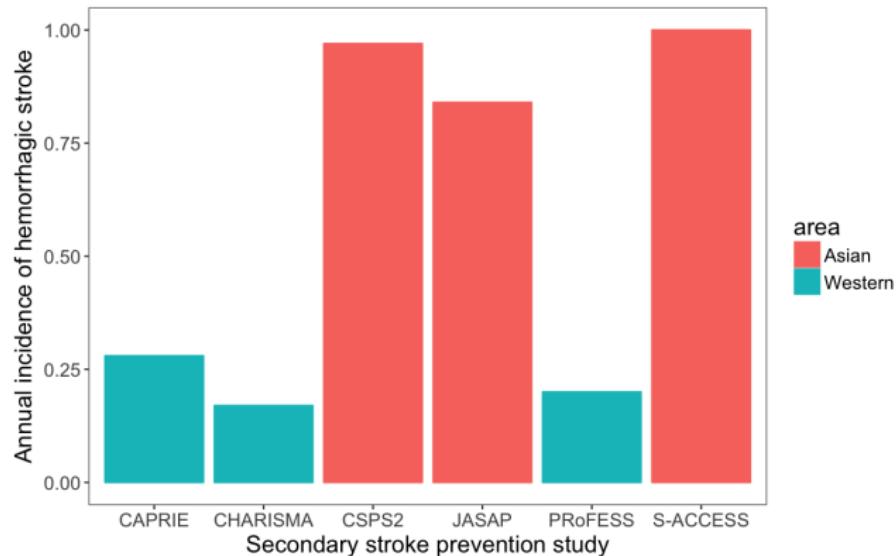
Ischemic stroke on warfarin



hemorrhagic stroke on warfarin



Incidence of Cerebral Hemorrhage with Aspirin



Age

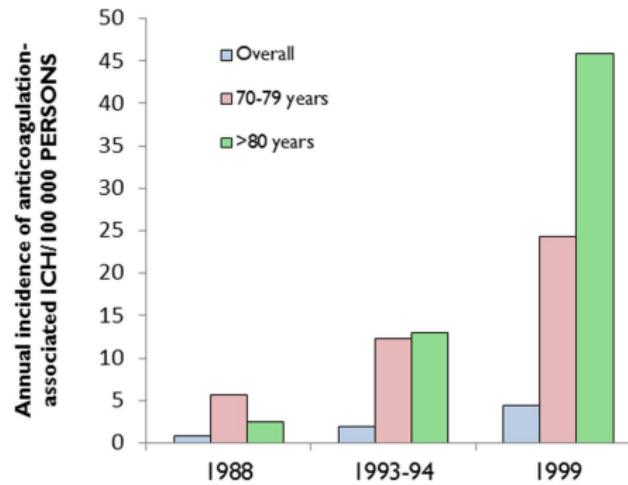


FIGURE 1 |The increasing incidence of anticoagulation-associated intracerebral hemorrhage (ICH), especially in the elderly. Data extracted from (Flaherty et al., 2007).

Burden of SVD

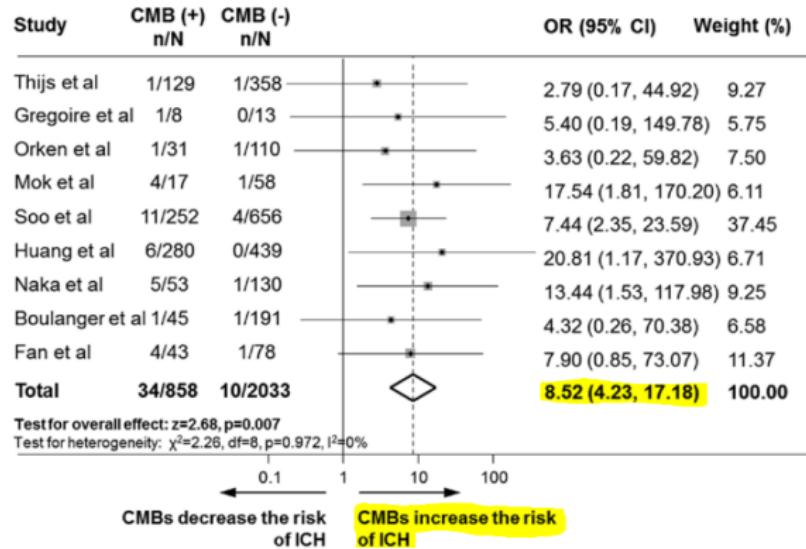
	Recent small subcortical infarct	White matter hyperintensity	Lacune	Perivascular space	Cerebral microbleed
Example image					
Schematic	DWI	FLAIR	FLAIR	T2 T1/FLAIR	T2*/SWI
Usual diameter	≤20 mm	Variable	3–15 mm	≤2 mm	≤10 mm
Comment	Best identified on DWI	Located in white matter	Usually have hyperintense rim	Most linear without hyperintense rim	Detected on GRE seq., round or ovoid; blooming
DWI	↑	++	↔/↓(L)	++	++
FLAIR	↑	↑	↓	↓	++
T2	↑	↑	↑	↑	++
T1	↓	↔/(↓)	↓	↓	++
T2*-weighted GRE	++	↑	↔ (↓ if haemorrhage)	++	↓↓
↑ Increased signal ↓ Decreased signal ↔ Iso-intense signal					

Figure 2: MRI findings for lesions related to small vessel disease

Anticoagulation after stroke

└ Case studies

└ ICH



Anticoagulation after stroke

Case studies

ICH

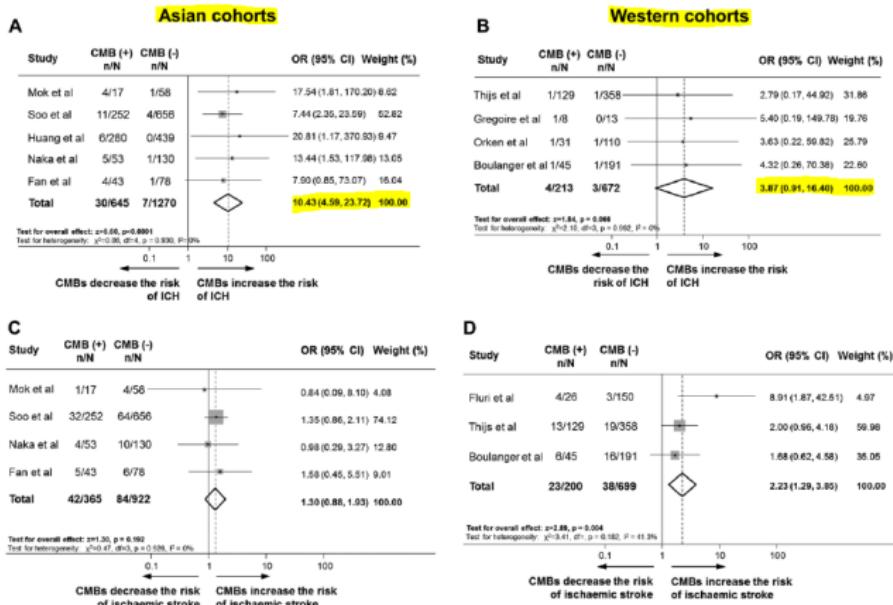


Figure 4. Meta-analysis of the risk of spontaneous intracerebral hemorrhage (ICH; A and B) and ischemic stroke (C and D) stratified by the dominant ethnicity of subjects included in each cohort as Asian or Western (white), with and without cerebral microbleeds (CMBs).

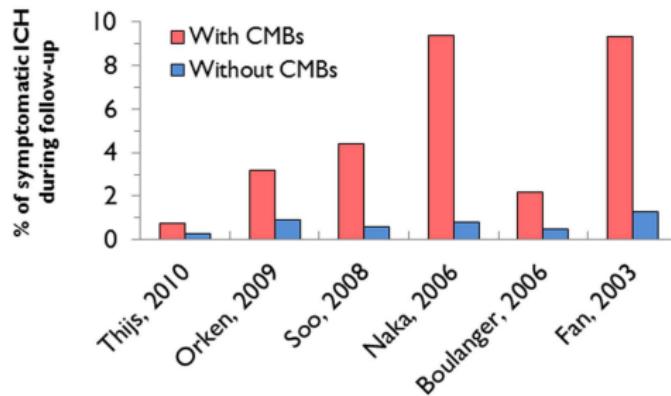
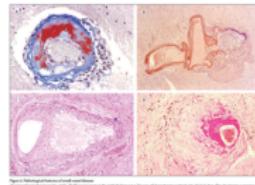


FIGURE 5 | Incidence of intracerebral hemorrhage in relation to the presence of cerebral microbleeds (CMBs) in the main prospective cohort studies which have assessed this risk in patients with ischemic stroke or TIA (Table 3).

CAA or lobar bleed

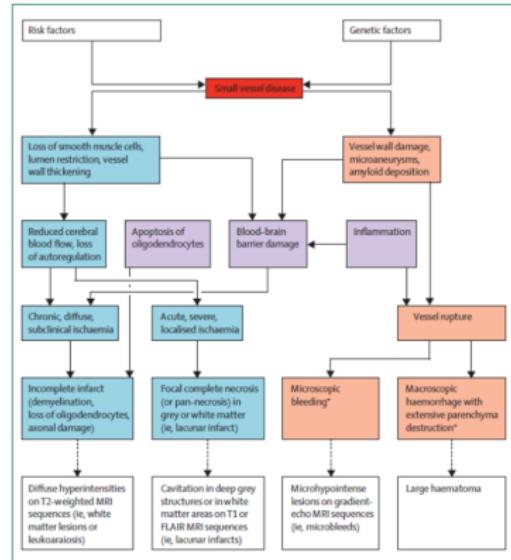
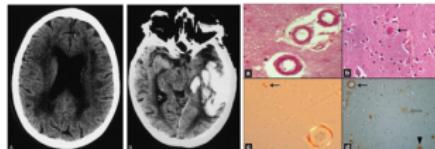
Arteriolosclerosis

- Hypertensive SVD
- Age-related SVD
- Associated with Aging, diabetes, and hypertension
- Pathology
 - Lipohyalinosis
 - Microatheroma
 - Microaneurysm



Cerebral Amyloid Angiopathy

- Progressive accumulation of congophilic amyloid protein
- Small to medium sized arteries in the leptomeningeal space and cortex
- AD and general elderly population (as frequent as 50% in the ninth decade)



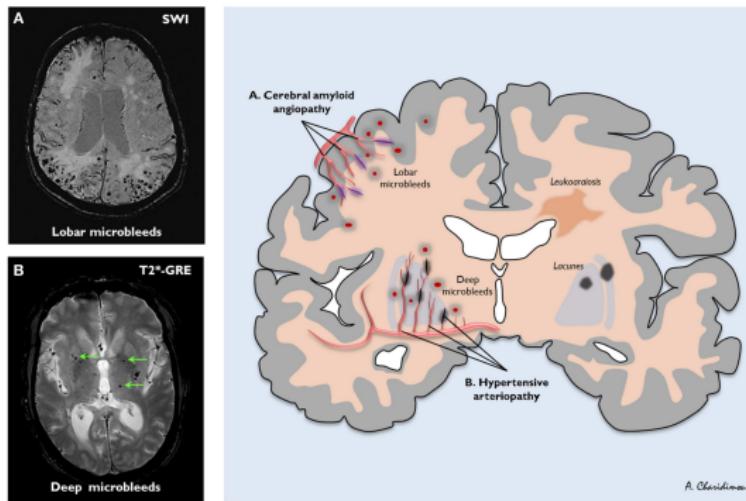


FIGURE 3 |The distribution of sporadic small vessel disease in the brain and the topography of cerebral microbleeds (CMBs). **(A)** Cerebral amyloid angiopathy (CAA) preferentially affects the small arteries and arterioles of the cerebral cortex and gray-white matter junction by the deposition of amyloid- β in the vessel walls (purple), **(B)** hypertensive arteriopathy typically affects small deep arterial perforators (black). CMBs are a marker for the severity and type of small vessel disease; their

anatomic distribution is meant to reflect the underlying pathological vessel damage. Hence, CMBs (dark, rounded lesions) located in cortical-subcortical regions are presumably caused by CAA **(A)**, whereas CMBs located in deep brain regions mainly result from hypertensive arteriopathy **(B)**. **(A)** is an axial susceptibility-weighted imaging (SWI) which is currently the most sensitive means to image CMBs. **(B)** is an axial T2*-weighted gradient-recalled echo (T2*-GRE) MRI.

Cerebrovascular disease

RESEARCH PAPER

Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis

Michael Tin Chung Poon,¹ Arthur François Fonville,² Rustam Al-Shahi Salman³**Table 2** Risk of recurrent intracerebral haemorrhage (ICH) at least 1 year after ICH, in cohorts that stratified their results by ICH location

Recurrent ICH ≥1 year after index ICH, stratified by index ICH location

Study	Sample size	Inception point	Follow-up		Recurrence risk (%; 95% CI)		
			Mean duration (years)	Analytical method	Overall	Lobar	Non-lobar
Passero et al ³⁰	111	Hospital discharge	1	Proportion	7.2 (3.5 to 13.8)	14.3 (6.3 to 28.2)†	2.9 (0.2 to 10.6)†
Zia et al ³⁷	353	28 days after onset	3	Rate‡	2.3	2.5	2.3
O'Donnell et al ⁶⁴	71	30 days after onset	3	Rate‡	—	14.3	—
Yen et al ⁶²	585	At ICH onset	1	Proportion	1.9 (1.0 to 3.4)	5.0 (1.9 to 11.4)†	1.3 (0.5 to 2.8)†

Studies are arranged by the start year of their study periods.

†Significant difference ($p<0.05$) between lobar and non-lobar ICH.

‡Rate reported per patient-year.

To resume AC (Modifiable)

- ▶ Uncontrolled HTN
- ▶ Triple therapy
- ▶ High INR on VKA

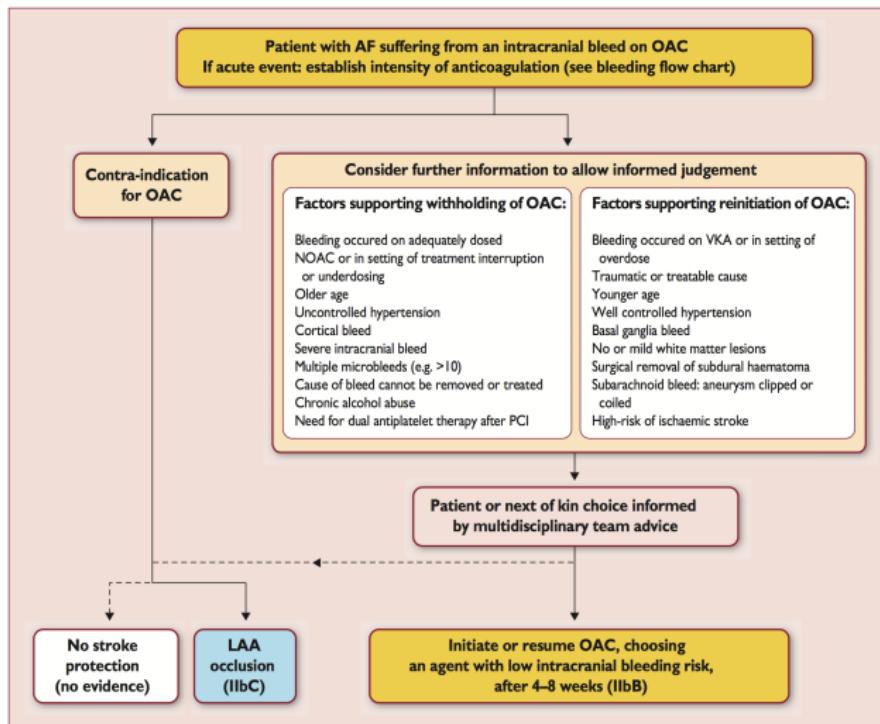
Not to resume AC (Not modifiable)

- ▶ older age
- ▶ persistent uncontrolled hypertension
- ▶ lobar bleeds
- ▶ severe WM lesions
- ▶ multiple CMBs > 30
- ▶ chronic alcoholism
- ▶ need for DAPT after PCI

Anticoagulation after stroke

Case studies

ICH



Take-Home Message

- ▶ There are challenges associated with the acute treatment of patients who are receiving long-term anticoagulation treatment for NVAF
- ▶ Thrombectomy may be considered in patients with hyperacute ischemic stroke.
- ▶ OAC should be resumed after ICH since the benefit of OAC for the prevention of ischaemic stroke is higher than the bleeding risk