

경피적 좌심방 중재술 연구회 심포지움 2017

How to deal with patients with recurrent bleeding events while taking NOACs



Kwang-Yeol Park

Dep. of Neurology, Chung-Ang University

Table of Contents

1 Atrial Fibrillation and Stroke

2 Stroke in Asia

3 Bleeding on NOAC

- Change to another NOAC
- Reduced dosage
- LAAO

4 Summary

Cardioembolic stroke

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

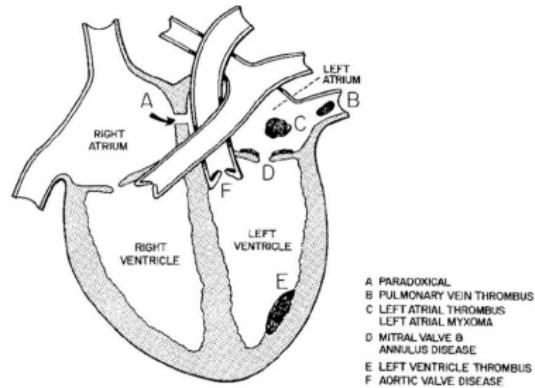


Figure 1. Cardiac causes of stroke (Adapted from Barnett et al)

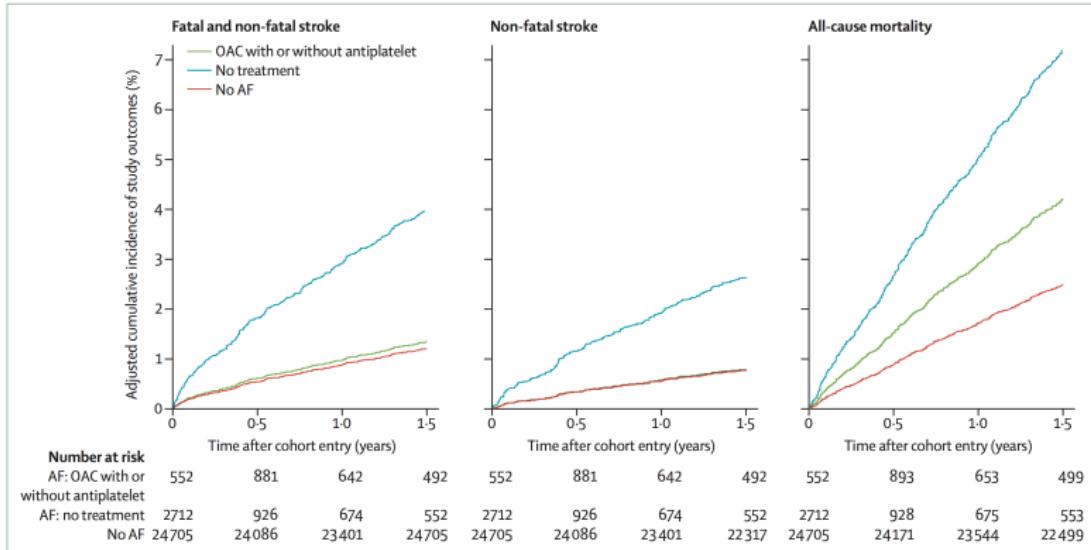
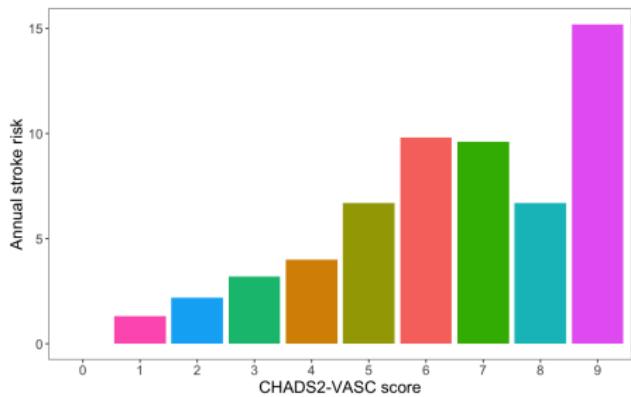


Figure 2: Effect of treatment on incidentally detected atrial fibrillation

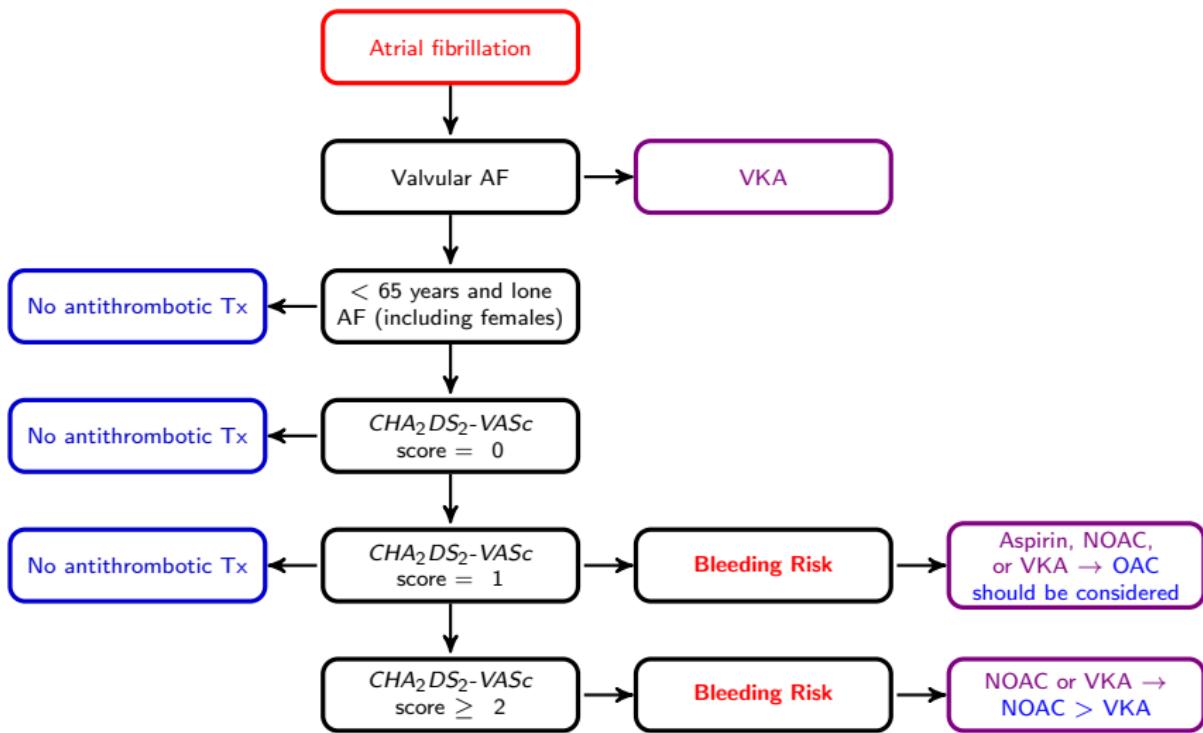
AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.²¹

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

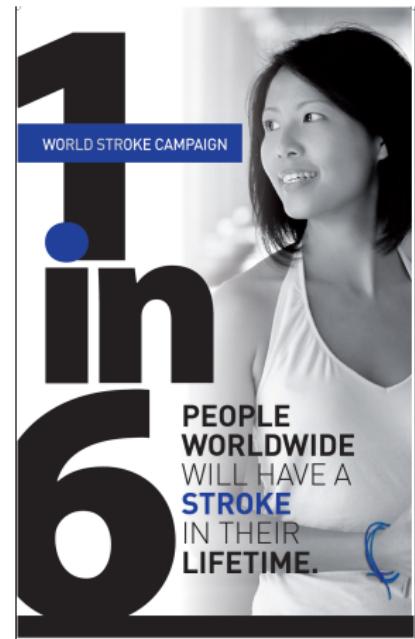
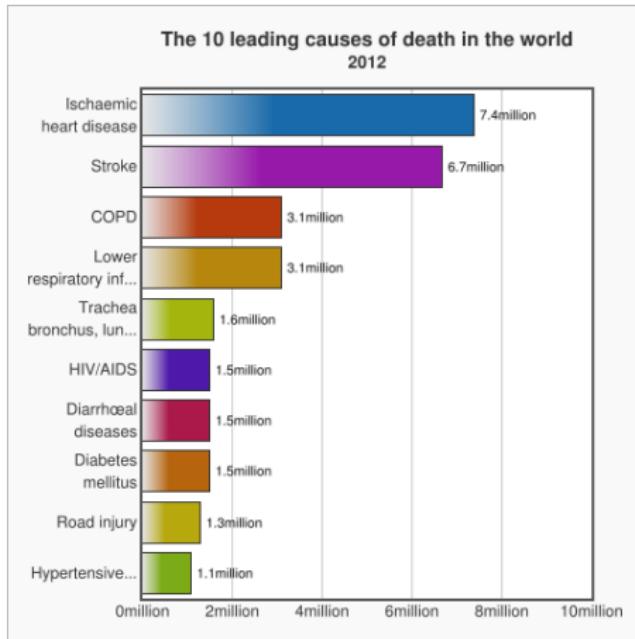


Gage BF et al. JAMA 2001;285:2864–70; Lip G et al. Chest 2010;137:263–72
January, C. T., et al. Circulation 2014



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

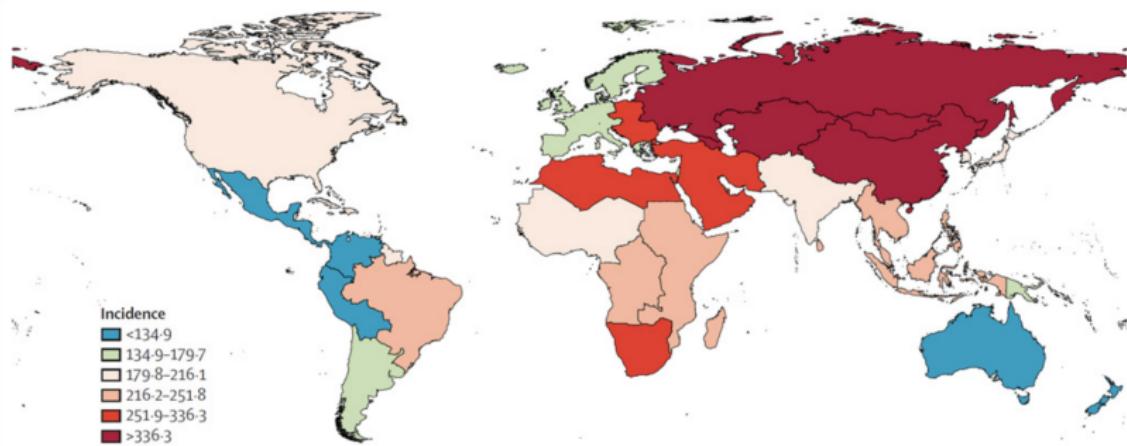
Global burden of stroke



<http://www.who.int/mediacentre/factsheets/fs310/en/> accessed on Jan 16, 2016

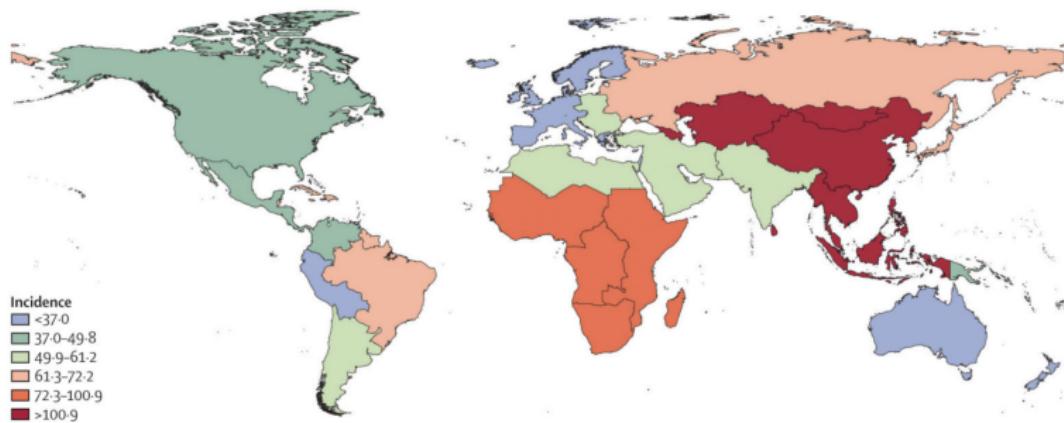
<http://www.worldstrokecampaign.org/get-involved/2015-08-20-01-49-19/campaign-posters.html>

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



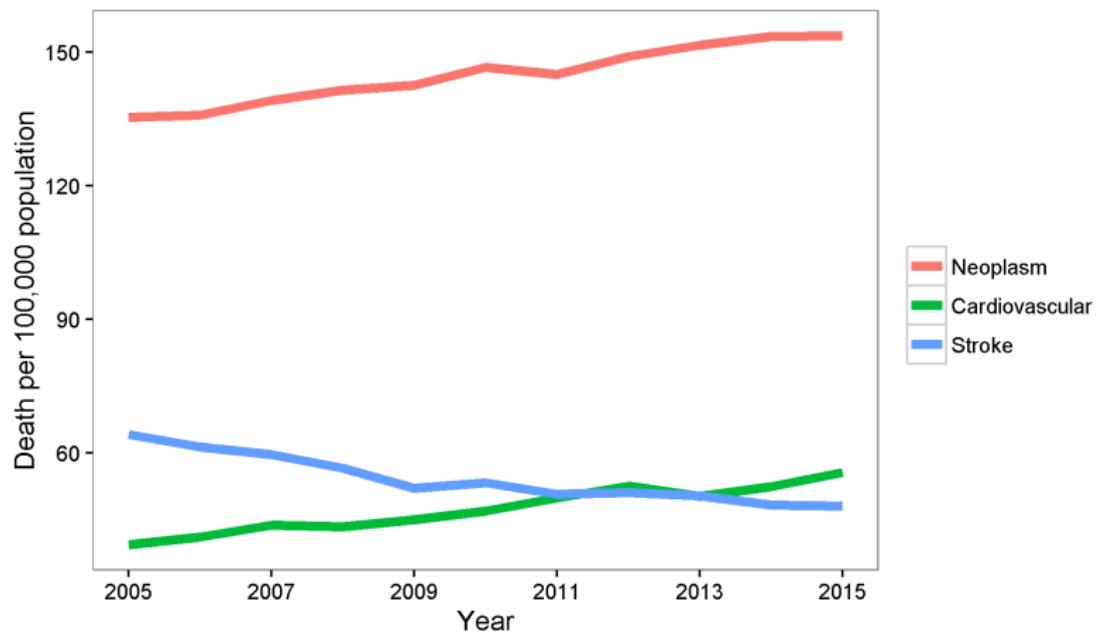
Lancet Neurol. 2014 383(9913): 245–254.

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



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

Secular trend of mortality in Korea



http://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1012 accessed on Nov 03, 2016

Etiologies of stroke

Ischemic Stroke

- Atherosclerosis
- Small artery occlusion
- Cardiac disease causing embolism
- Other causes such as moyamoya disease

Hemorrhagic Stroke

- Hypertensive hemorrhage
- Cerebral amyloid angiopathy
- Arteriovenous malformations
- Subarachnoid hemorrhage

Higher risk of hemorrhagic stroke should be considered when choosing the anti-thrombotic medication in Asians.

MRI findings of small vessel disease

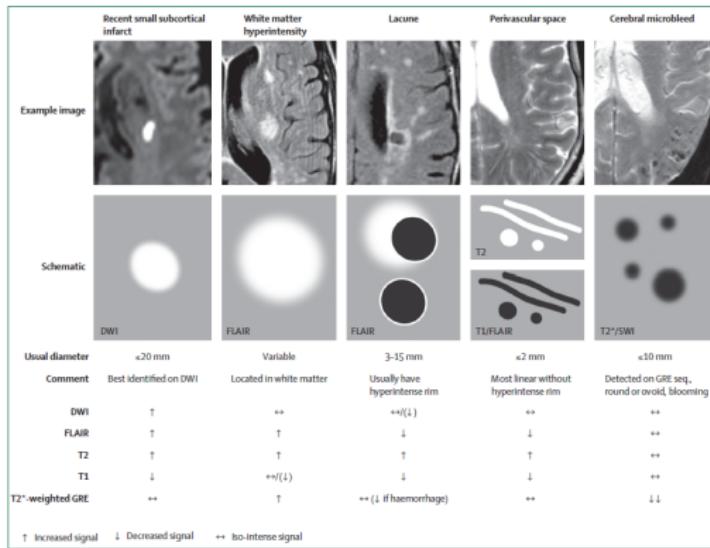


Figure 2: MRI findings for lesions related to small vessel disease

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

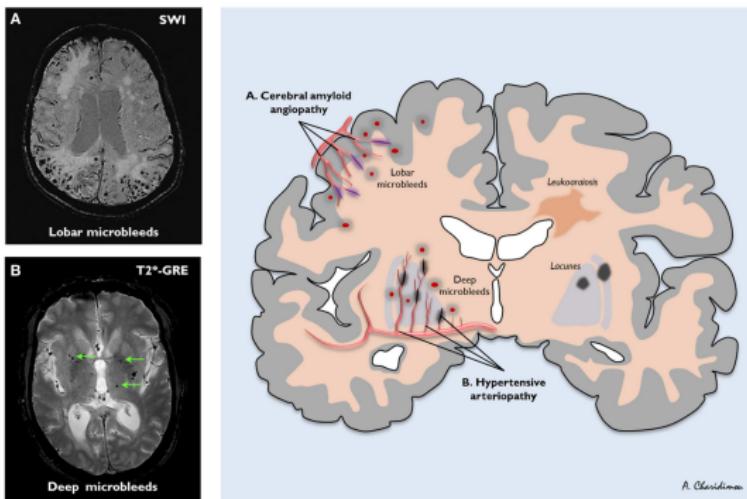


FIGURE 3 |The distribution of sporadic small vessel disease in the brain and the topography of cerebral microbleeds (CMBs). **(A)** Cerebral amyloid angiopathy (CAA) preferentially affects the small arteries and arterioles of the cerebral cortex and gray-white matter junction by the deposition of amyloid-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

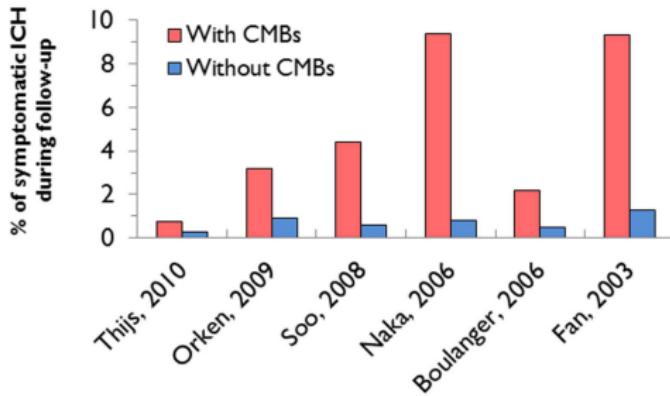
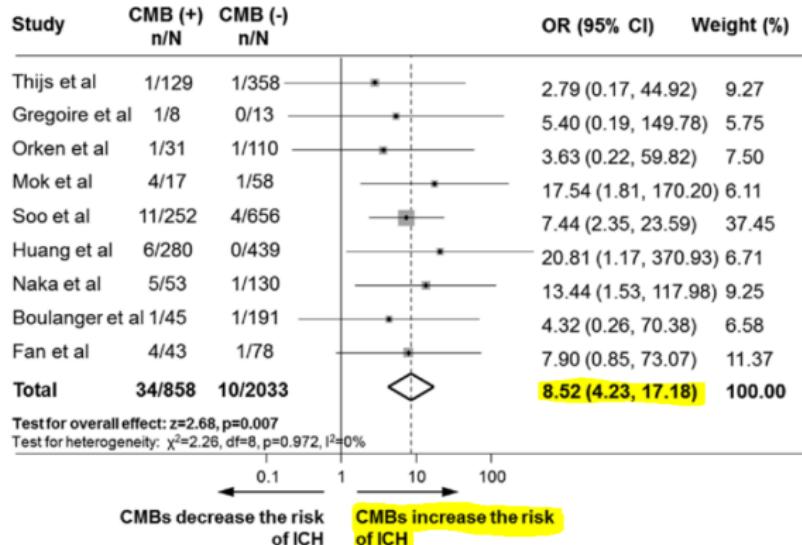


FIGURE 5 | Incidence of intracerebral hemorrhage in relation to the presence of cerebral microbleeds (CMBs) in the main prospective cohort studies which have assessed this risk in patients with ischemic stroke or TIA (Table 3).



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

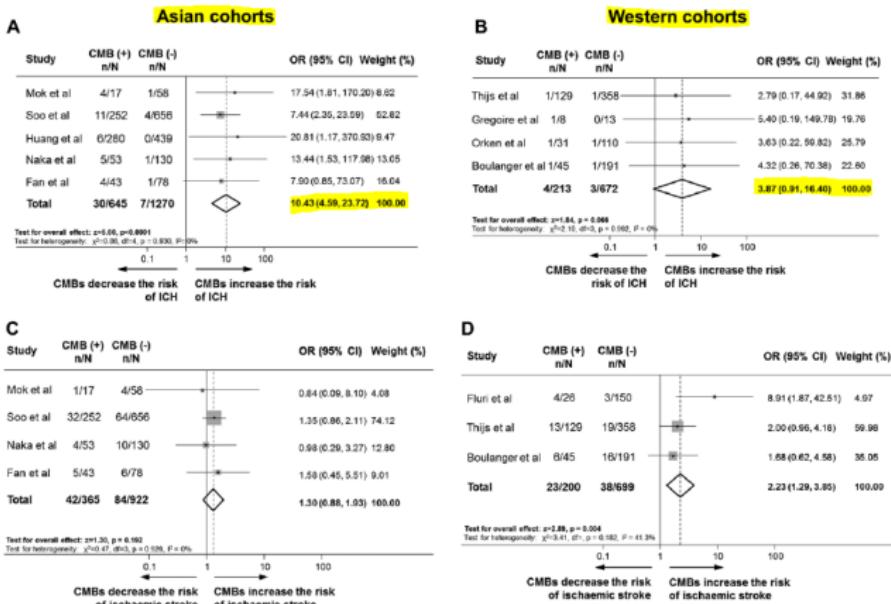
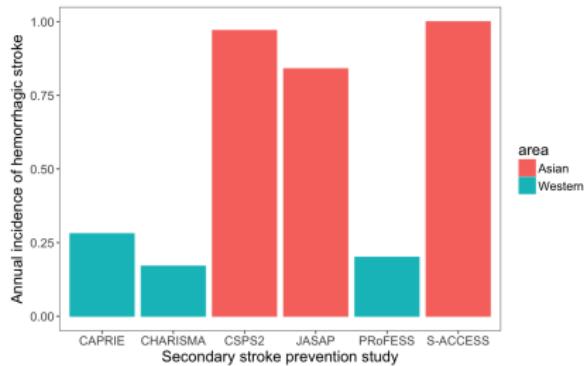
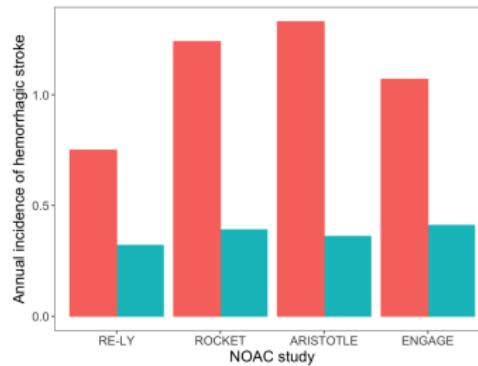


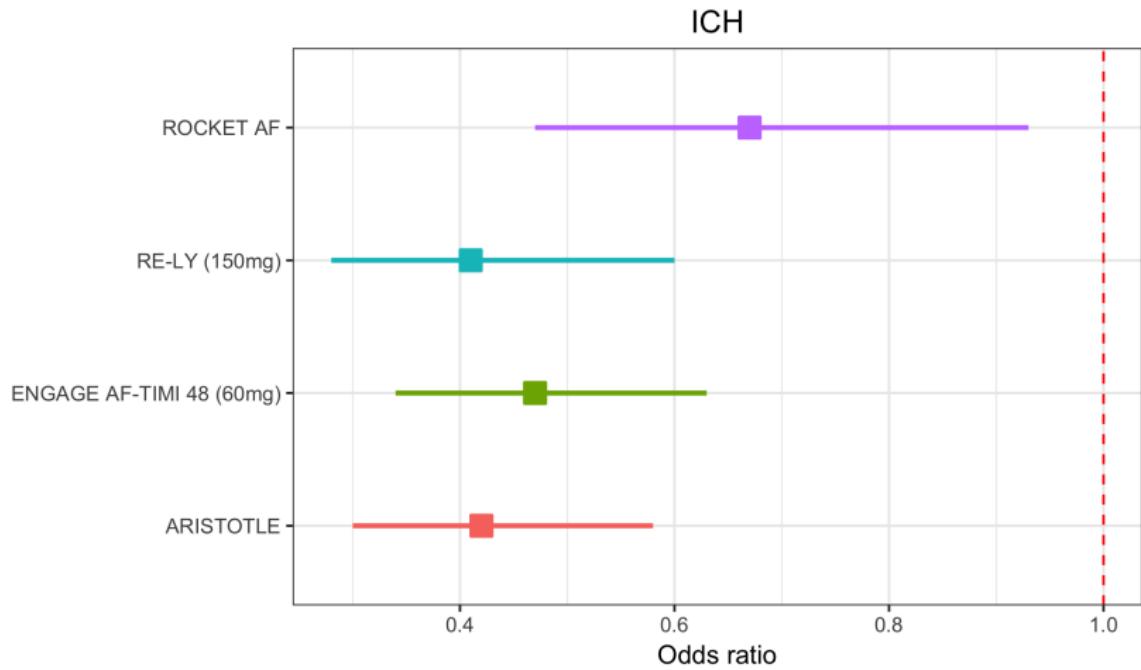
Figure 4. Meta-analysis of the risk of spontaneous intracerebral hemorrhage (ICH; A and B) and ischemic stroke (C and D) stratified by the dominant ethnicity of subjects included in each cohort as Asian or Western (white), with and without cerebral microbleeds (CMBs).

Hemorrhagic stroke on warfarin and aspirin



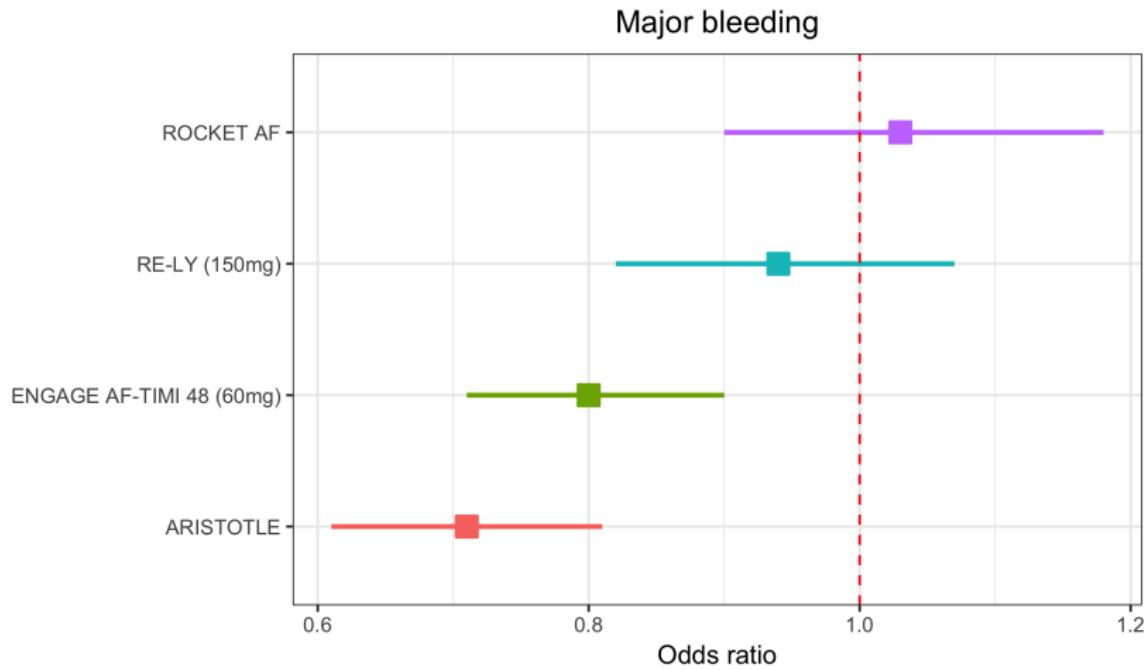
Lip GYH et al, Int J Cardiol 2015;180:246; Kim JS, et al. Int J Stroke 2015;10 Suppl 1:1-9.

NOAC and ICH



Ruff CT et al. Lancet. 2014;383:955-962

NOAC and Major Bleeding



Ruff CT et al. Lancet. 2014;383:955-962

Management of bleeding complication

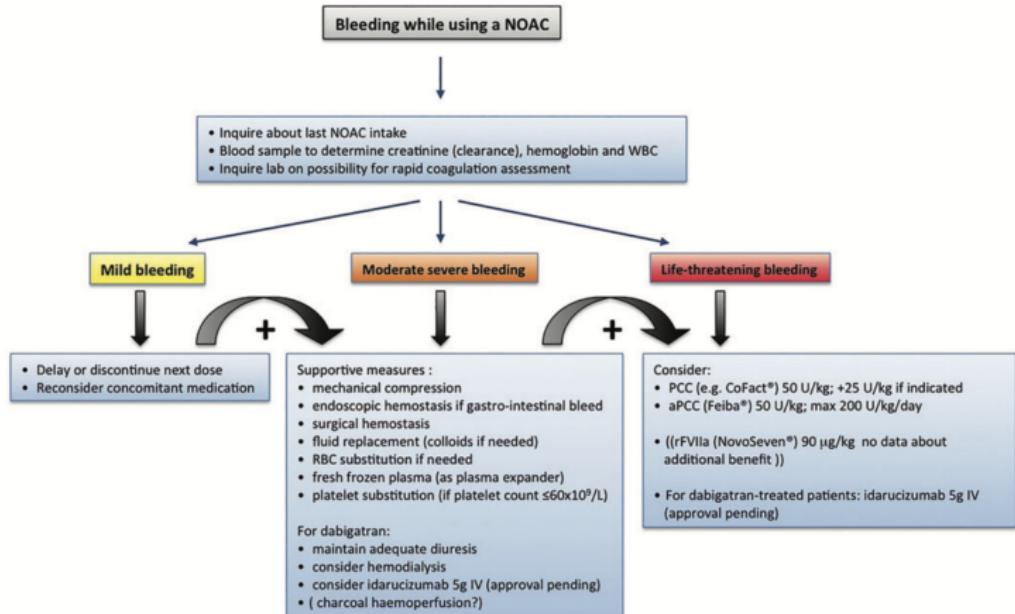


Figure 5 Management of bleeding in patients taking NOACs. Possible therapeutic measures in case of minor or severe bleeding in patients on NOAC therapy. Based on van Ryn et al.³⁹

NOAC with antidote

Research



Antagonizing dabigatran by idarucizumab in cases of ischemic stroke or intracranial hemorrhage in Germany – A national case collection

Pawel Kermer¹, Christoph C Eschenfelder²,
Hans-Christoph Diener³, Martin Grond⁴, Yasser Abdalla⁵,
Katharina Althaus⁶, Jörg Berrouschat⁷, Hakan Cangür⁸,
Michael Daffertshofer⁹, Sebastian Edelbusch¹⁰, Klaus Gröschel¹¹,
Claus G Haase¹², Andreas Harloff¹³, Valentin Held¹⁴,
Andreas Kauert¹⁵, Peter Kraft¹⁶, Arne Lenz¹⁷,
Wolfgang Müllges¹⁶, Mark Obermann¹⁸, Someieh Partowi¹⁹,
Jan Purrucker²⁰, Peter A Ringleb²⁰, Joachim Röther²¹,
Raluca Rossi²², Niklas Schäfer²³, Andreas Schneider¹²,
Ramona Schuppner²⁴, Rüdiger J Seitz²⁵, Kristina Szabo¹⁴
and Robert Wruck⁹

International Journal of Stroke

2017, Vol. 12(4) 383–391



© 2017 World Stroke Organization

Reprints and permissions:

sagepub.co.uk/journalsPermissions.nav

DOI: 10.1177/1747493017701944

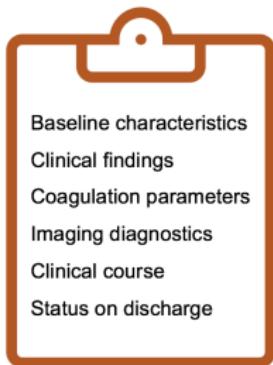
journals.sagepub.com/home/wso

Idarucizumab use from German stroke centers

22 stroke centers

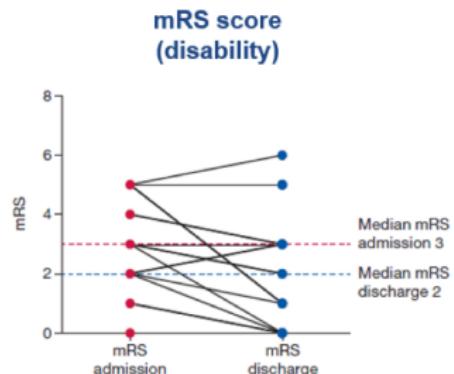
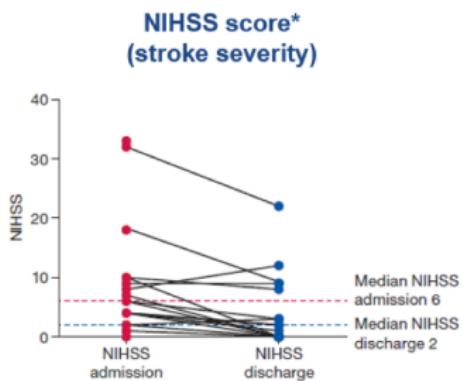
Retrospective study
Jan 2016 – March 2017

30 acute ischaemic stroke
19 intracranial haemorrhage



Kermer P et al. Int J Stroke 2017; Diener H-C et al. ESOC 2017; Grond M et al. ESOC 2017

Most patients experienced improvement in neurological status and physical function after idarucizumab administration

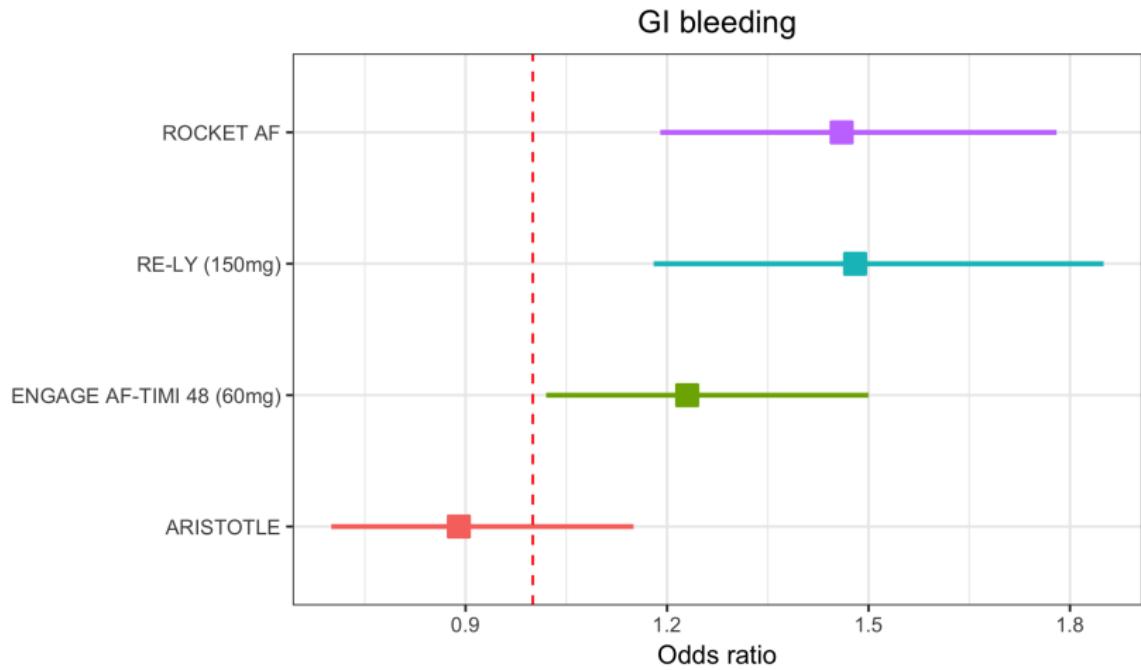


At discharge, mRS score was 0–3 in 15/19 patients.
One patient died (presenting with 134.5 mL haematoma volume)

As it has the potential to prevent haematoma growth, reversing anticoagulation with idarucizumab may have aided neurological and functional improvement

*The NIHSS score for two patients at admission and one patient at discharge was not available
Grond M et al. ESOC 2017

NOAC and GI Bleeding



Ruff CT et al. Lancet. 2014;383:955-962

GI bleeding on NOAC: Proposed pathophysiology

Non-absorbed, active anticoagulant drug within the GI tract lumen promotes GI bleeding

TABLE 2. Comparison of the absorption and elimination of warfarin, apixaban, dabigatran, and rivaroxaban

	Bioavailability	Active anticoagulant present in GI tract	Renal excretion	Hepatic metabolism
Warfarin	100%	None	None	High
Dabigatran	7%	High	High	Low
Rivaroxaban	66%	Moderate	Moderate	Moderate
Apixaban	50%	Moderate	Moderate	Moderate

Desai et al. GASTROINTESTINAL ENDOSCOPY. 2013 Vol 78, No 2.

Via	Dabigatran	Apixaban	Edoxaban ^a	Rivaroxaban
Atorvastatin	P-gp competition and CYP3A4 inhibition +18% ²⁹	No data yet	No effect ³⁰	No effect ^{27,31}
Digoxin	P-gp competition No effect ³²	No data yet	No effect ³⁰	No effect ^{27,33}
Verapamil	P-gp competition (and weak CYP3A4 inhibition) +12–180% ²⁴ (reduce dose and take simultaneously)	No data yet	+53% (SR) ³⁰ (reduce dose by 50%) ^a	Minor effect (use with caution if CrCl 15–50 mL/min)
Diltiazem	P-gp competition and weak CYP3A4 inhibition No effect ²⁴	+40% ^{5nPC}	No data yet	Minor effect (use with caution if CrCl 15–50 mL/min)
Quinidine	P-gp competition +50%	No data yet	+80% ³⁰ (reduce dose by 50%) ^a	+50%
Amiodarone	P-gp competition +12–60% ²⁴	No data yet	No effect ³⁰	Minor effect (use with caution if CrCl 15–50 mL/min)
Dronedarone	P-gp and CYP3A4 inhibitor +70–100% (US: 2 × 75 mg)	No data yet	+85% (reduce dose by 50%) ^a	No data yet
Ketoconazole; itraconazole; voriconazole; posaconazole	P-gp and BCRP competition; CYP3A4 inhibition +140–150% (US: 2 × 75 mg)	+100% ^{5nPC}	No data yet	Up to +160% ²⁷
Fluconazole	Moderate CYP3A4 inhibition No data yet	No data yet	No data yet	+42% (if systemically administered) ²⁷
Cyclosporin; tacrolimus	P-gp competition No data yet	No data yet	No data yet	+50%
Clarithromycin; erythromycin	P-gp competition and CYP3A4 inhibition +15–20%	No data yet	No data yet	+30–54% ^{26,27}
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition No data yet	Strong increase ³⁰ inhibition	No data yet	Up to +153% ²⁷
Rifampicin; St John's wort; carbamazepine; phenytoin; phenobarbital	P-gp/ BCRP and CYP3A4/CYP2J2 inducers -66% ³⁴	-54% ^{5nPC}	-35%	Up to -50%
Antacids (H2B; PPI; Al-Mg-hydroxide)	GI absorption -12–30% ^{22–24}	No data yet	No effect	No effect ^{21,25}
Other factors				
Age ≥80 years	Increased plasma level		No data yet	
Age ≥75 years	Increased plasma level		No data yet	
Weight ≤60 kg	Increased plasma level			
Renal function	Increased plasma level		See Table 7	
Other increased bleeding risk		Pharmacodynamic interactions (antiplatelet drugs; NSAID; systemic steroid therapy; other anticoagulants); history or active GI bleeding; recent surgery on critical organ (brain; eye); thrombocytopenia (e.g. chemotherapy); HAS-BLED ≥3		

Reduced dosage

HD edoxaban vs. warfarin

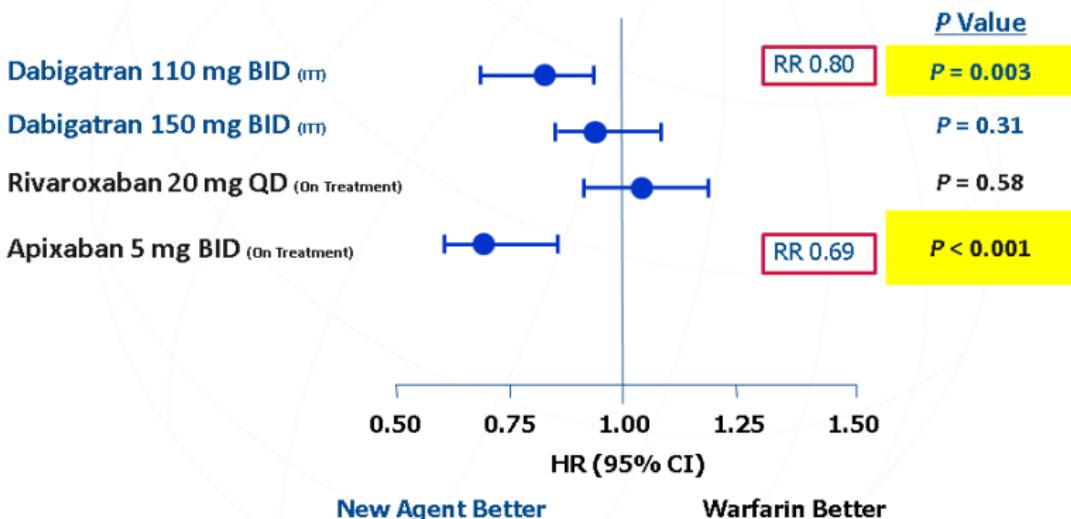
	No dose reduction, Dose reduced, HR (95% CI) 60mg	HR (95% CI) 30mg	$p_{\text{interaction}}$
Stroke or SEE	0·78 (0·61–0·99)	0·81 (0·58–1·13)	0·85
Ischaemic stroke	0·94 (0·70–1·24)	0·96 (0·63–1·46)	0·91
All-cause mortality	0·94 (0·76–1·17)	0·85 (0·62–1·17)	0·59
Major bleed	0·88 (0·76–1·03)	0·63 (0·50–0·81)	0·023
Fatal bleed	0·61 (0·35–1·07)	0·46 (0·23–0·92)	0·54
ICH	0·47 (0·32–0·68)	0·46 (0·27–0·78)	0·94
GI bleed	1·32 (1·06–1·65)	1·00 (0·67–1·47)	0·21

Lancet. 2015;385(9984):2288-95

Recent Oral Anticoagulation trials: Major bleeding

Acute or subacute clinically overt bleeding + ≥ 1 of

- ↓ in Hb level of ≥ 2 g/dL (for Apixaban, over a 24-hour period)
- transfusion of ≥ 2 U packed RBCs
- bleeding that is fatal or occurs in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular



Not head to head comparison – For illustrative purposes only

Connolly SJ, et al. N Engl J Med 2009;361:1139-51; Connolly SJ et al. N Engl J Med 2010;363:1875-6;
 Patel MR, et al. N Engl J Med 2011;365:883-91; Granger C, et al. N Engl J Med 2011;365:981-92.

Case 1 (M/63) and Case 2 (F/78)



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 ⁸²	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.

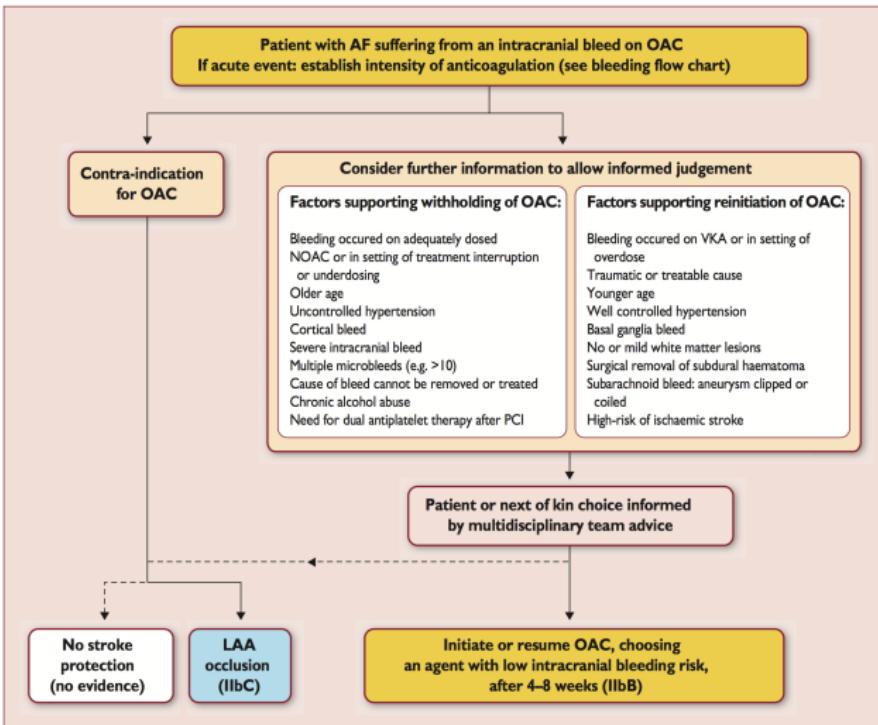
‡Rate reported per patient-year.

To resume AC (Modifiable)

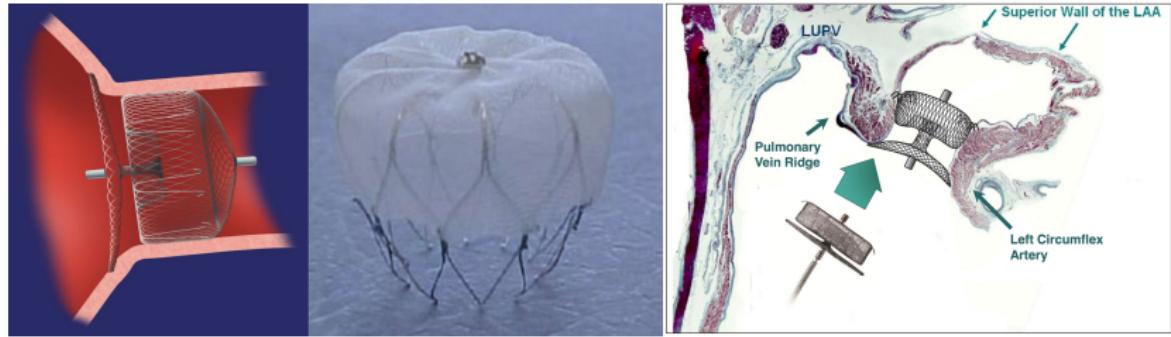
- Uncontrolled HTN
- Triple therapy
- High INR on VKA

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



Left atrial appendage occlusion



Courtesy of Shin SY, Dep. of Cardiology CAUH

Take-Home Message

- In Asian countries, the rate of stroke mortality and the risk of hemorrhagic stroke are higher than Western countries.
- In patients with atrial fibrillation and an increased risk of (intracranial) bleeding, NOAC might be a better option than warfarin.
- In case of bleeding on NOAC, change of NOAC or use of reduced dosage might be options. Especially, in patients with repeated bleeding, we have to consider the use of LAAO.