MASTER CLASS Symposium

Recent advance in the treatment of stroke patients with AF

중앙대학교 의과대학 신경과학교실

박 광 열

Patients with atrial fibrillation

Case studies

- Hyperacute ischemic stroke
- ICH

Summary

Cardioembolic stroke

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

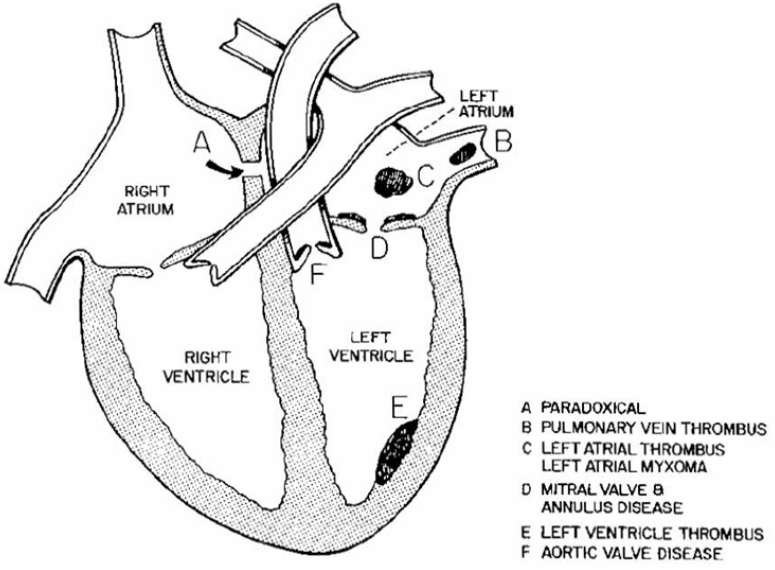


Figure 1. Cardiac causes of stroke (Adapted from Barnett et al)

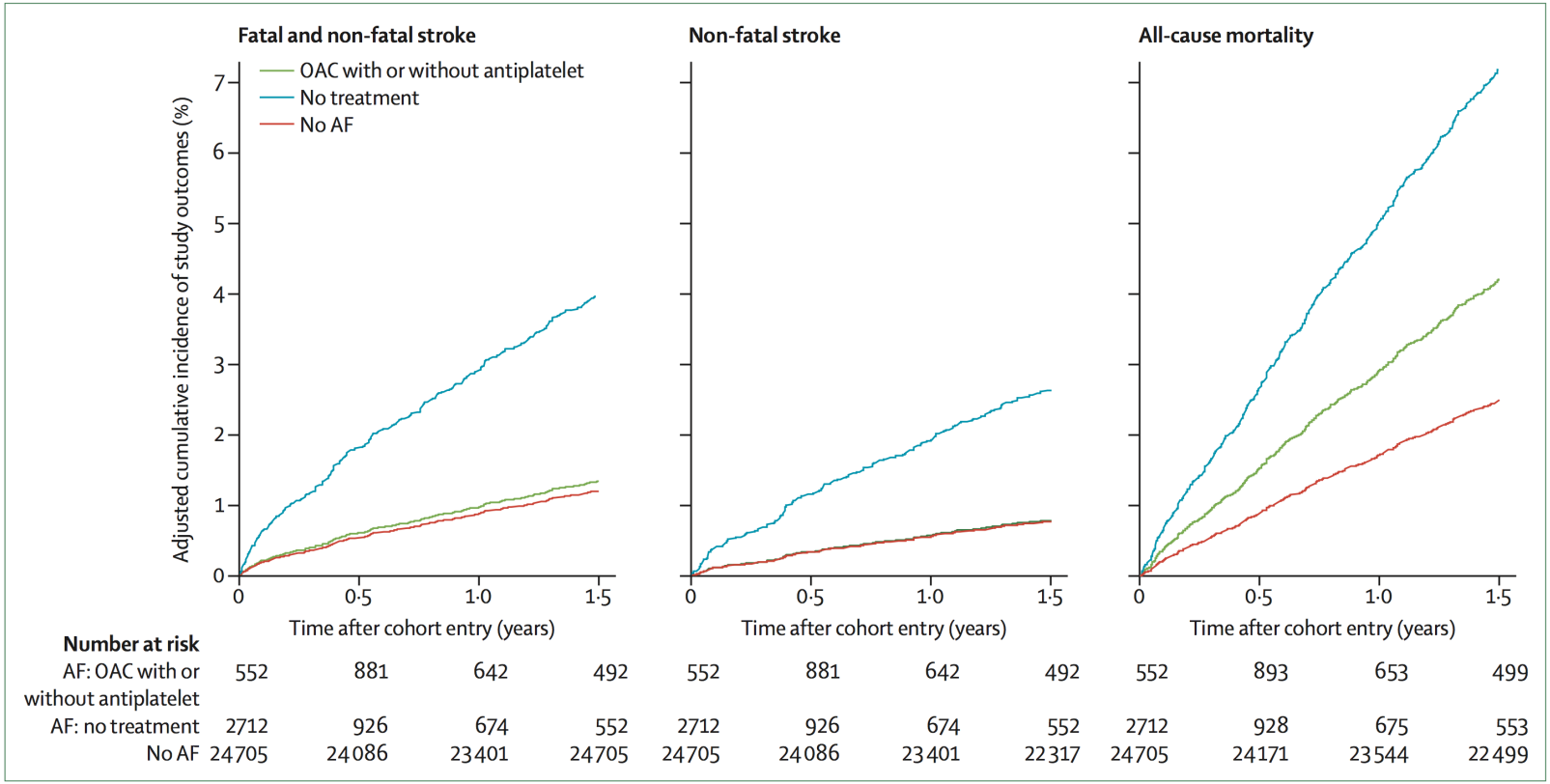
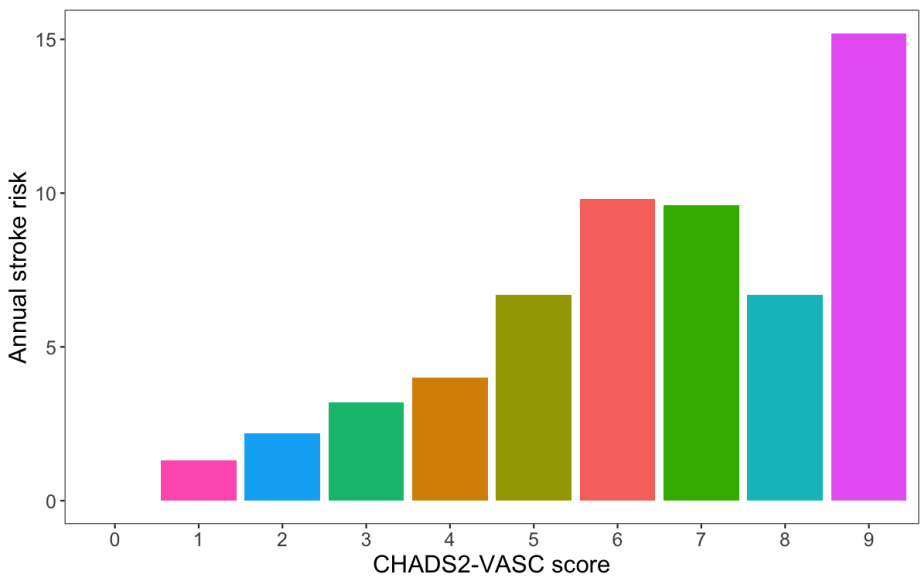


Figure 2: **Effect of treatment on incidentally detected atrial fibrillation**
AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.[21]

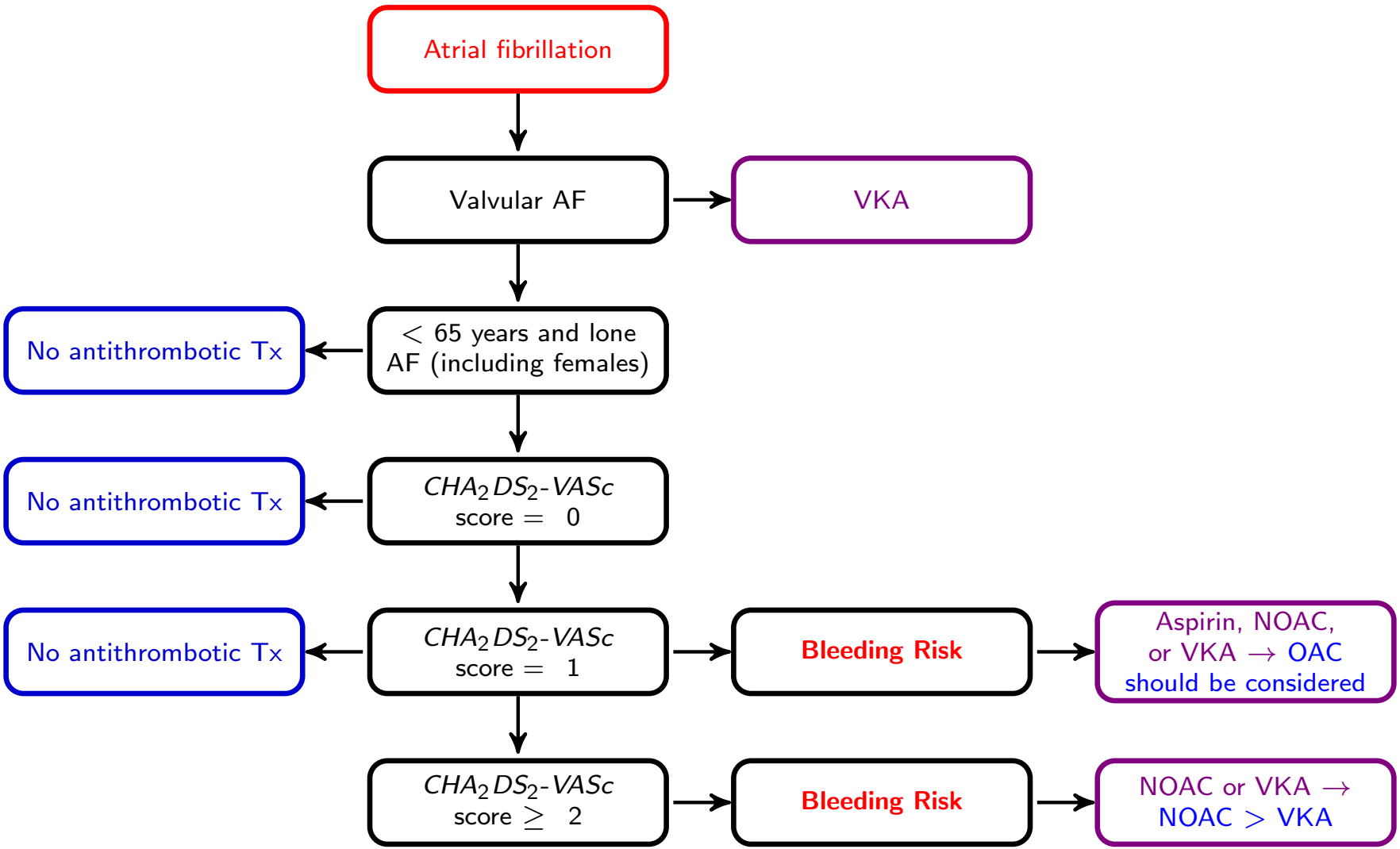
Freedman B. et al. Lancet 2016; 388: 806–17

Thromboembolic risk of AF

CHA_2DS_2-$VASc$ 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



Gage BF et al. JAMA 2001;285:2864–70; Lip G et al. Chest 2010;137:263–72
January, C. T., et al. Circulation 2014



Camm, A. J., et al. Eur Heart J. 2012; Meschia, J. F., et al. Stroke 2014; Kirchhof et al. Eur Heart J 2016

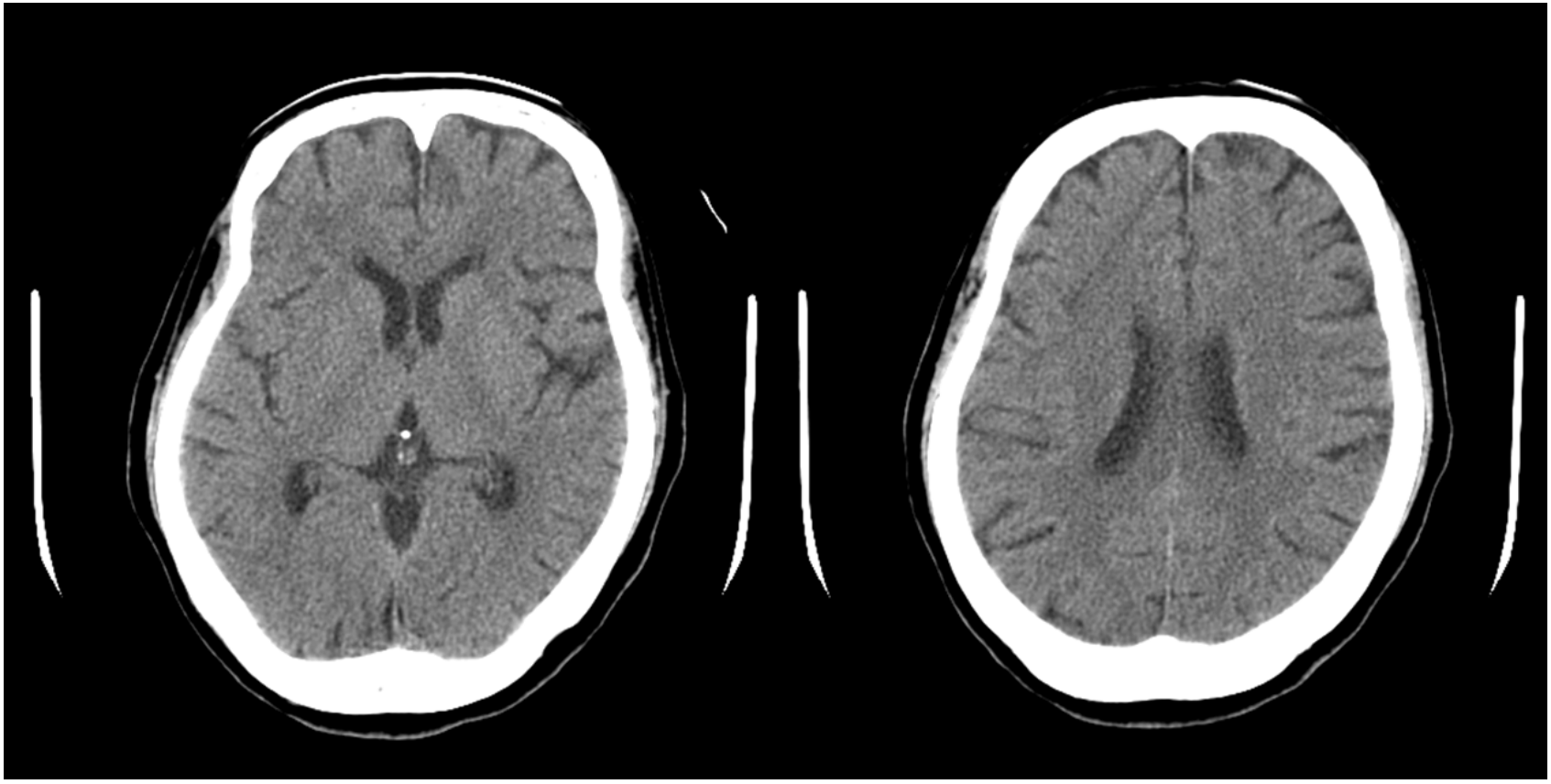
Case 1, F/75

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

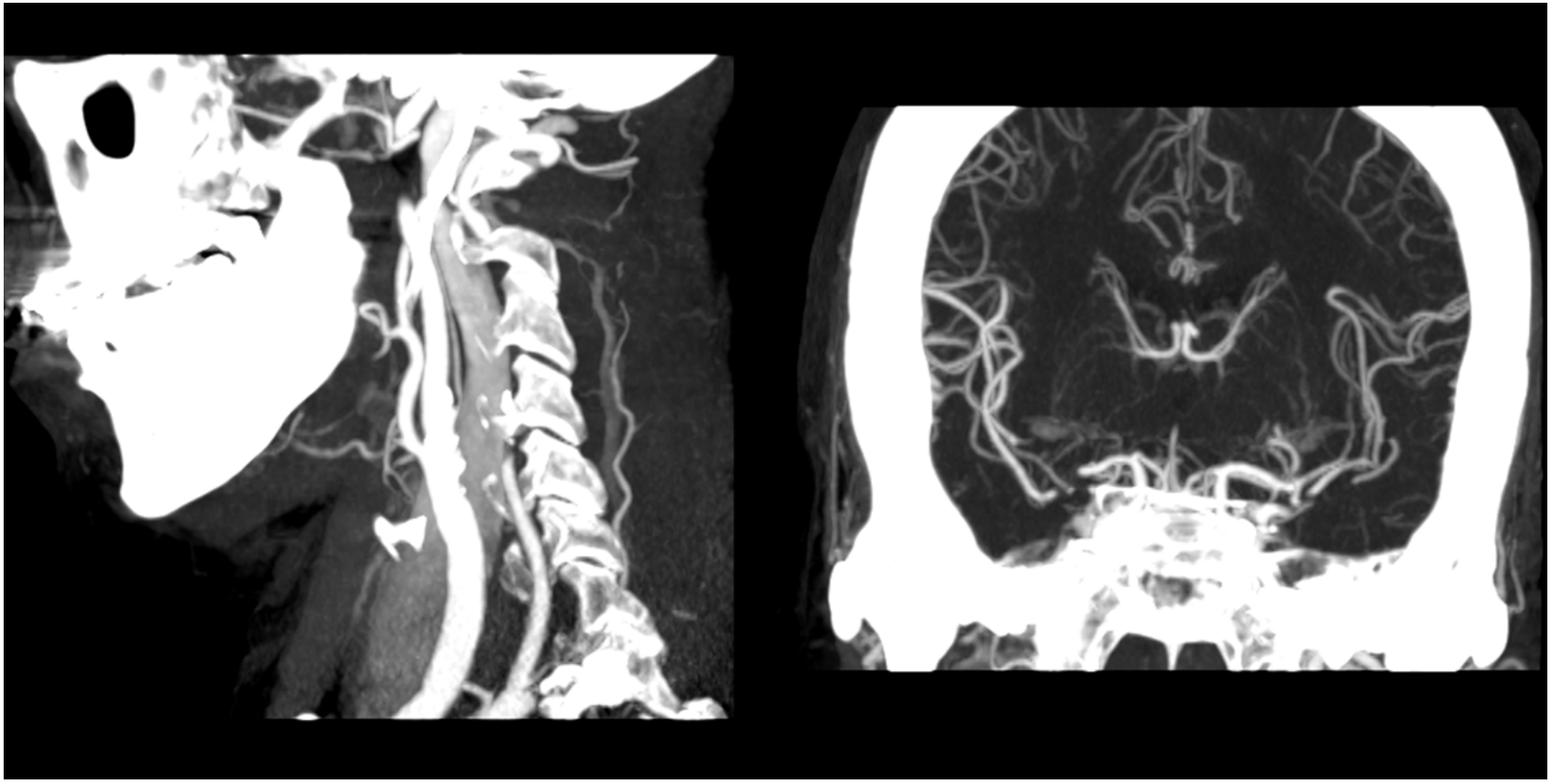
NIHSS 10
Lt. central type facial palsy, dysarthria, neglect Lt. hemiparesis
(U/Ex I, L/Ex IV-)

HTN, AF (NOAC - 금일 약을 드시지 않음)

Brain CT, 51min



Brain CTA



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.

Heidbuchel, H., et al. Europace 2013

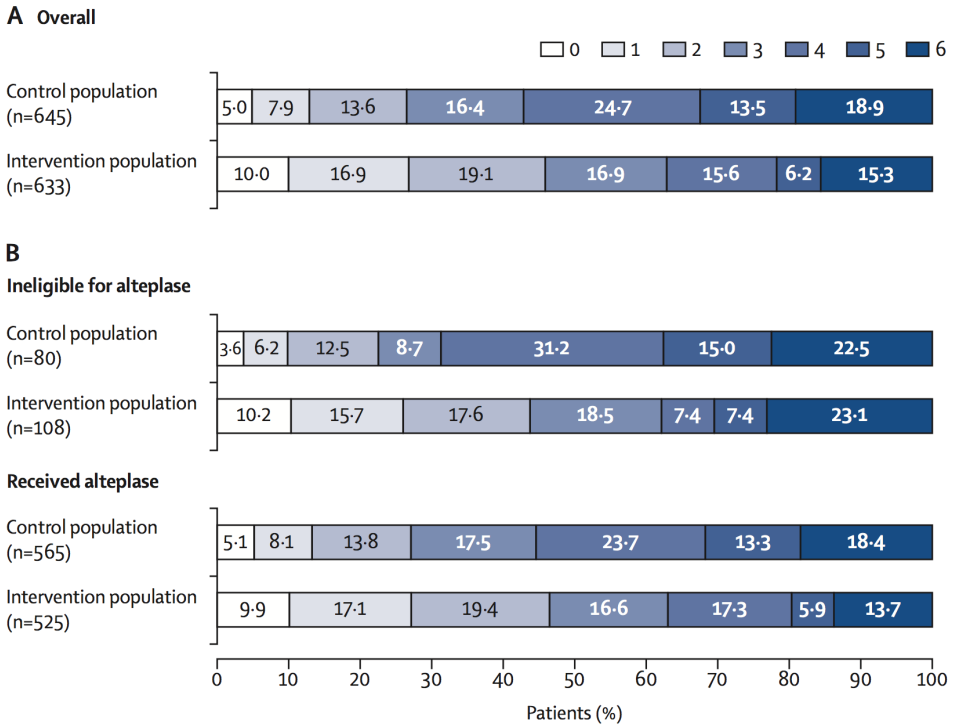
Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials

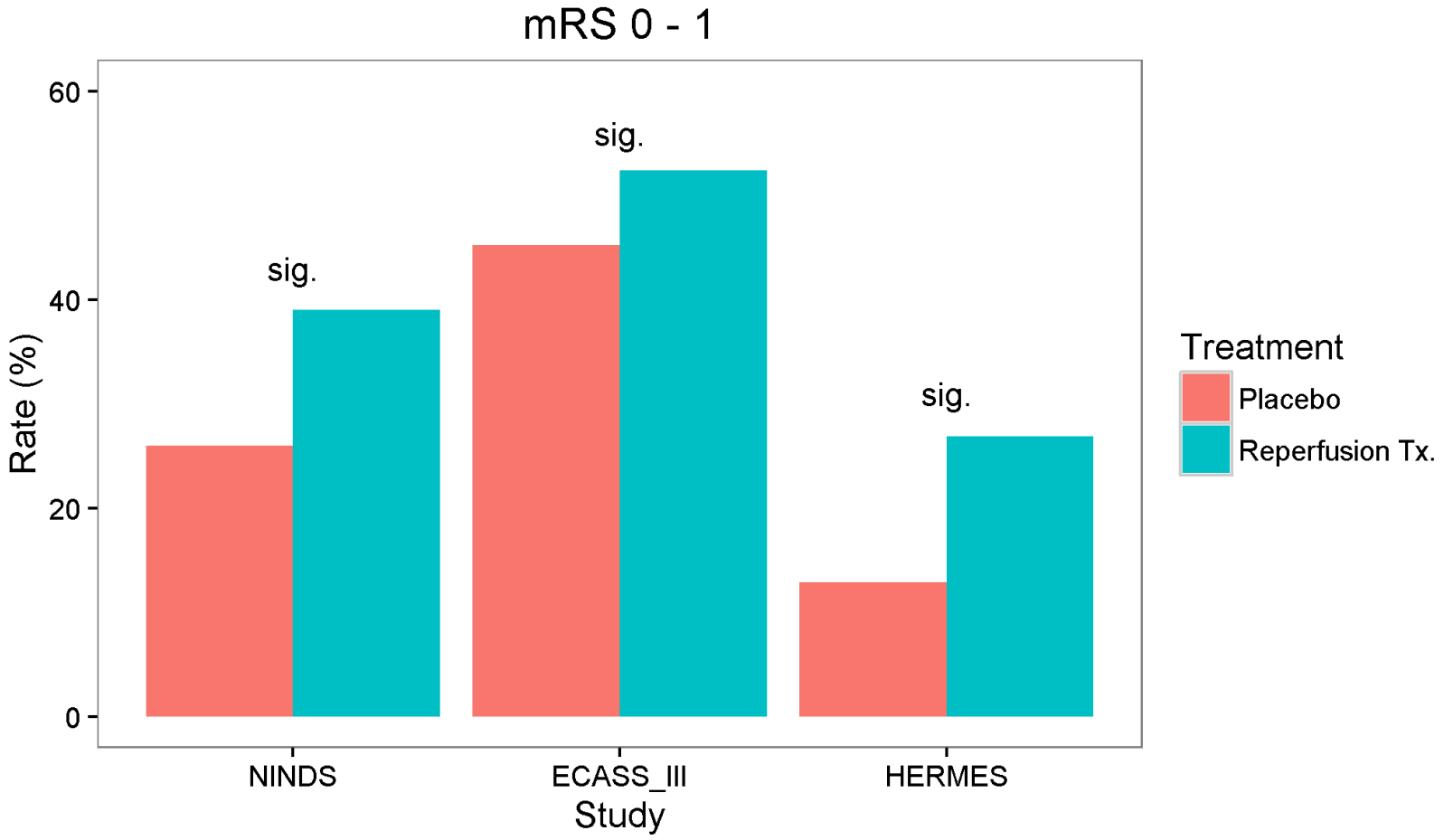
Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Diederik W J Dippel, Peter J Mitchell, Andrew M Demchuk, Antoni Dávalos, Charles B L M Majoie, Aad van der Lugt, Maria A de Miquel, Geoffrey A Donnan, Yvo B W E M Roos, Alain Bonafe, Reza Jahan, Hans-Christoph Diener, Lucie A van den Berg, Elad I Levy, Olvert A Berkhemer, Vitor M Pereira, Jeremy Rempel, Mònica Millán, Stephen M Davis, Daniel Roy, John Thornton, Luis San Román, Marc Ribó, Debbie Beumer, Bruce Stouch, Scott Brown, Bruce C V Campbell, Robert J van Oostenbrugge, Jeffrey L Saver, Michael D Hill, Tudor G Jovin, for the HERMES collaborators

Summary

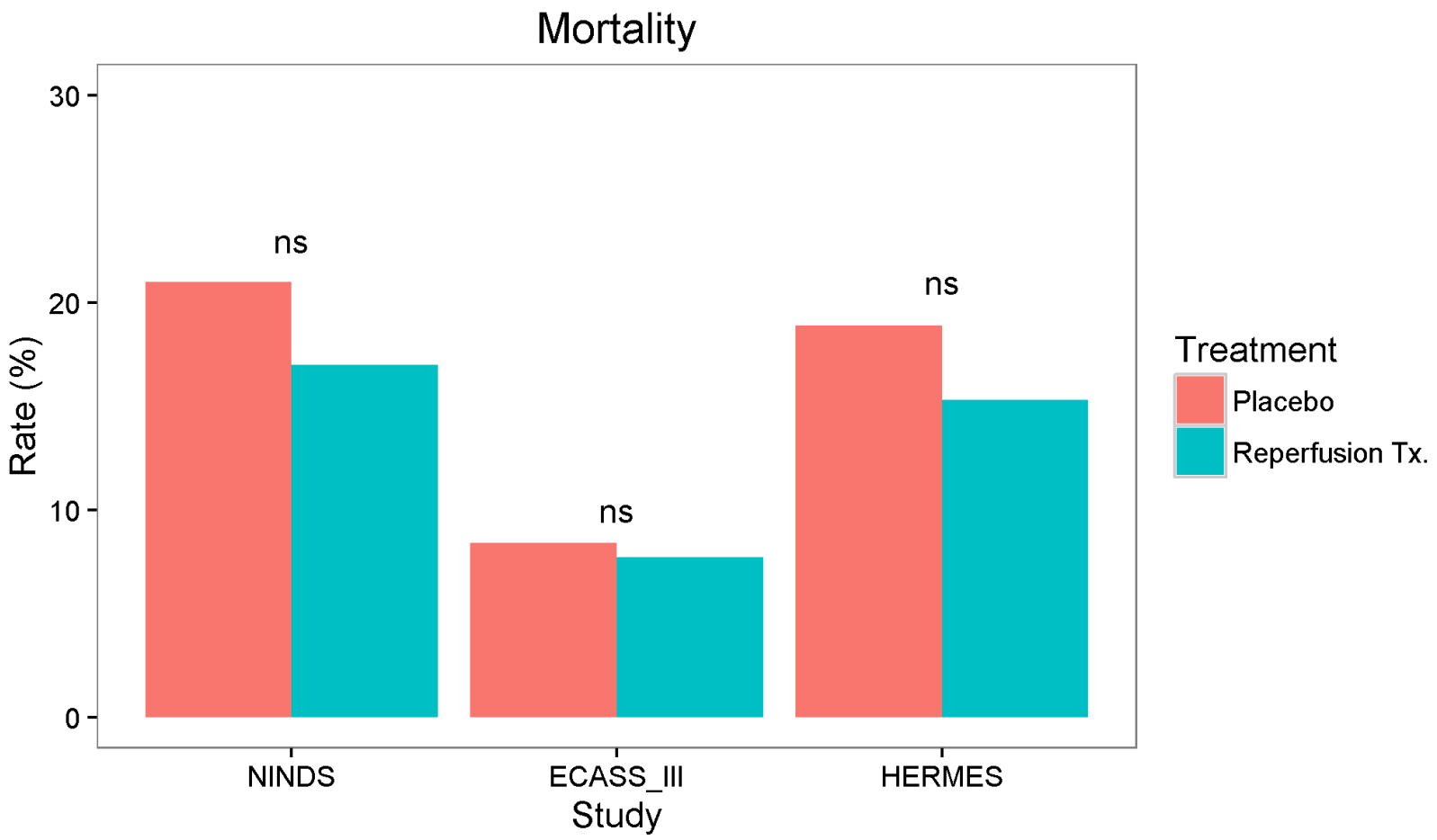
Background **In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual 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/S0140-6736(16)00163-X

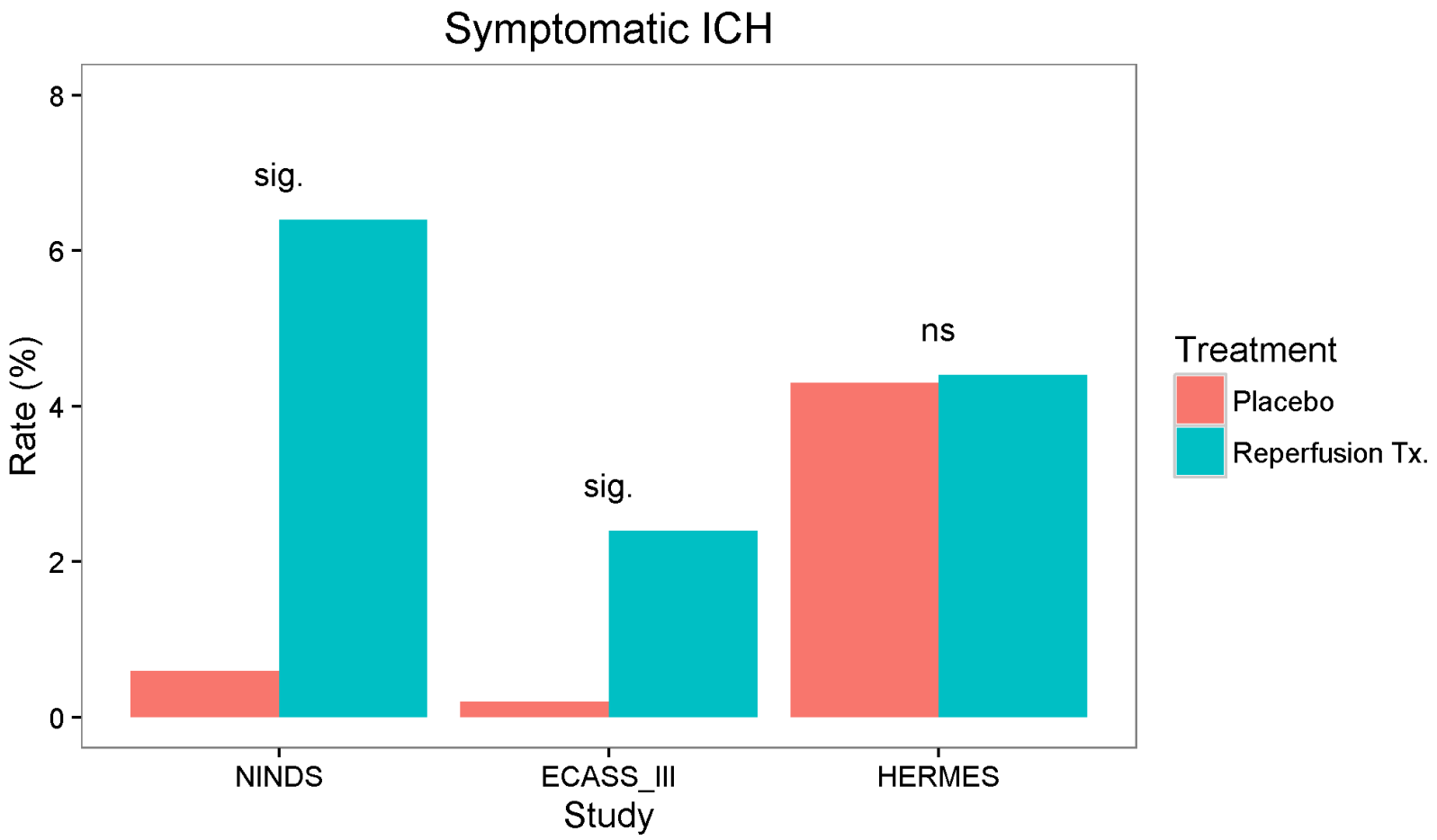




NINDS study group NEJM 1995; Hacke W et al. NEJM 2008; Goyal M et al. Lancet 2016

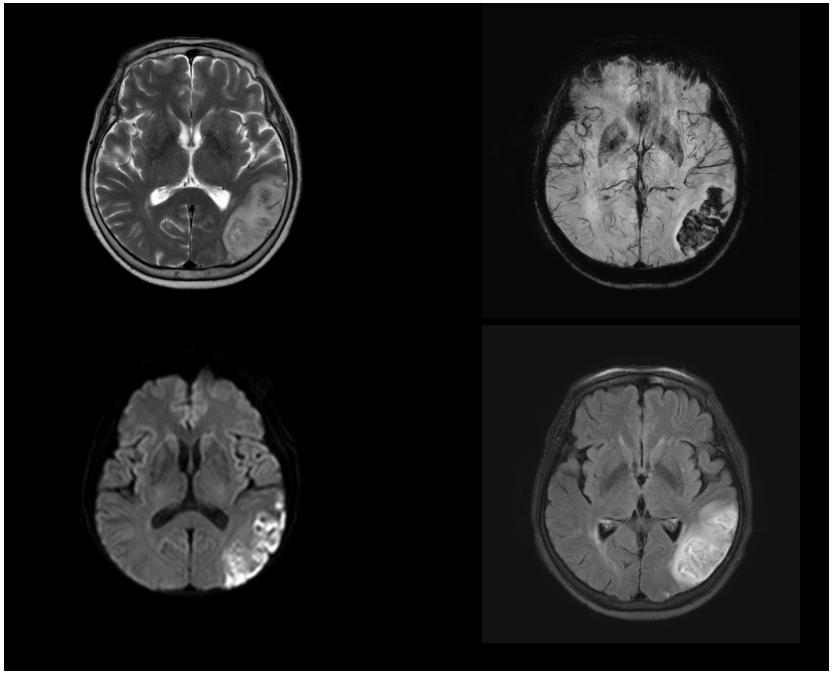


NINDS study group NEJM 1995; Hacke W et al. NEJM 2008; Goyal M et al. Lancet 2016



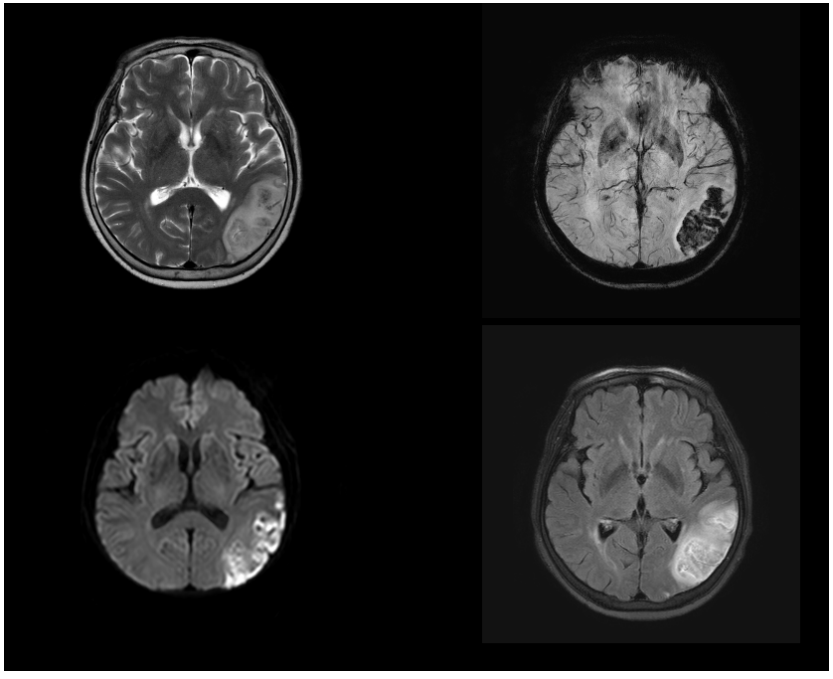
NINDS study group NEJM 1995; Hacke W et al. NEJM 2008; Goyal M et al. Lancet 2016

When to resume NOAC ?



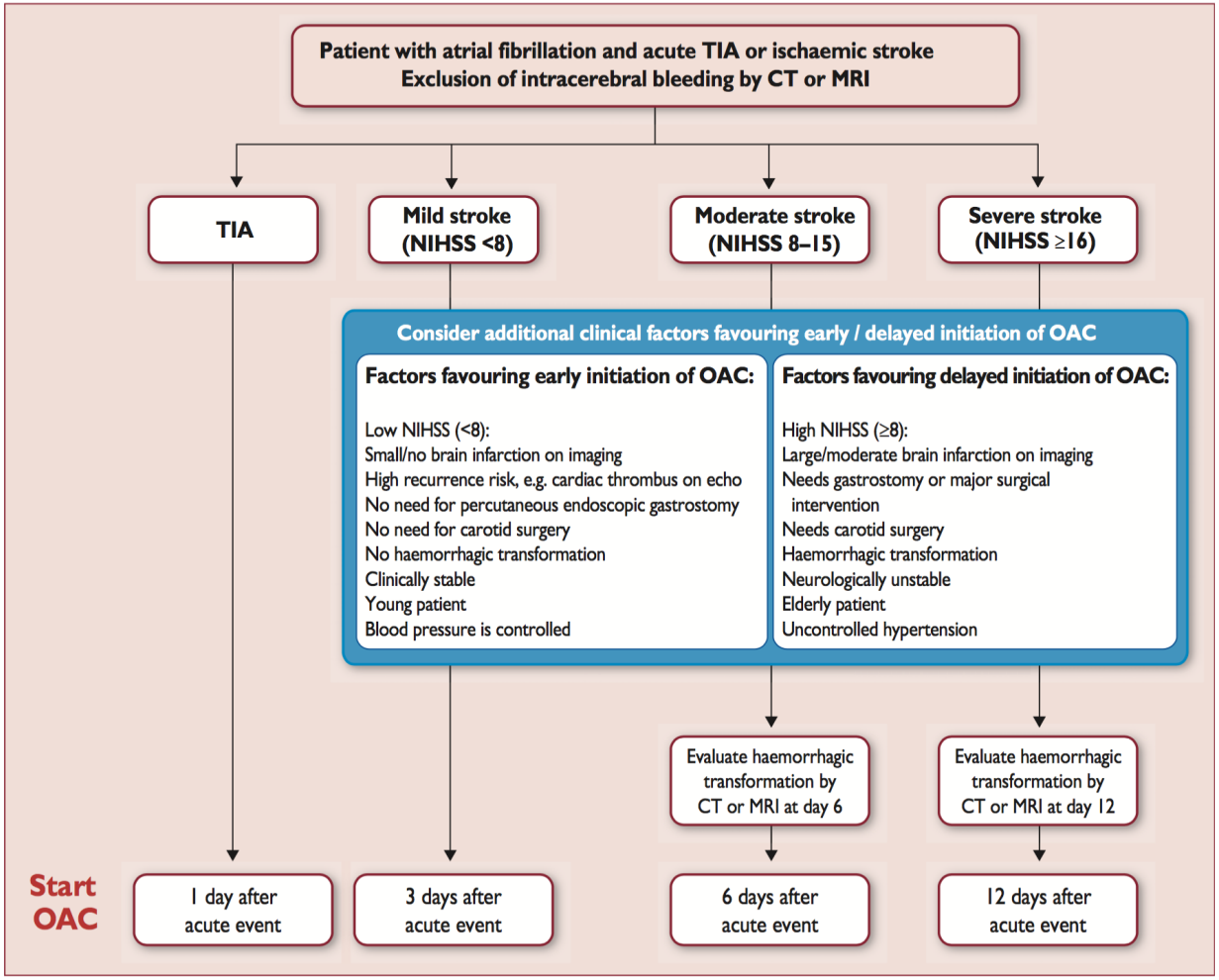
Heidbuchel, H., et al. Europace 2013

When to resume NOAC ?



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

Heidbuchel, H., et al. Europace 2013



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

Kirchhof, P. et al. Eur Heart J 2016

Dosage adjustment ?

- 75/F

Kirchhof, P. et al. Eur Heart J 2016

Dosage adjustment ?

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

Kirchhof, P. et al. Eur Heart J 2016

Dosage adjustment ?

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

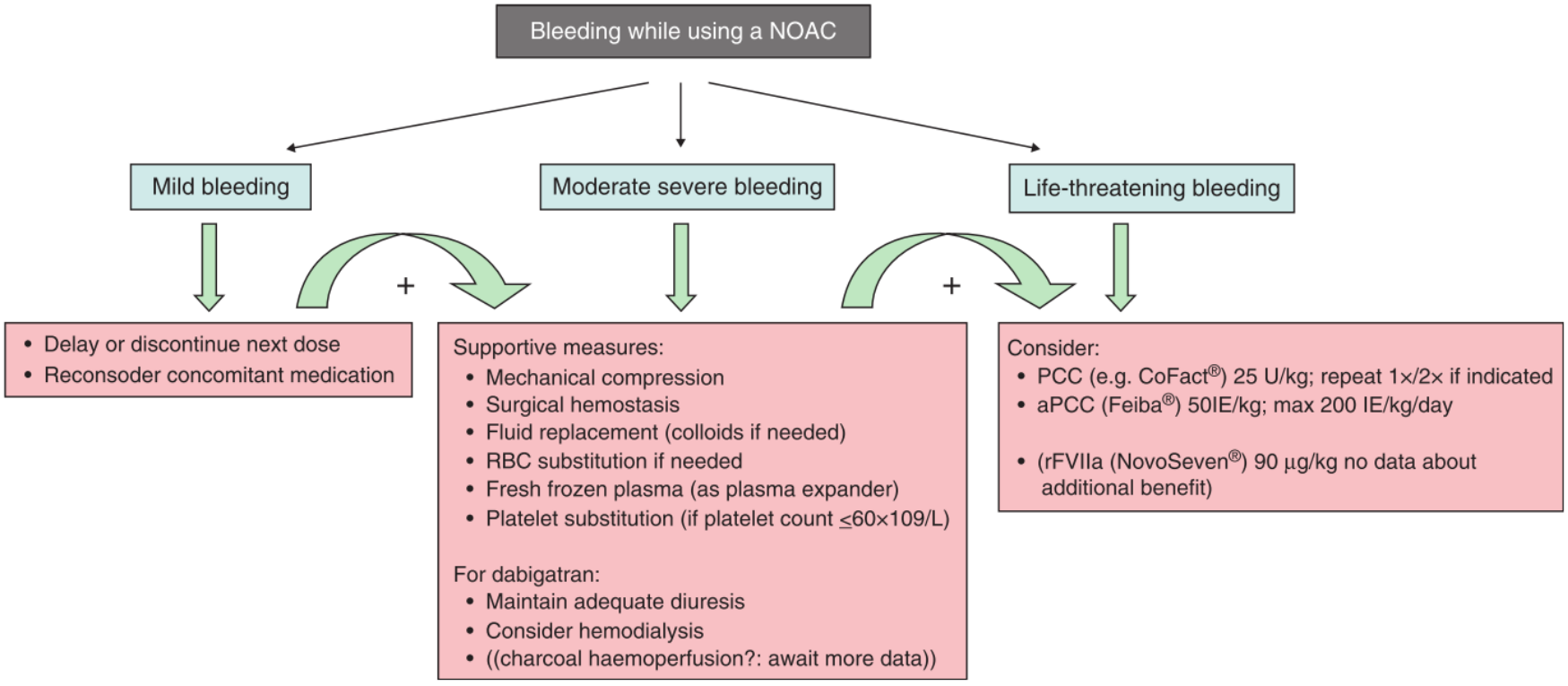
Apixaban 2.5 mg twice daily if at least 2 of

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

Kirchhof, P. et al. Eur Heart J 2016

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

Management of bleeding complication



Camm, A. J., et al. Eur Heart J. 2012

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.

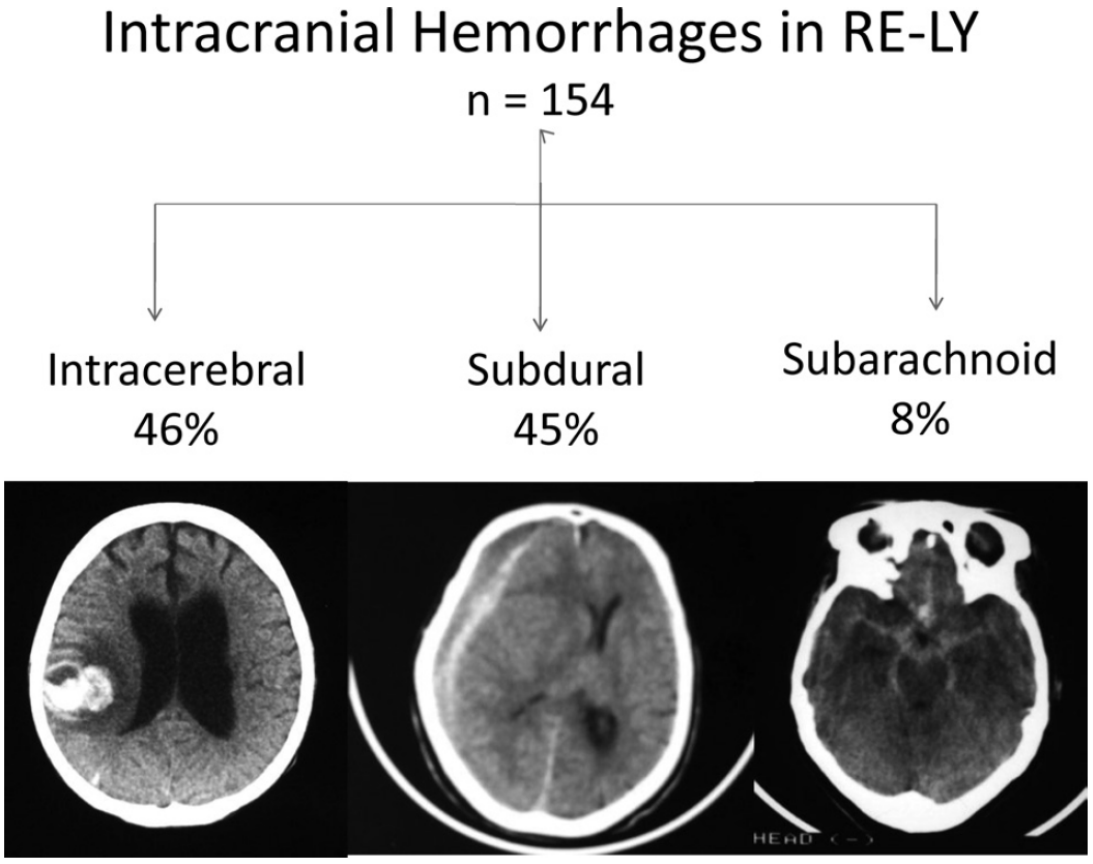
Results: We included 500 patients (97 NOAC-ICH and 403 VKA-ICH). Median baseline ICH volume was 14.4 mL (interquartile range [IQR] 3.6–38.4) for NOAC-ICH vs 10.6 mL (IQR 4.0–27.9) for VKA-ICH ($p = 0.78$). We did not find any difference between NOAC-ICH and VKA-ICH for all-cause mortality within 90 days (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



Hart, R. G. et al. Stroke 2012

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, $p=0.001$)

Hart, R. G. et al. Stroke 2012

Anticoagulation in patients with Af and ICH

To resume or Not to resume

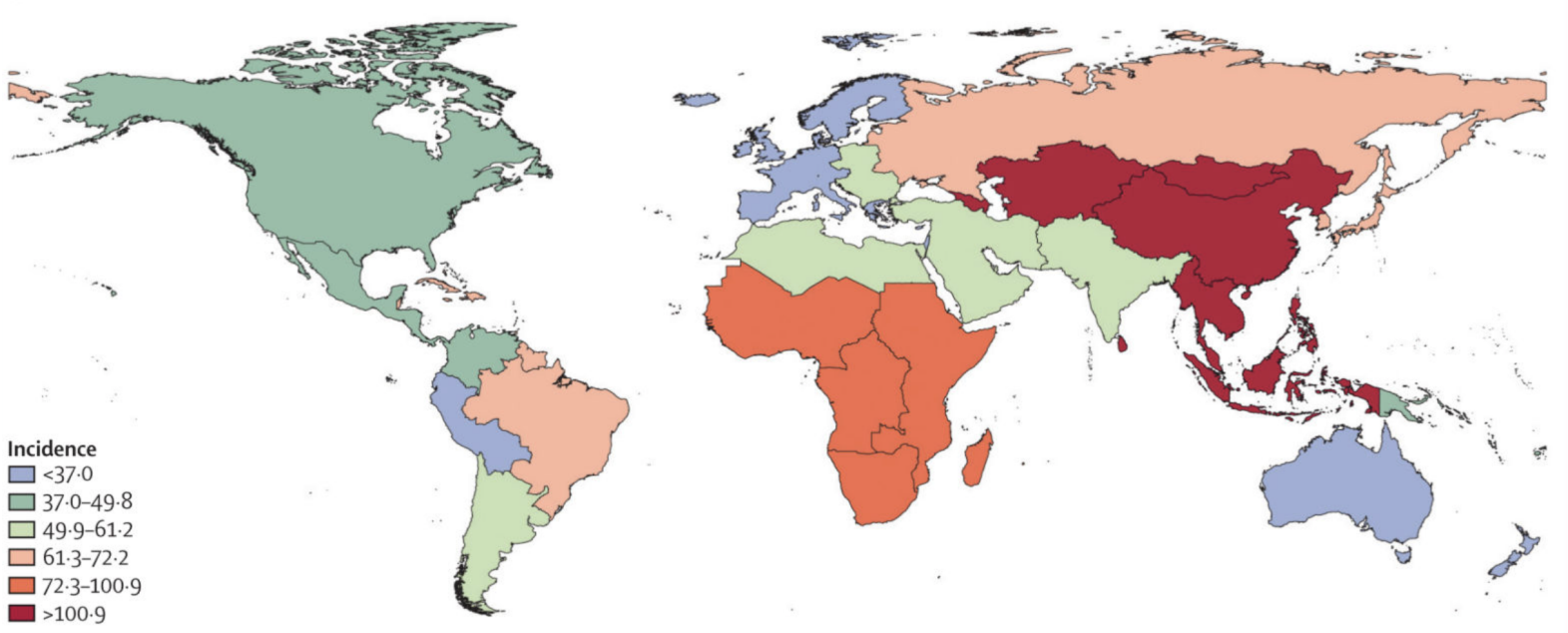
Asian

Knowing the characteristics of race is important !

https://starcraft.com/ko-kr/articles/20695698 accessed on May 25 2017

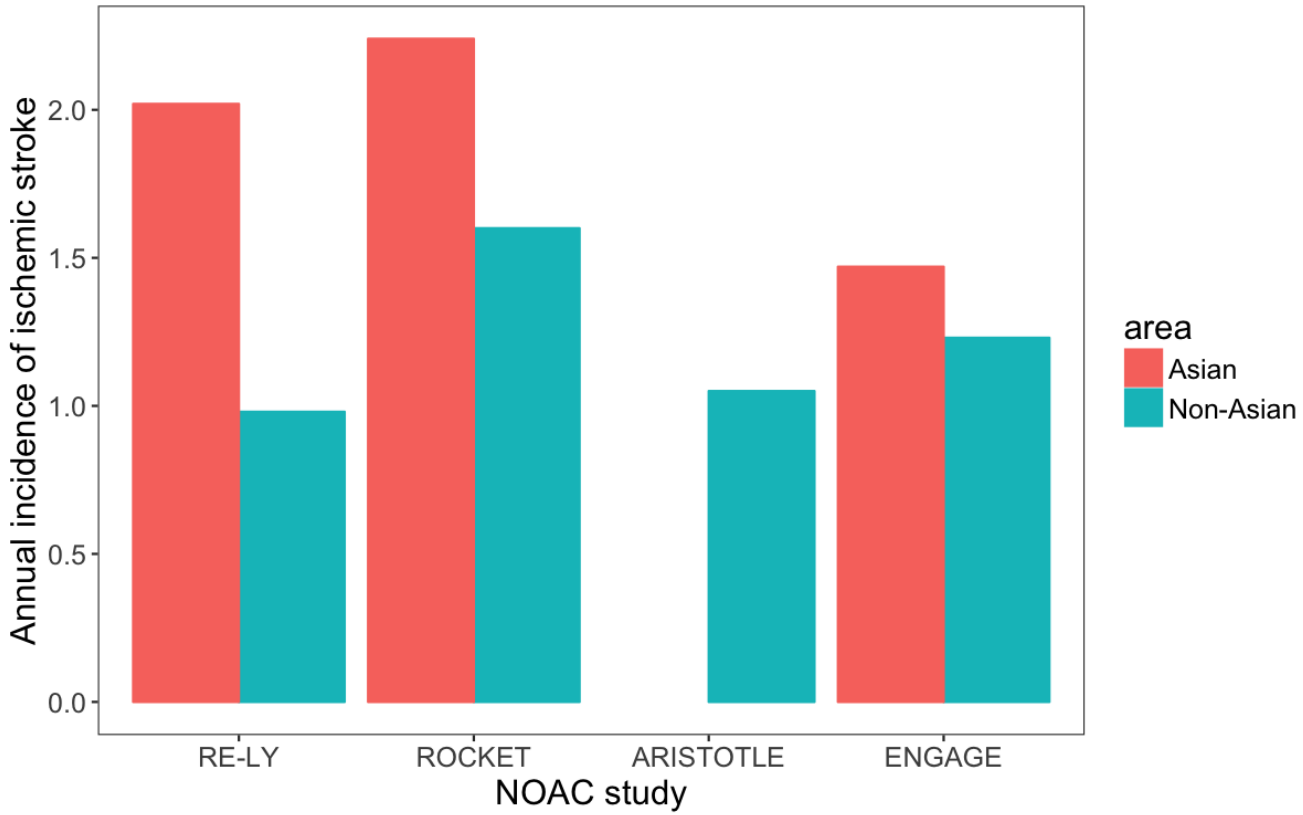
Age-standardised incidence of haemorrhagic stroke

per 100 000 person-years for 2010



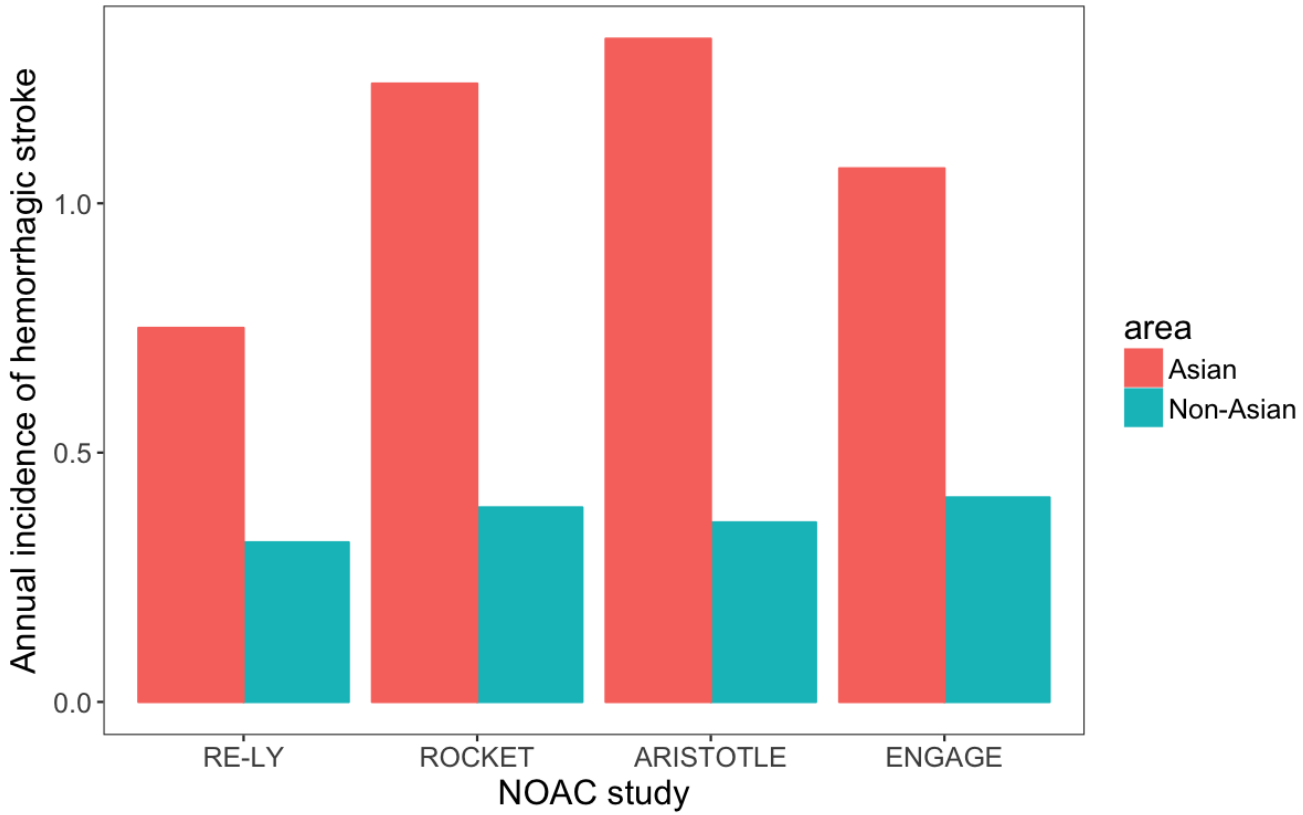
Lancet Glob Health. 2013 Nov; 1(5): e259–e281.

Ischemic stroke on warfarin



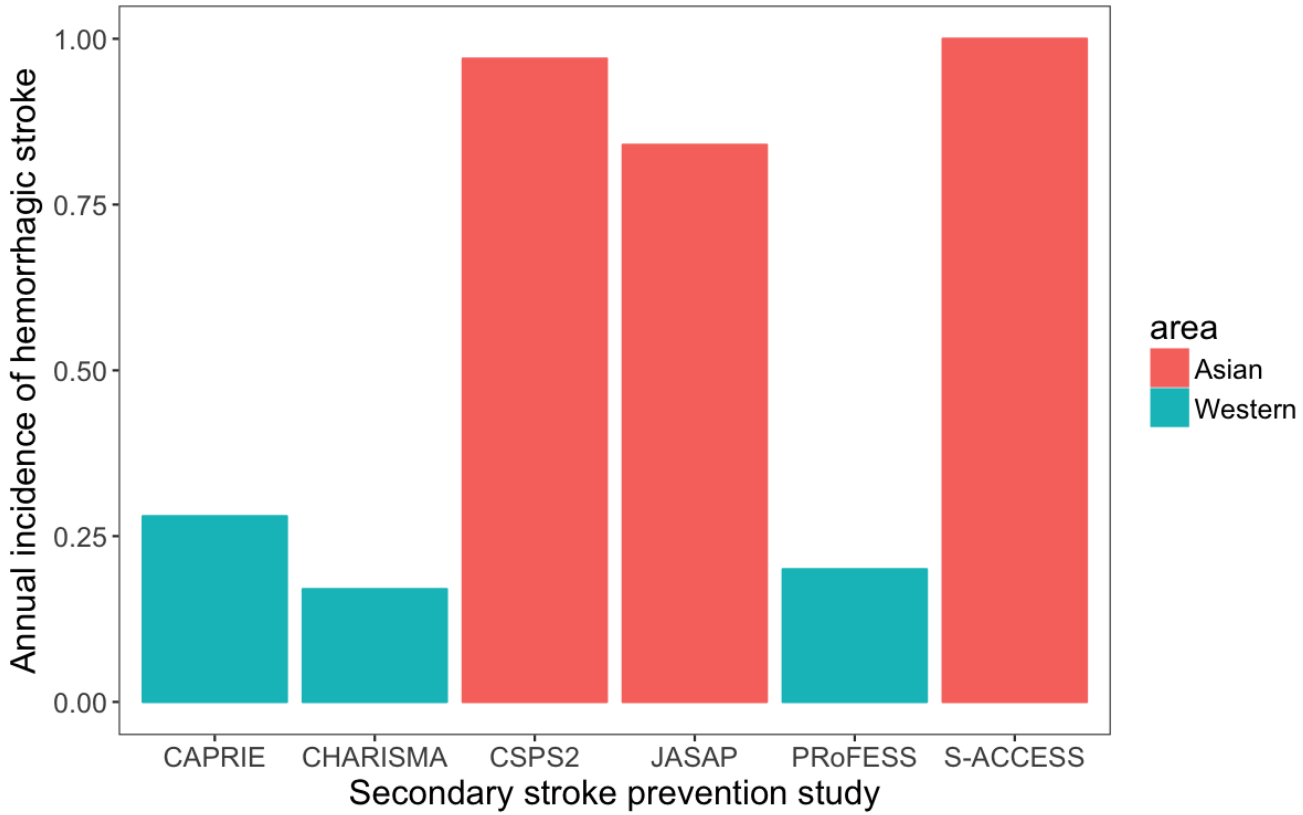
Lip GYH et al, Int J Cardiol 2015;180:246

hemorrhagic stroke on warfarin



Lip GYH et al, Int J Cardiol 2015;180:246

Incidence of Cerebral Hemorrhage with Aspirin



1. Kim JS, et al. Int J Stroke 2015;10 Suppl 1:1-9.

Age

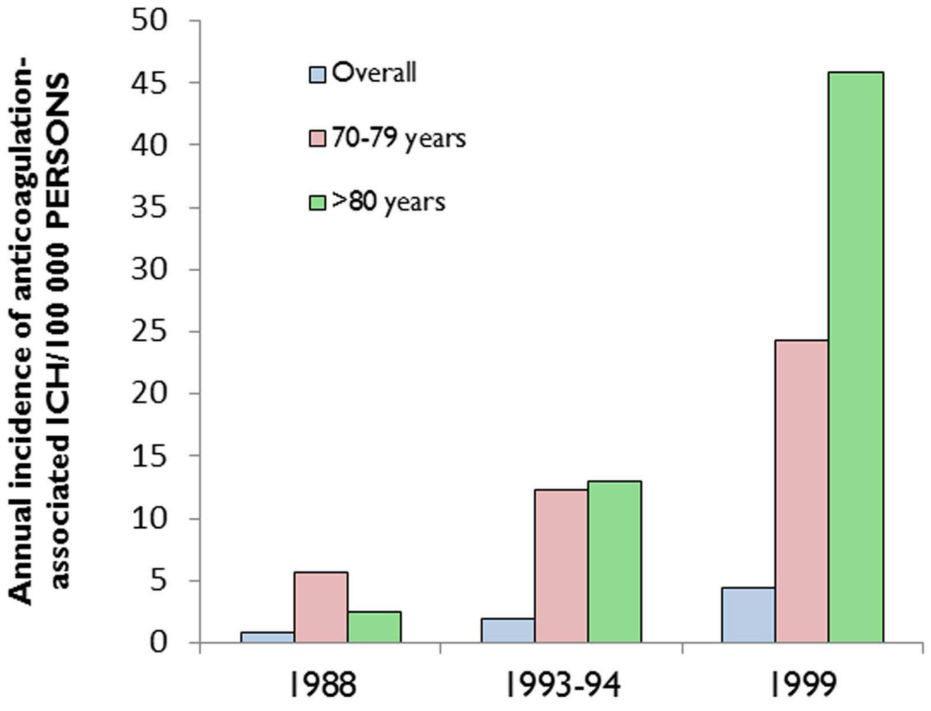


FIGURE 1 | The increasing incidence of anticoagulation-associated intracerebral hemorrhage (ICH), especially in the elderly. Data extracted from (Flaherty et al., 2007).

Charidimou A et al. Front Neurol 2012;3:133

Burden of SVD

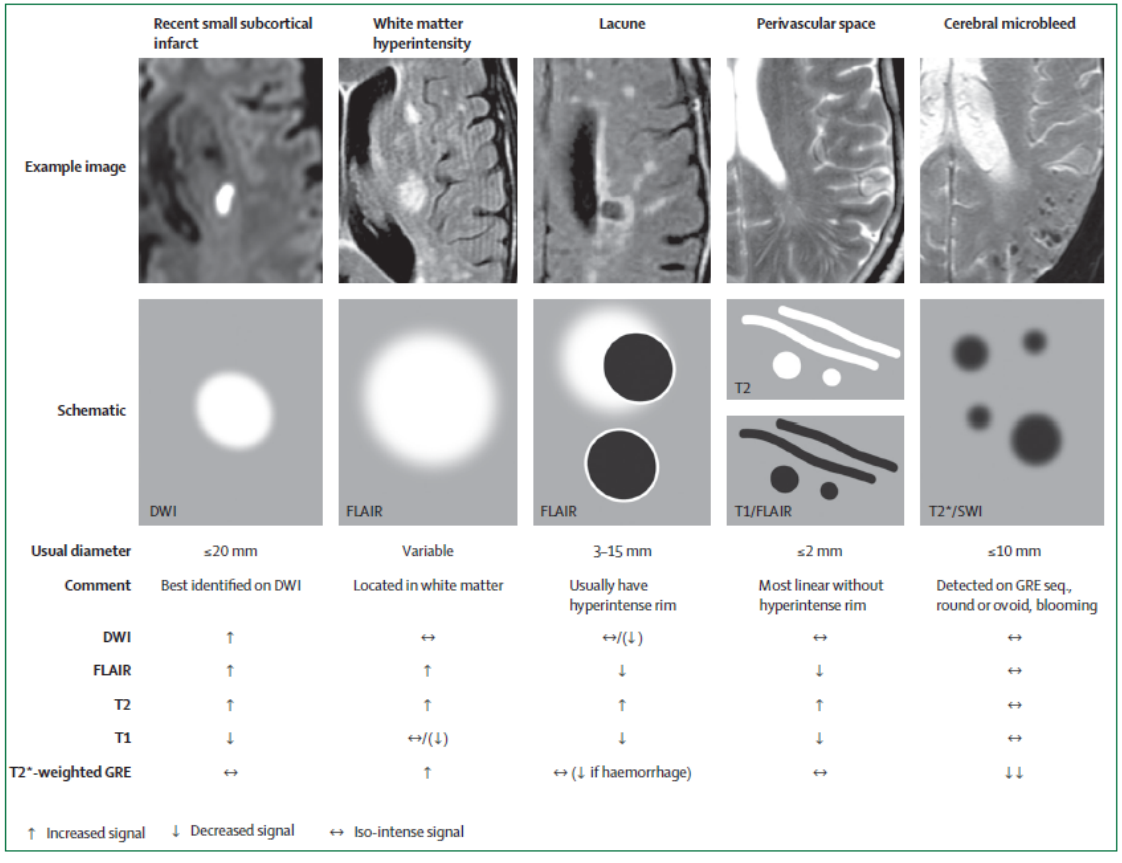
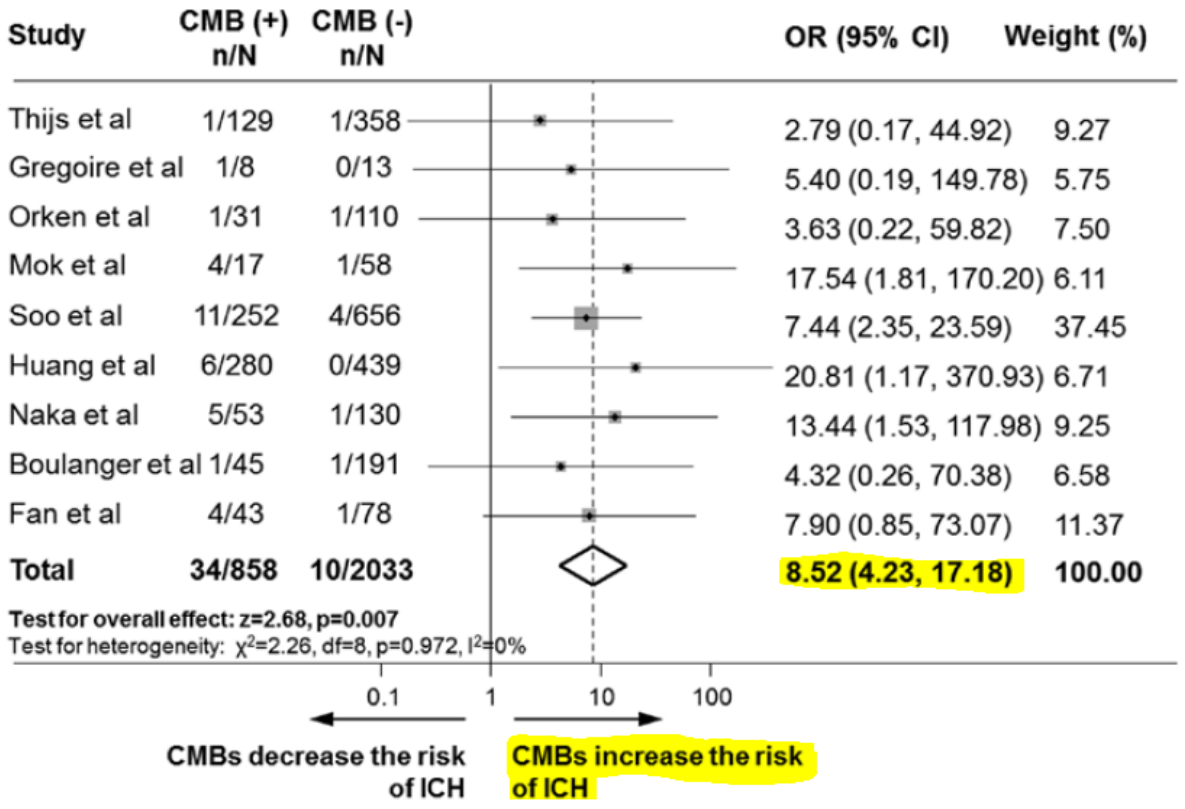


Figure 2: **MRI findings for lesions related to small vessel disease**

Wardlaw JM et al. Lancet Neurol 2013; 12: 822–38



Charidimou A et al. Am J Cardiol 2013;112:1230e1234

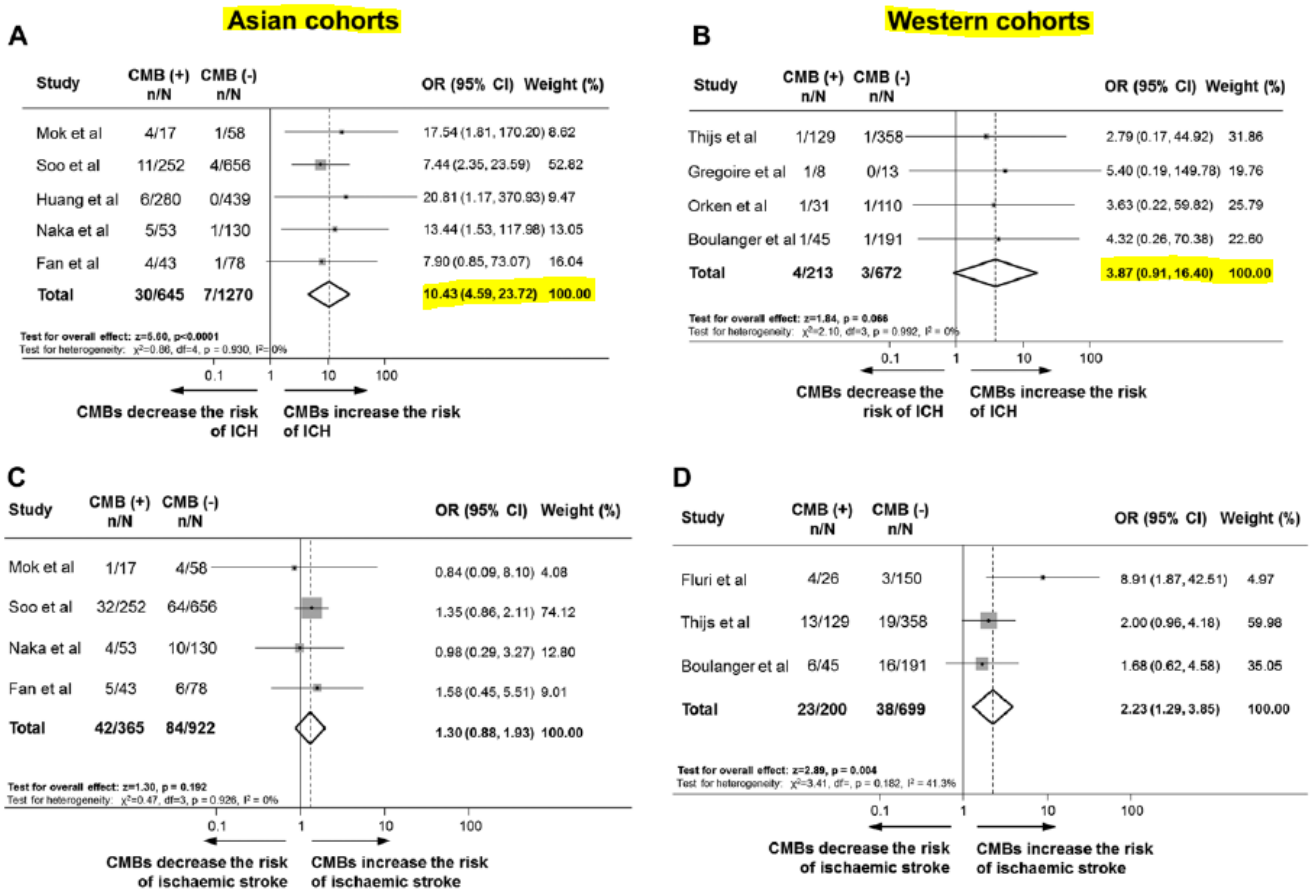


Figure 4. Meta-analysis of the risk of spontaneous intracerebral hemorrhage (ICH; **A** and **B**) and ischemic stroke (**C** and **D**) stratified by the dominant ethnicity of subjects included in each cohort as Asian or Western (white), with and without cerebral microbleeds (CMBs).

Charidimou A et al. Am J Cardiol 2013;112:1230e1234

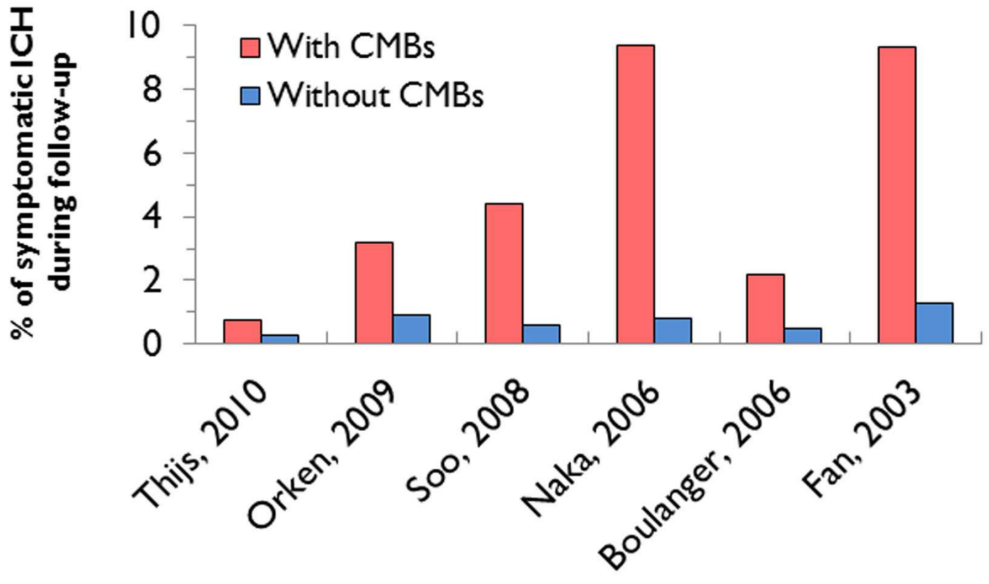


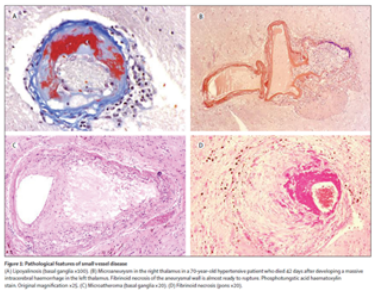
FIGURE 5 | Incidence of intracerebral hemorrhage in relation to the presence of cerebral microbleeds (CMBs) in the main prospective cohort studies which have assessed this risk in patients with ischemic stroke or TIA (Table 3).

Charidimou A et al. Front Neurol 2012;3:133

CAA or lobar bleed

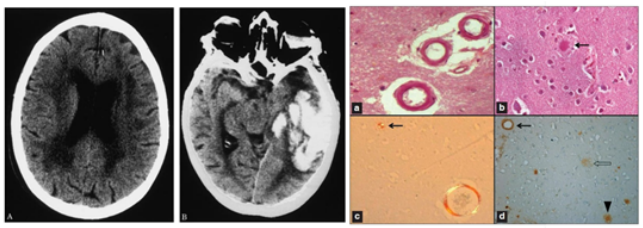
Arteriolosclerosis

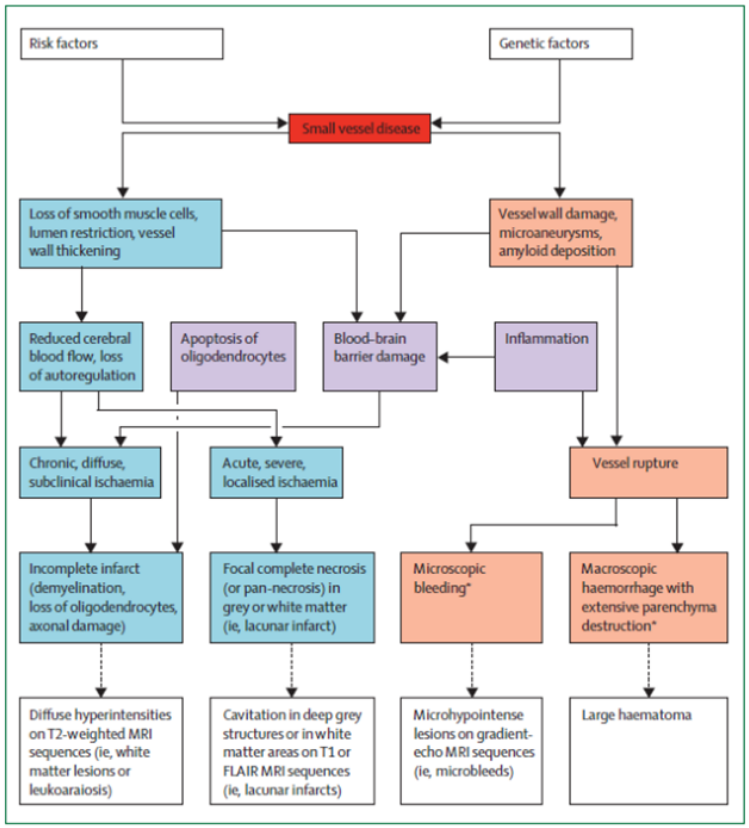
- Hypertensive SVD
- Age-related SVD
- Associated with Aging, diabetes, and hypertension
- Pathology
  - Lipohyalinosis
  - Microatheroma
  - Microaneurysm



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)





Pantoni L. Lancet Neurol 2010; 9: 689–701

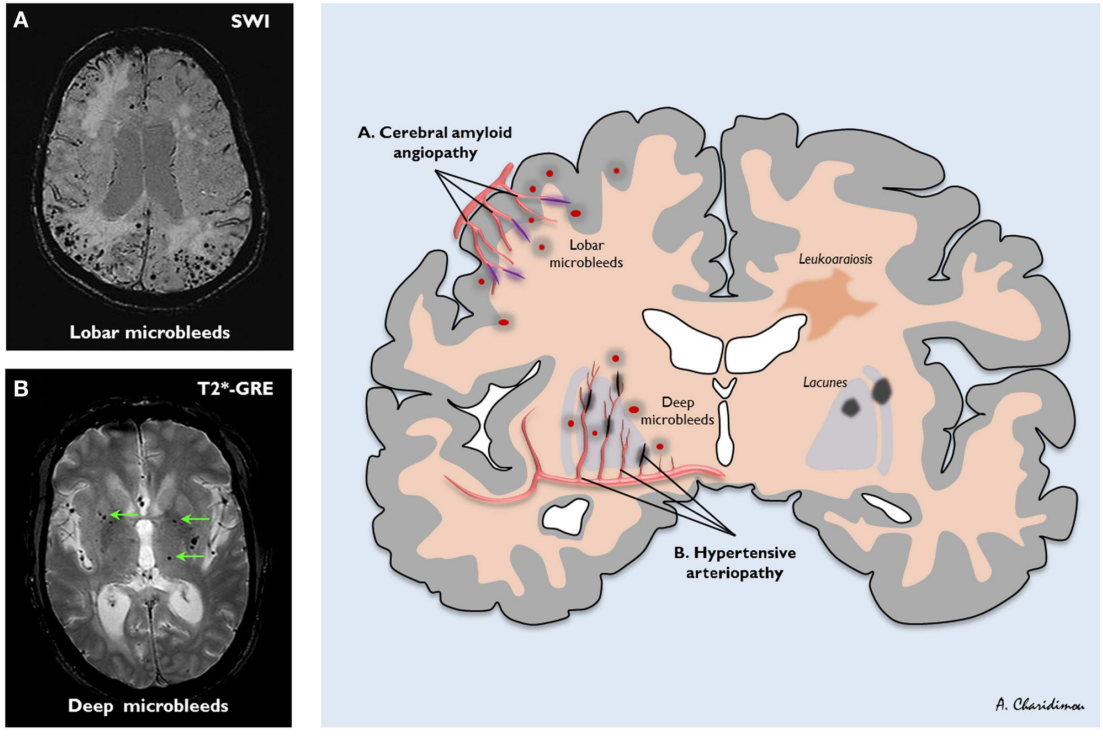


FIGURE 3 | The distribution of sporadic small vessel disease in the brain and the topography of cerebral microbleeds (CMBs). (A) Cerebral amyloid angiopathy (CAA) preferentially affects the small arteries and arterioles of the cerebral cortex and gray–white matter junction by the deposition of amyloid-β 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.

Charidimou A et al. Front Neurol 2012;3:133

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 Salman[3]

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

			Follow-up		Recurrence risk (%, 95% CI)		
Study	**Sample size**	**Inception point**	**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*[54]	71	30 days after onset	3	Rate‡	–	14.3	–
Yen *et al*[42]	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.

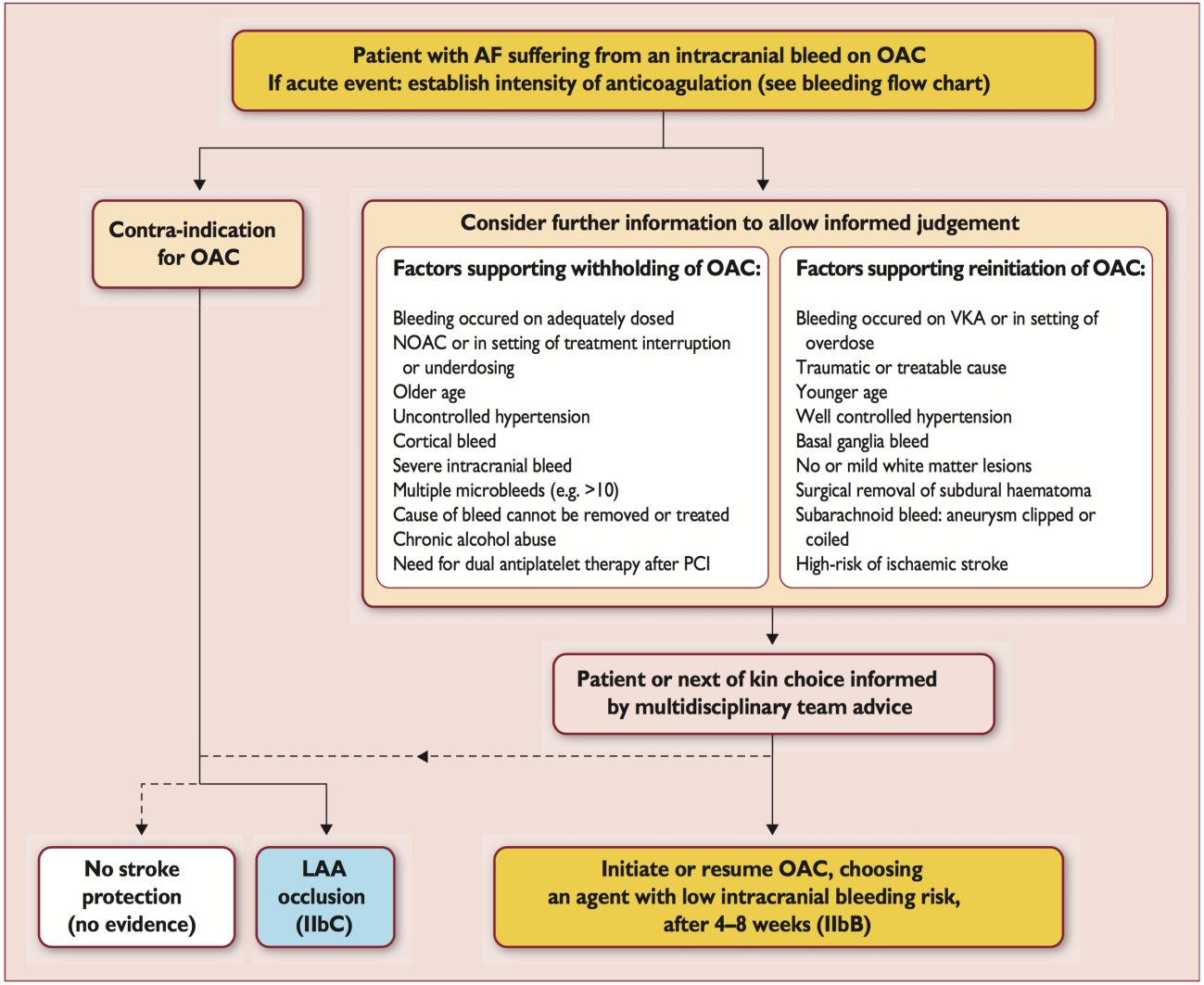
Poon MTC, et al. J Neurol Neurosurg Psychiatry 2014;85:660–667

To resume AC (Modifiable)

- Uncontrolled HTN
- Triple therapy
- High INR on VKA

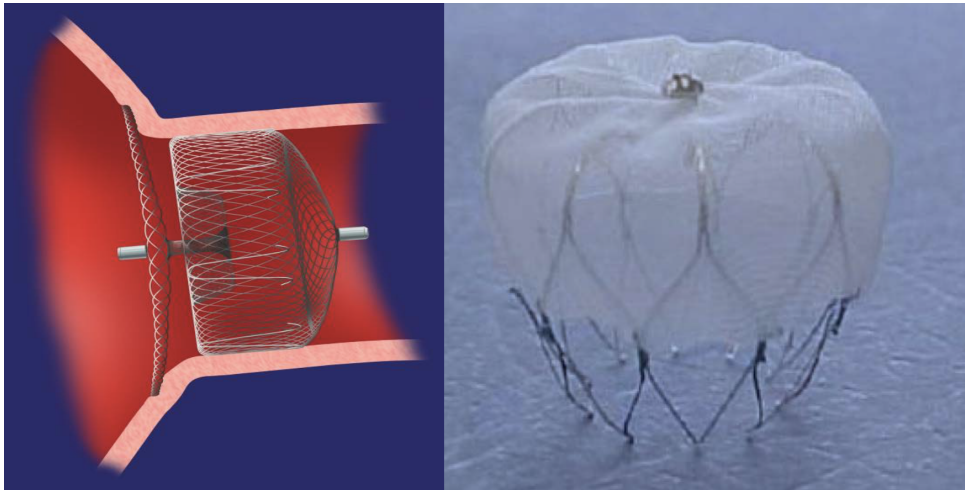
Not to resume AC (Not modifiable)

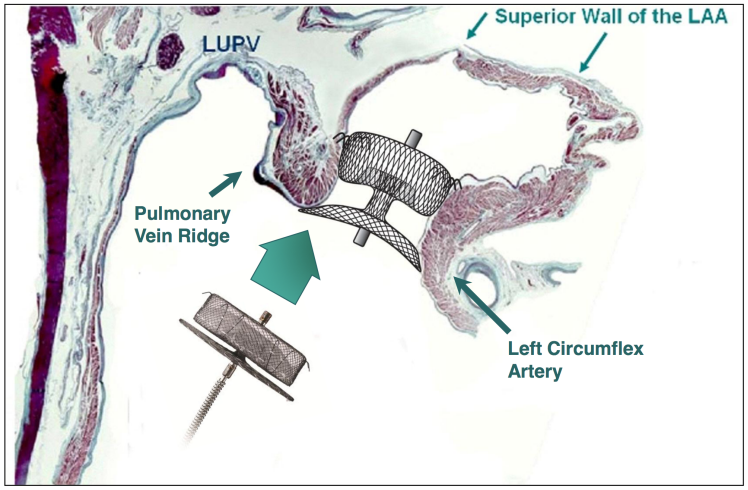
- older age
- persistent uncontrolled hypertension
- lobar bleeds
- severe WM lesions
- multiple CMBs > 30
- chronic alcoholism
- need for DAPT after PCI



Kirchhof, P. et al. Eur Heart J 2016

Left atrial appendage occlusion





Courtesy of Shin SY, Dep. of Cardiology CAUH

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