

FOCUS SPAF in Seoul

Best choice of NOAC
focusing on stroke prevention



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Table of Contents

1 Stroke in Asia

2 Atrial fibrillation and Stroke

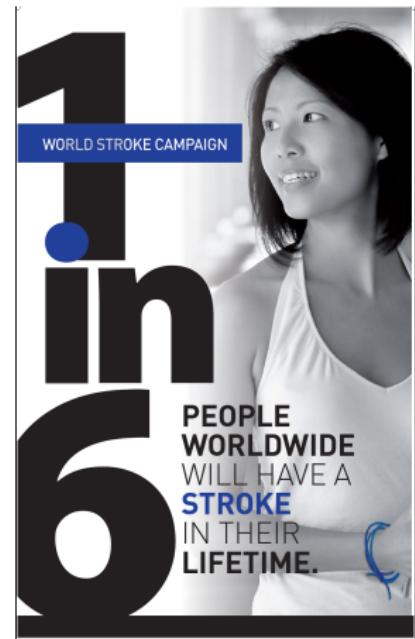
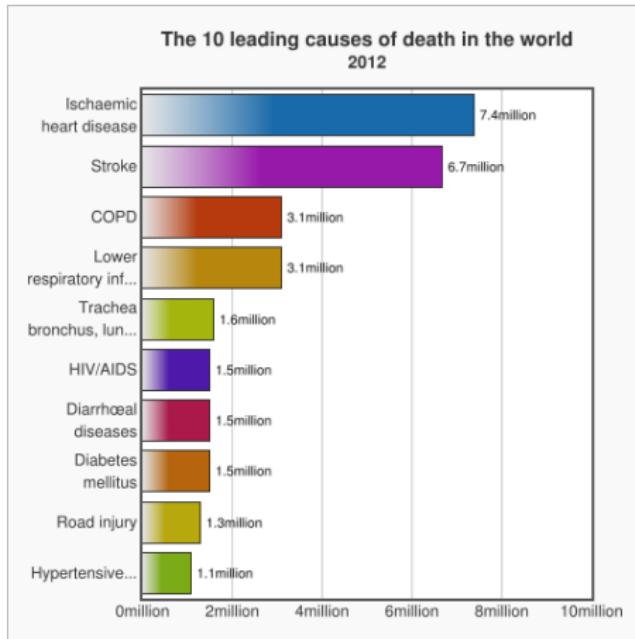
- Vit. K antagonist
- NOACs

3 Summary

Section 1

Stroke in Asia

Global burden of stroke

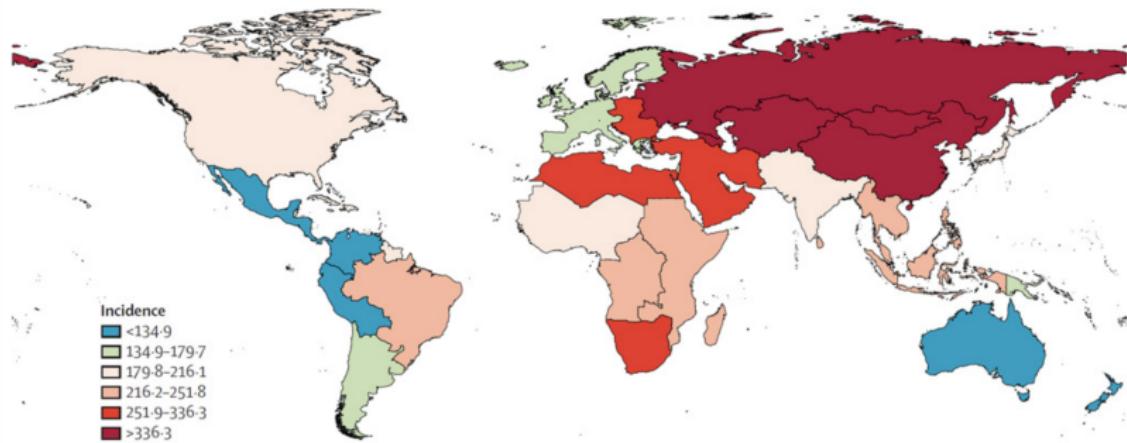


<http://www.who.int/mediacentre/factsheets/fs310/en/> accessed on Jan 16, 2016

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

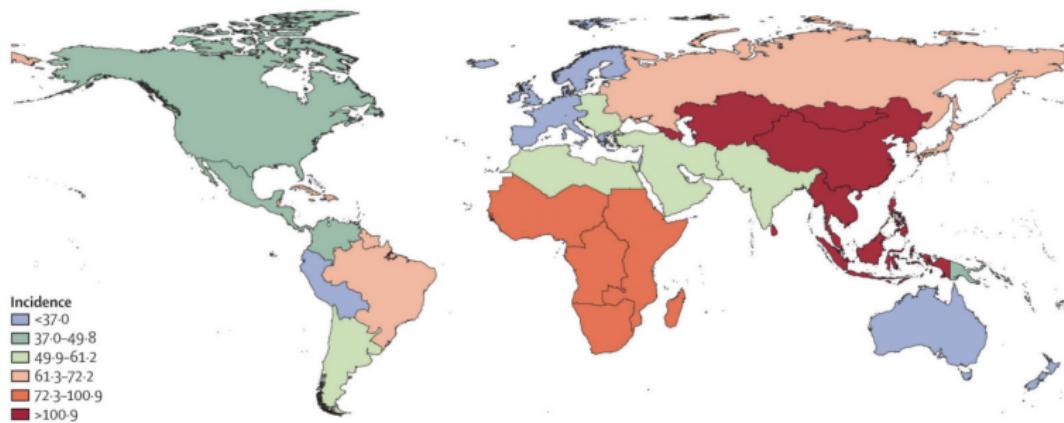
Age-standardised stroke incidence

per 100 000 person-years for 2010



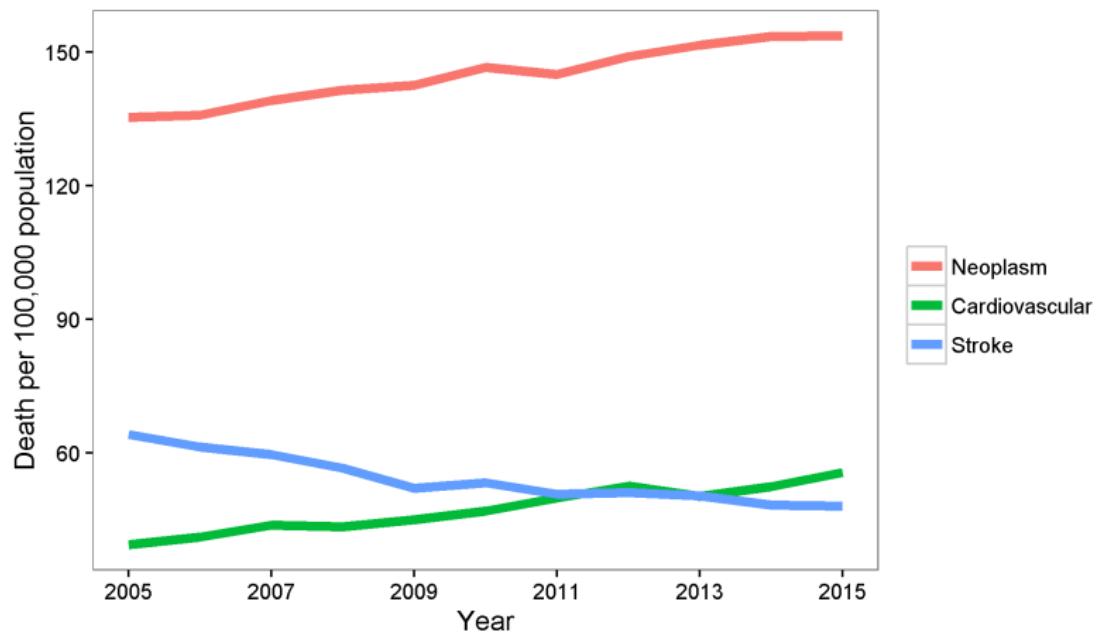
Lancet Neurol. 2014 383(9913): 245–254.

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



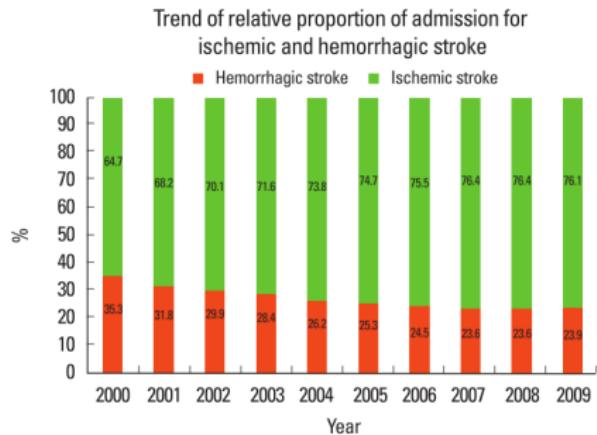
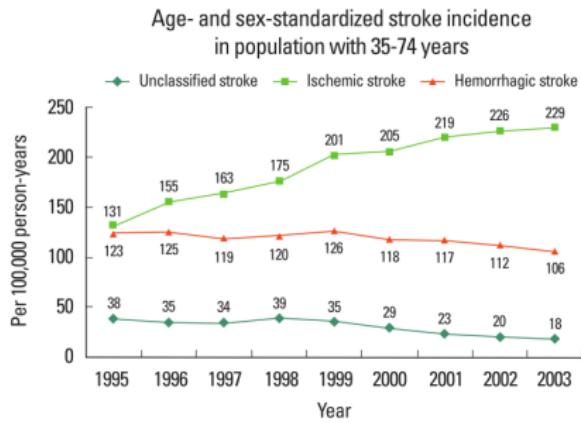
Lancet Glob Health. 2013 Nov; 1(5): e259-e281.

Secular trend of mortality in Korea



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

Incidence of stroke is increasing



Hong KS, et al. J Stroke 2013

Etiologies of stroke

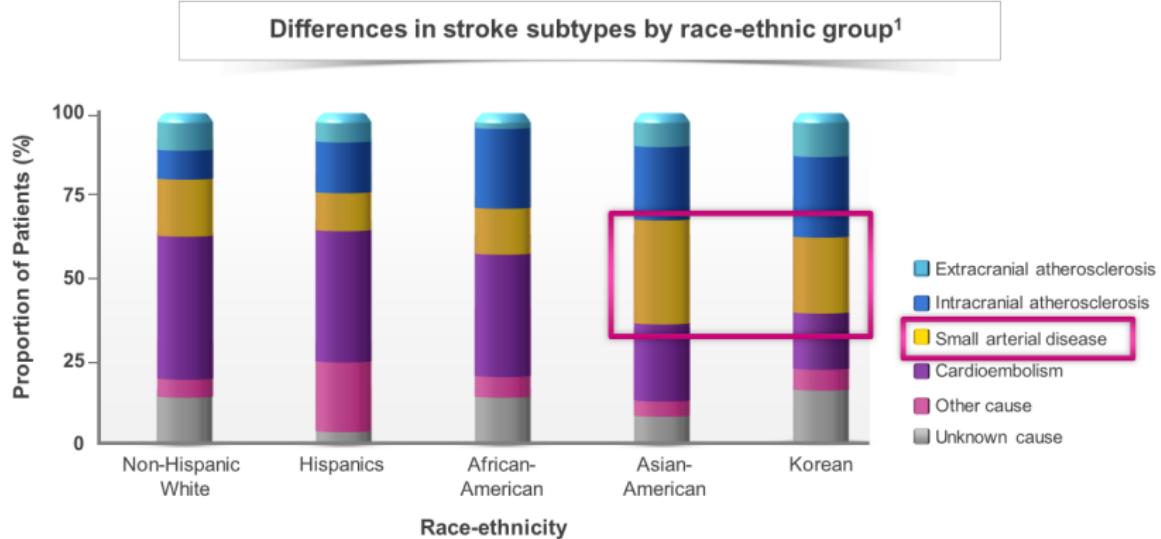
Ischemic Stroke

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

Hemorrhagic Stroke

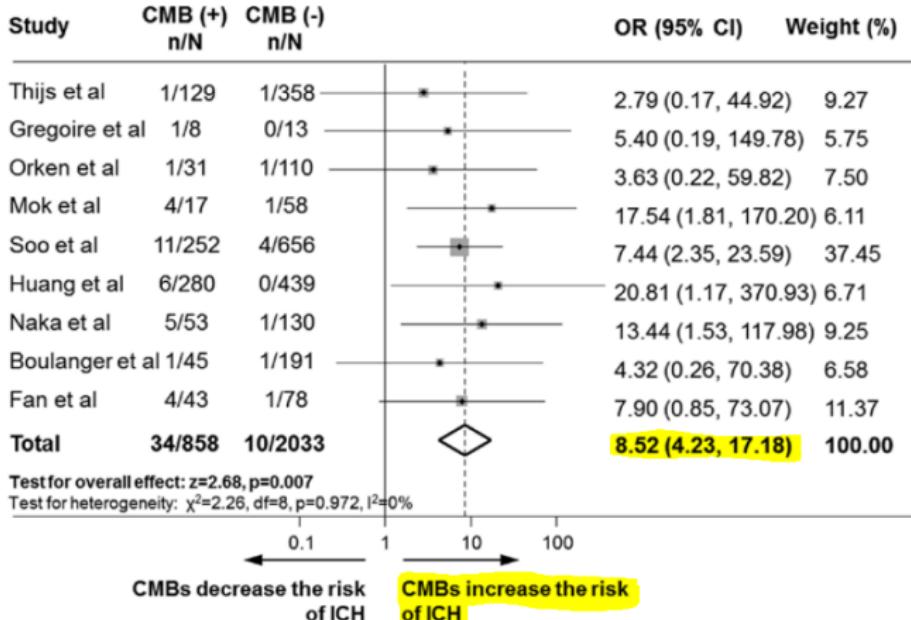
- Hypertensive hemorrhage
- Cerebral amyloid angiopathy
- Arteriovenous malformations
- Subarachnoid hemorrhage

SVD is more prevalent in Asians than Western populations



Data collected over 4 yr-period in prospectively maintained registries on 3,053 subjects with ischemic cerebrovascular events (1,982 South Korean & 1,071 Southern Californian).

1. Bang OY, et al. Cerebrovasc Dis 2009;27:13–21. 2. Kim BJ, et al. J Stroke 2014;16:8–17.



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

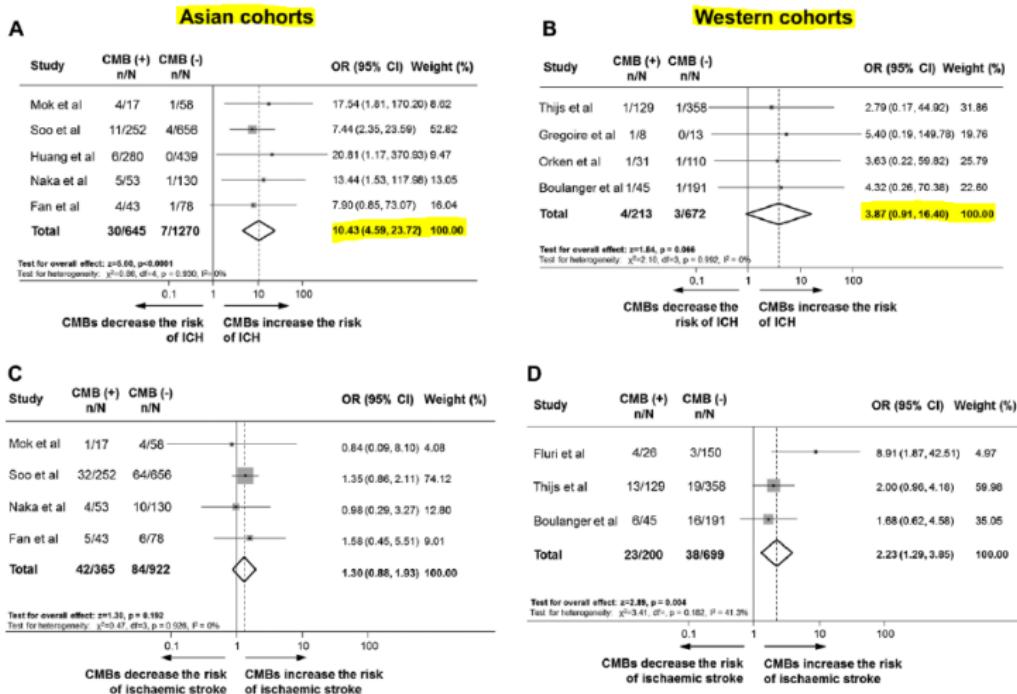
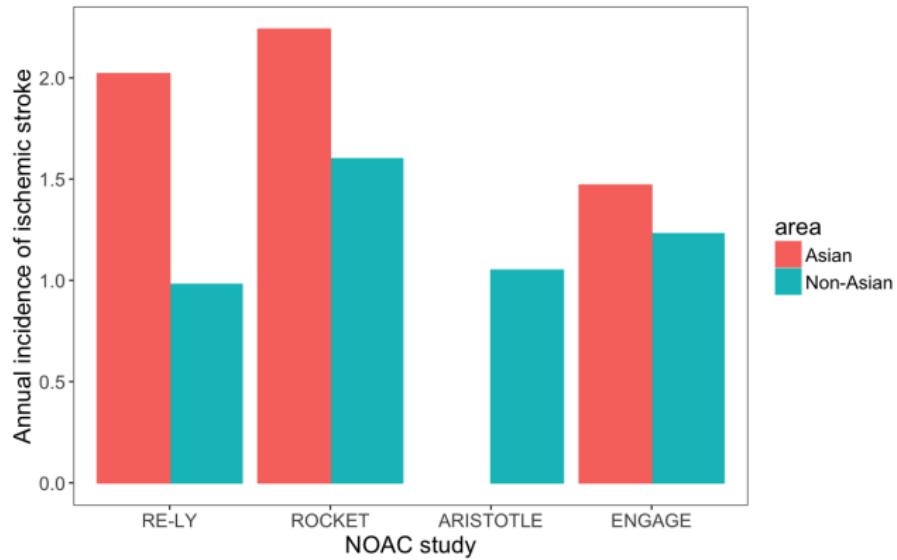


Figure 4. Meta-analysis of the risk of spontaneous intracerebral hemorrhage (ICH; A and B) and ischemic stroke (C and D) stratified by the dominant ethnicity of subjects included in each cohort as Asian or Western (white), with and without cerebral microbleeds (CMBs).

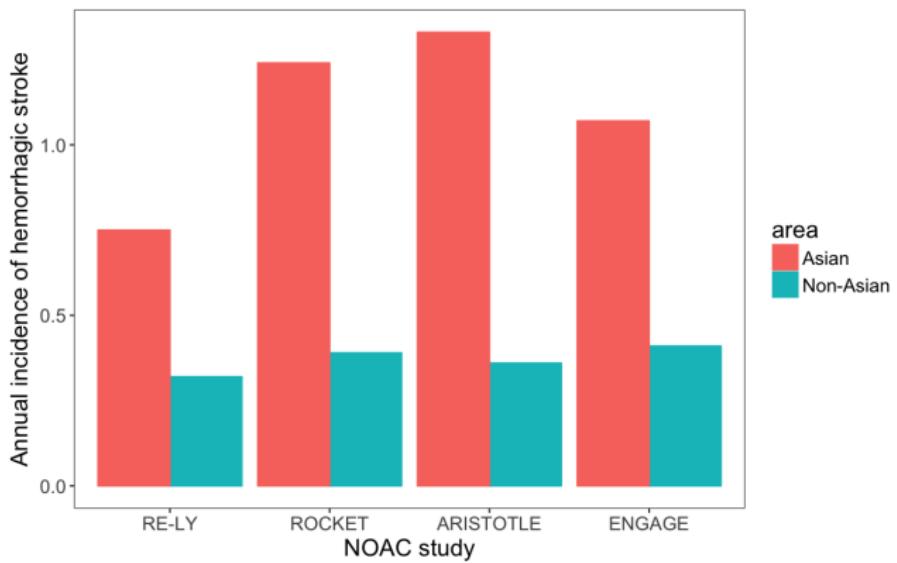
Charidimou A et al. Am J Cardiol 2013;112:1230e1234

Ischemic stroke on warfarin



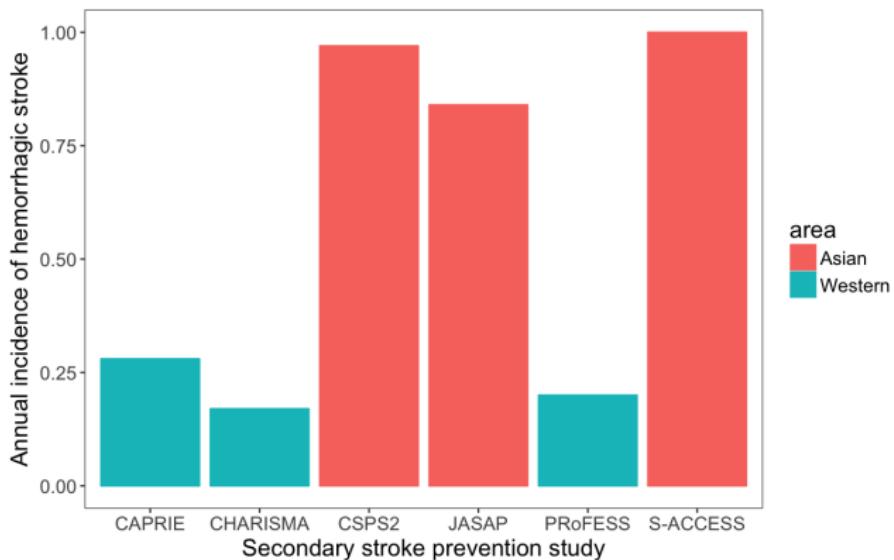
Lip GYH et al, Int J Cardiol 2015;180:246

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.

IGSR and the 1000 Genomes Project

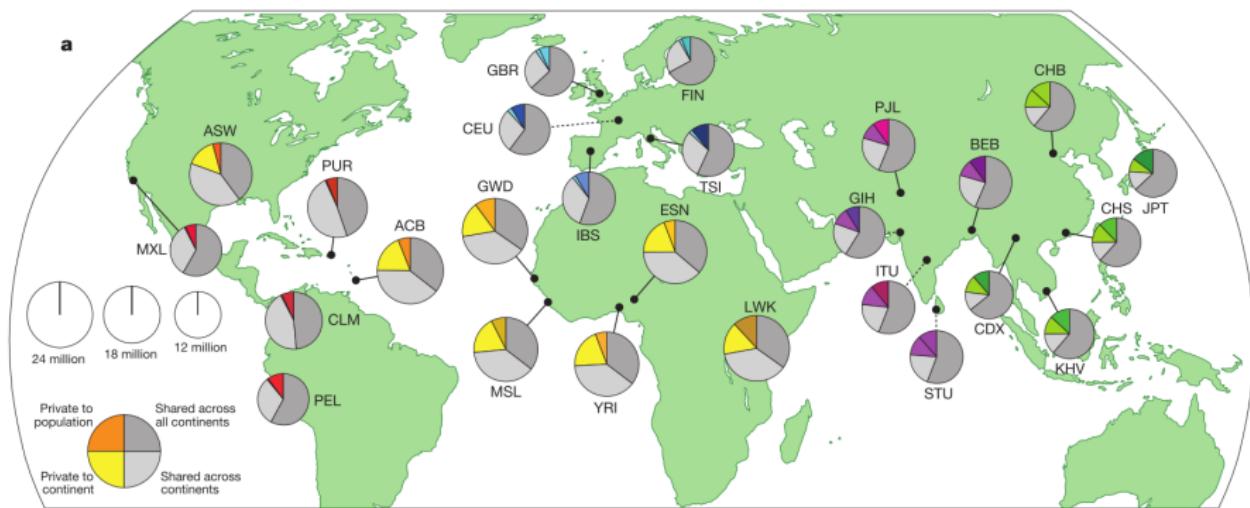


Populations: ● - African; ● - American; ● - East Asian; ● - European; ● - South Asian;

2,504 individuals from 26 populations

<http://www.internationalgenome.org/>

A global reference for human genetic variation



The 1000 Genomes Project. Nature 2015

Stroke in Asian

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.

Section 2

Atrial fibrillation and Stroke

In patients with Af and 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

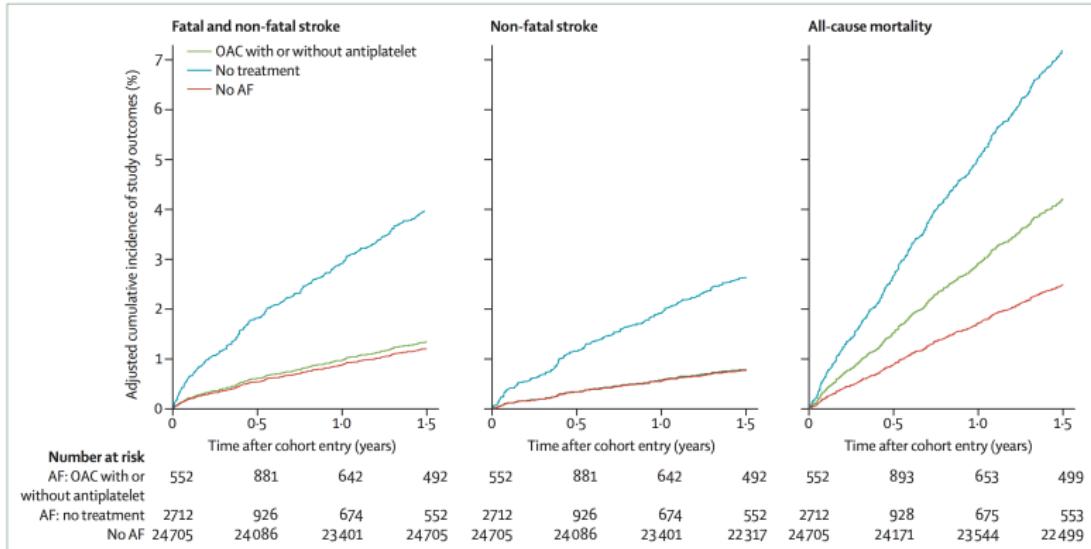
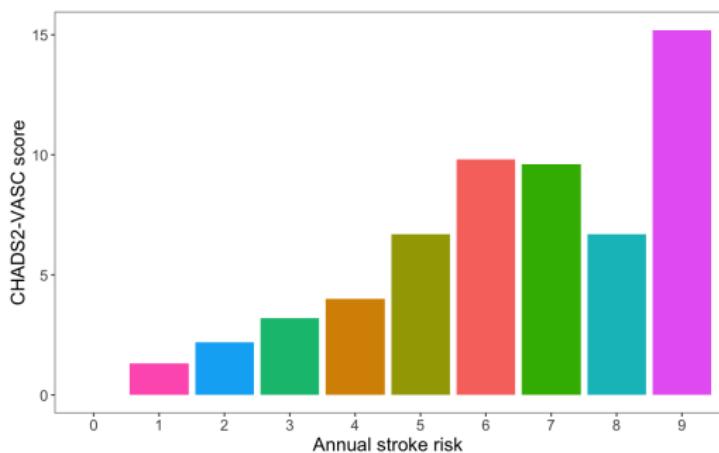


Figure 2: Effect of treatment on incidentally detected atrial fibrillation

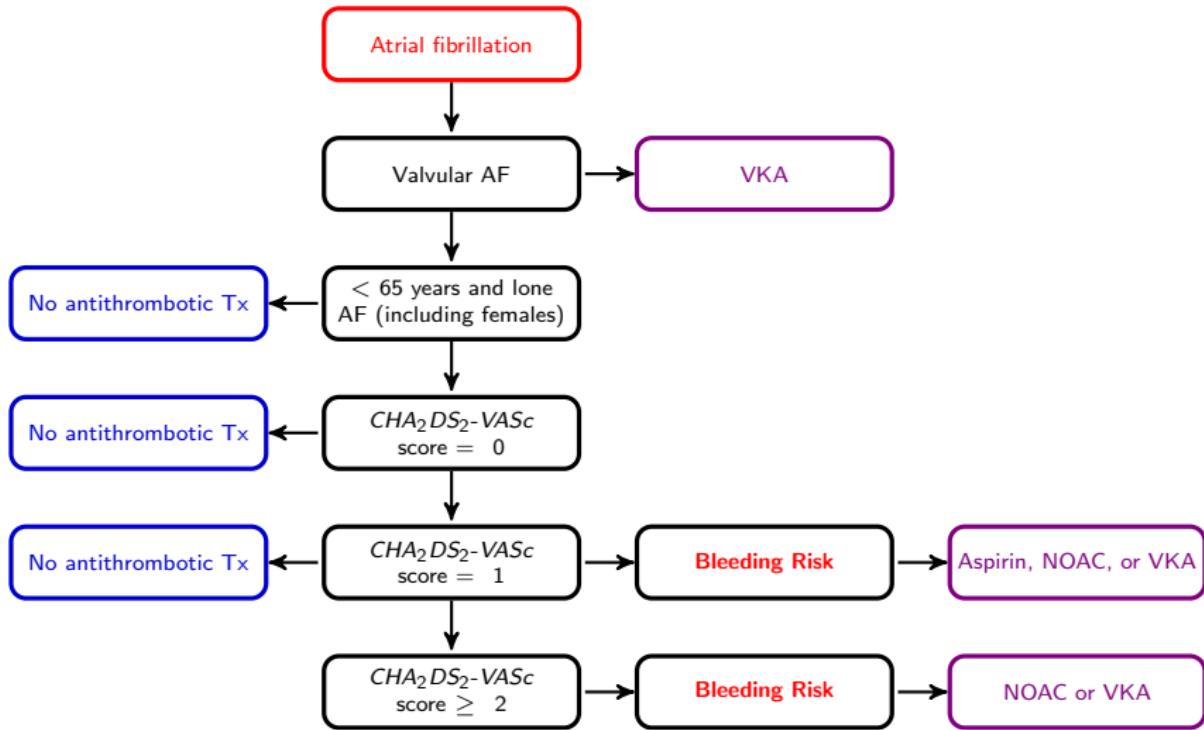
AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.²¹

Assessment of Thromboembolic Risk in AF patients

<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



Europace (2016) 18, 1609–1678
doi:10.1093/europace/euw295

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation
European Society of Cardiology (ESC)

Developed with the special contribution of the European Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Paulus Kirchhof⁶ (Chairperson), Stefano Benussi¹ (Co-Chairperson) (Switzerland), Dipak Kotecha² (UK), Anders Ahlsson¹ (Sweden), Dan Atar (Norway), Barbara Casadei³ (Italy), Manuel Castella⁴ (Spain), Hans-Christoph Diener² (Germany), Jeroen Hendriks (The Netherlands), Gerhard Hindricks⁵ (Germany), Antonis S. Manolis (Greece), Jonas Oldgren (Sweden), Bogdan Popescu⁶ (Romania), Ulrich Schotten (The Netherlands), Bart Van Poppel⁶ (Belgium), and Panagiotis Vardas (Greece)

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2016 European guidance:

OAC therapy to prevent thromboembolism is recommended in all patients with a CHA₂DS₂-VASC score of ≥2 (men) or ≥3 (women)

A NOAC is recommended in preference to a VKA in patients who are eligible for NOACs

VKA is effective in preventing embolism when INR is > 2.0

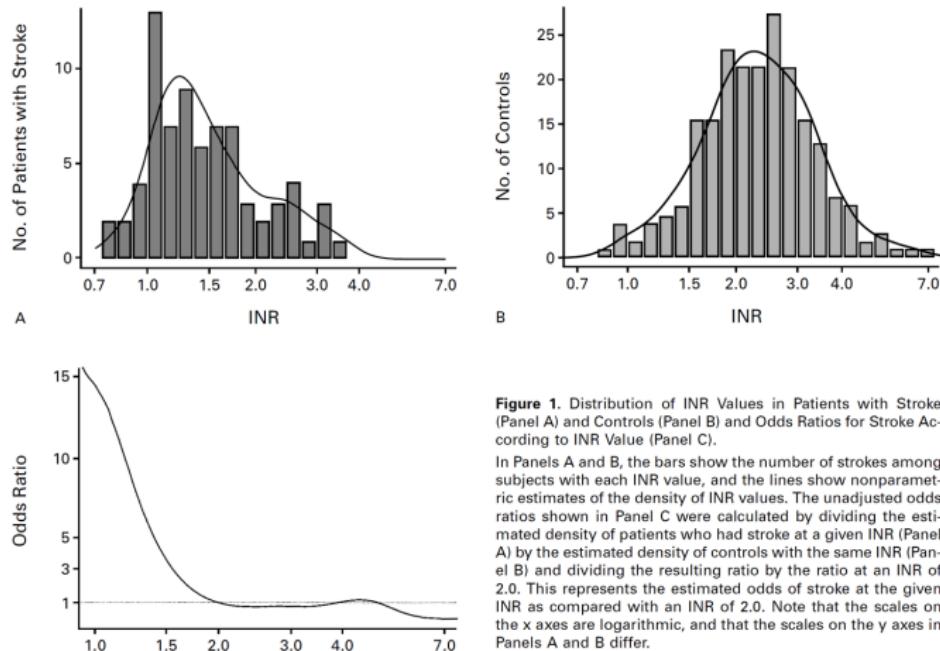


Figure 1. Distribution of INR Values in Patients with Stroke (Panel A) and Controls (Panel B) and Odds Ratios for Stroke According to INR Value (Panel C).

In Panels A and B, the bars show the number of strokes among subjects with each INR value, and the lines show nonparametric estimates of the density of INR values. The unadjusted odds ratios shown in Panel C were calculated by dividing the estimated density of patients who had stroke at a given INR (Panel A) by the estimated density of controls with the same INR (Panel B) and dividing the resulting ratio by the ratio at an INR of 2.0. This represents the estimated odds of stroke at the given INR as compared with an INR of 2.0. Note that the scales on the x axes are logarithmic, and that the scales on the y axes in Panels A and B differ.

Haleket al N Eng J Med 1996

In-Depth Review

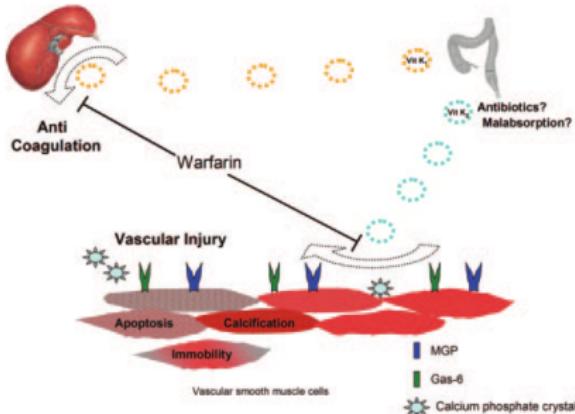
Vitamin K-dependent Proteins, Warfarin, and Vascular Calcification

John Danziger

Renal Division, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Vitamin K-dependent proteins (VKDPs) require carboxylation to become biologically active. Although the coagulant factors are the most well-known VKDPs, there are many others with important physiologic roles. Matrix Gla Protein (MGP) and Growth Arrest Specific Gene 6 (Gas-6) are two particularly important VKDPs, and their roles in vascular biology are just beginning to be understood. Both function to protect the vasculature; MGP prevents vascular calcification and Gas-6 affects vascular smooth muscle cell apoptosis and movement. Unlike the coagulant factors, which undergo hepatic carboxylation, MGP and Gas-6 are carboxylated within the vasculature. This peripheral carboxylation process is distinct from hepatic carboxylation, yet both are inhibited by warfarin administration. Warfarin prevents the activation of MGP and Gas-6, and in animals, induces vascular calcification. The relationship of warfarin to vascular calcification in humans is not fully known, yet observational data suggest an association. Given the high risk of vascular calcification in those patients with chronic kidney disease, the importance of understanding warfarin's effect on VKDPs is paramount. Furthermore, recognizing the importance of VKDPs in vascular biology will stimulate new areas of research and offer potential therapeutic interventions.

Clin J Am Soc Nephrol 3: 1504–1510, 2008. doi: 10.2215/CJN.00770208



Warfarin inhibits hepatic and peripheral carboxylation. Warfarin prevents vitamin K from participating in the carboxylation process, inhibiting both hepatic and peripheral production of VKDPs. The well-known therapeutic effect is anticoagulation. However, warfarin also inhibits activation of MGP and Gas-6, interrupting the protective mechanisms of these proteins. Vascular smooth muscle cells are unable to respond to injury in a normal manner, and potentially, cell death and eventual calcification ensue.

Increased Vascular Calcification in Patients Receiving Warfarin

Ekamol Tantisattamo, Kum Hyun Han, W. Charles O'Neill

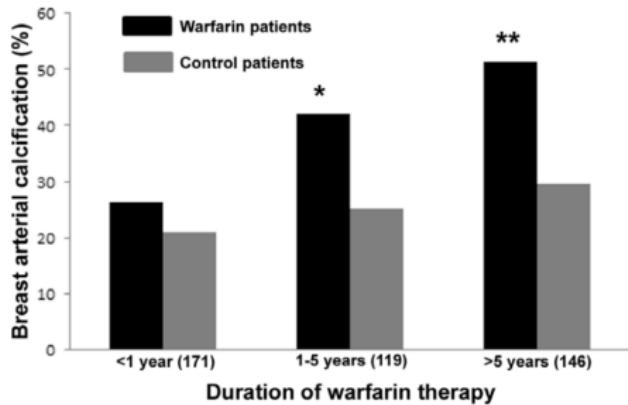


Figure 3. Effect of warfarin duration on breast arterial calcification. Control patients (no warfarin therapy) were matched for age and diabetes mellitus status. The number of patients is given in parentheses. * $P=0.009$; ** $P=0.0002$.

Tantisattamo, E., et al. (2015). *Arterioscler Thromb Vasc Biol* 35(1): 237-242.

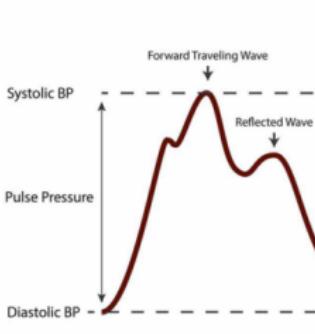
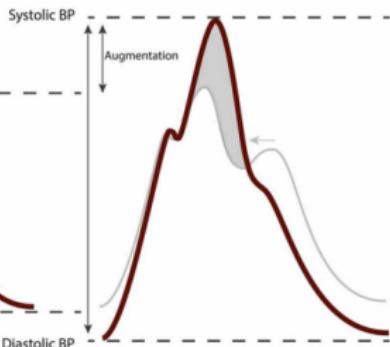
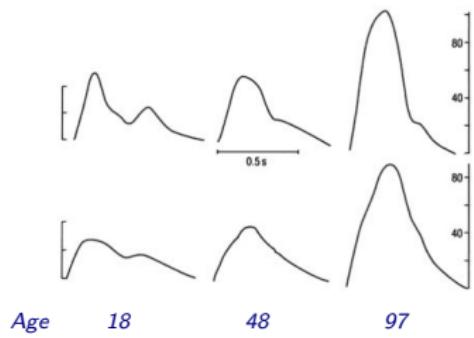
A Normal**B Arterial Stiffness**

FIGURE 4 | Hemodynamic changes in arterial stiffening. (A) Aortic blood pressure waveform of a healthy, normotensive person. The forwards traveling wave precedes the (backwards traveling) reflected wave. **(B)** Aortic pressure

waveform of a person with arterial stiffness. Due to increased pulse wave velocity, the forward traveling wave and reflected wave are summated leading to augmented pulse pressure.

Arterial stiffening and small vessel disease



these organs while mean flow is maintained.³⁶ Brain and kidney arteries of all sizes are thus subjected to higher pulsatile circumferential stress and higher longitudinal shear stress. Their ability to withstand increased stresses depends on their resilience, and this is markedly decreased in a number of diseases, particularly diabetes mellitus.^{11,12,34} Aging changes of large arteries thus promote a “set-up” for small arterial disease and the types of changes elegantly elucidated by Byrom and others 50 years ago.^{36–38}

Effects of Arterial Stiffening on the Kidney and Brain Microvasculature

Byrom's work was initially conducted on rats but was applied to the small-vessel disease seen in human hypertension.^{37,38} He showed that damage to small arteries could be induced by increased pulsatile stress and could lead to tearing of their endothelial and smooth muscle cells with disruption of the vessel. He thus explained development of small arterial dilations and aneurysms, and the features of lipohyalinoses and of fibrinoid necrosis as seen in the brains and kidneys of

O'Rourke MF et al. Hypertension. 2005; Byrom FB. Lancet. 1954

Choice of NOAC

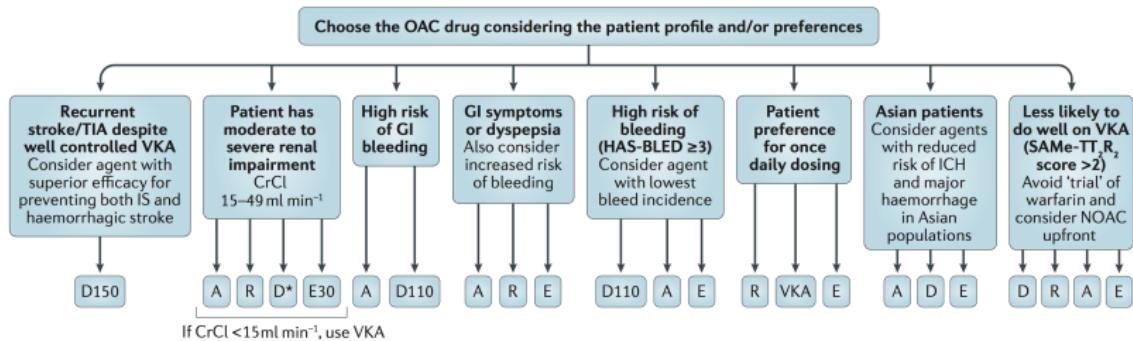
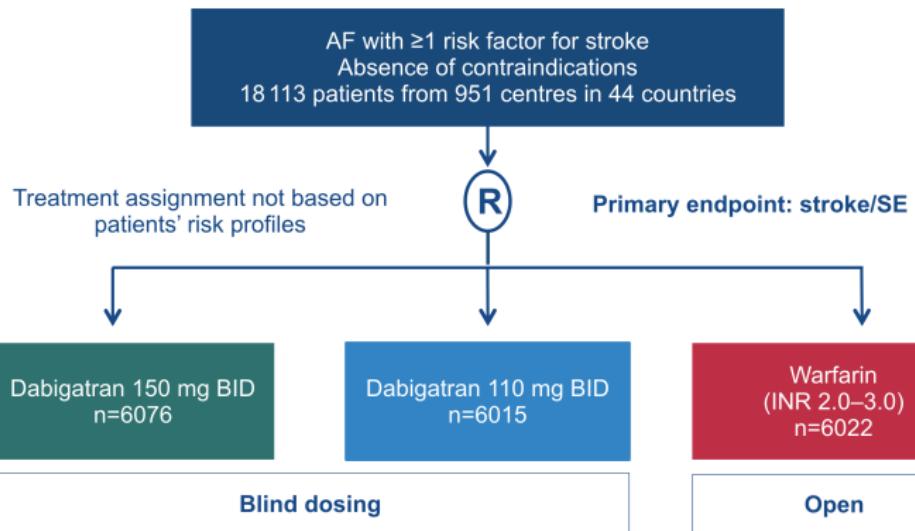


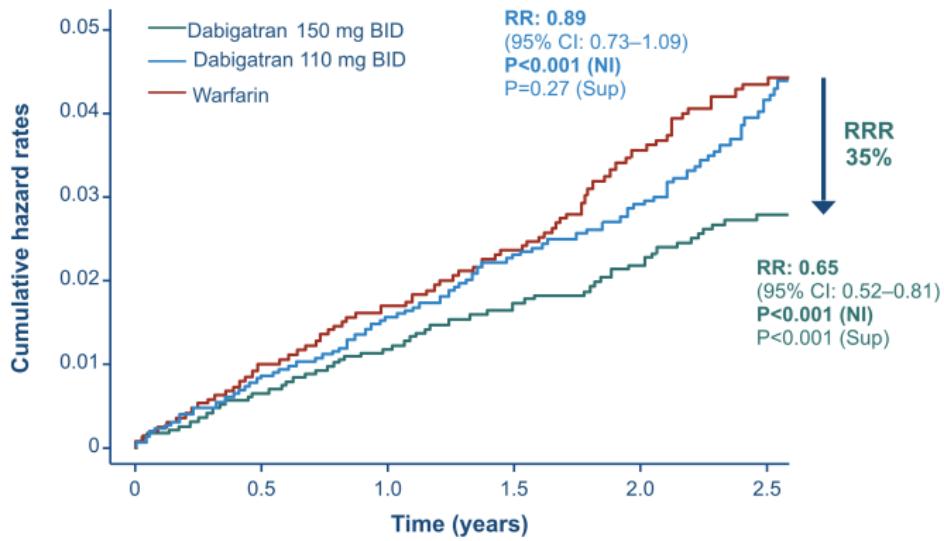
Figure 8 | Selection of oral anticoagulant drugs. A schematic representation of decision making in the selection of an oral anticoagulant (OAC) drug based on patient and drug characteristics using illustrative examples. A, apixaban; CrCl, creatinine clearance; D, dabigatran (D75, dabigatran 75 mg two times per day, available in the United States only; D110, dabigatran 110 mg, not available in the United States for AF; D150, dabigatran 150 mg); E, edoxaban (E30, edoxaban 30 mg); GI, gastrointestinal; ICH, intracranial haemorrhage; IS, ischaemic stroke; NOAC, non-vitamin K antagonist oral anticoagulant; R, rivaroxaban; TIA, transient ischaemic attack; VKA, vitamin K antagonist. *D110 for patients with a CrCl 30–49 ml min⁻¹ (most countries); in the United States only, D75 for patients with CrCl 15–29 ml min⁻¹ (and only 150 mg b.i.d. dose available in the United States, for CrCl >30 ml min⁻¹). Figure adapted with permission from REF. 250, Wiley.

RE-LY® is the only NOAC trial to independently evaluate two fully randomized doses which have then been approved



RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study
SE, systemic embolism. Connolly et al. N Engl J Med 2009

Dabigatran 150 mg BID associated with significant decrease in risk of stroke/SE vs warfarin in RE-LY®

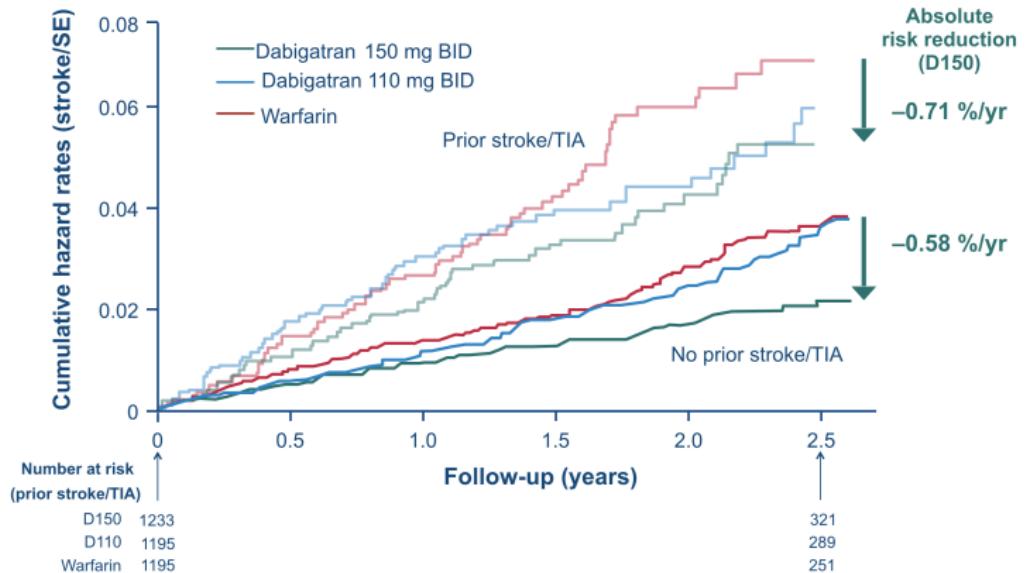


NI, non-inferiority; Sup, superiority

Connolly et al. N Engl J Med 2009; Connolly et al. N Engl J Med 2014

11

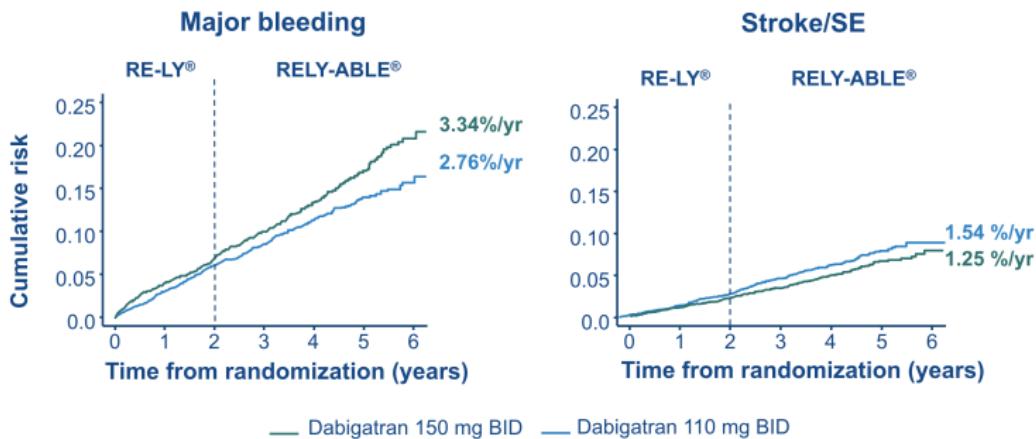
Sustained reduction in secondary stroke with both dabigatran 150 mg BD and 110 mg BD



Adapted from Diener et al. Lancet Neurol 2010; Boehringer Ingelheim data on file

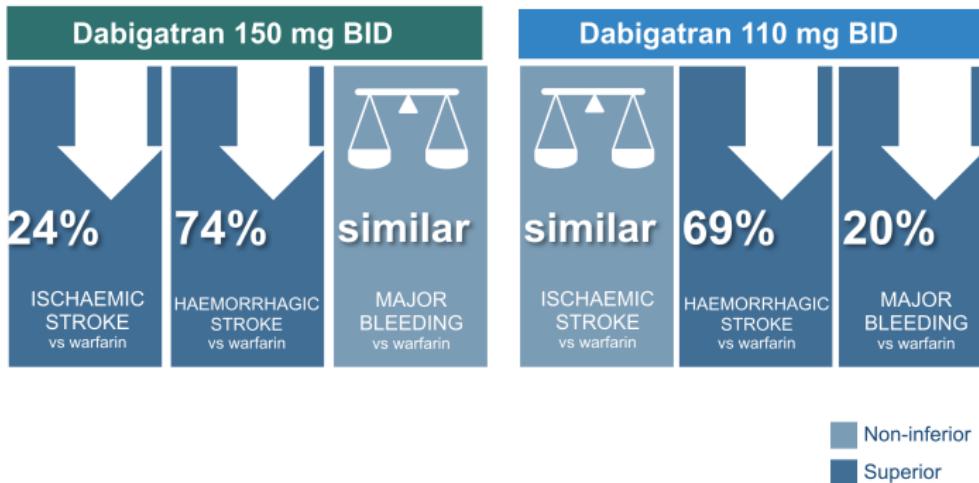
13

RELY-ABLE® confirmed the safety profile of dabigatran in the long term (>6 years)



Low rates of stroke and bleeding events maintained – patients can be reassured of favourable benefit–risk profile in the long-term
(RELY-ABLE® is the only long-term follow-up study of a NOAC in AF)

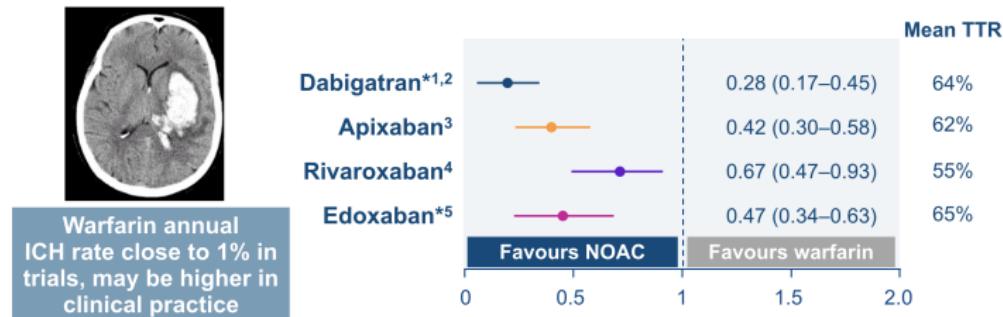
In RE-LY®, both doses of dabigatran were associated with significant safety and efficacy benefits vs warfarin



RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study
Connolly et al. N Engl J Med 2010; Connolly et al. N Engl J Med 2014; Pradaxa®: EU SPC, 2015;
Douketis et al. Thromb Res 2011; Dans et al. Circulation 2013

18

NOACs significantly reduce the risk of ICH vs warfarin



In clinical trials, NOAC benefits achieved vs warfarin with range of TTRs

Not head-to-head comparison; no clinical conclusions can be drawn; adapted from references 1–4

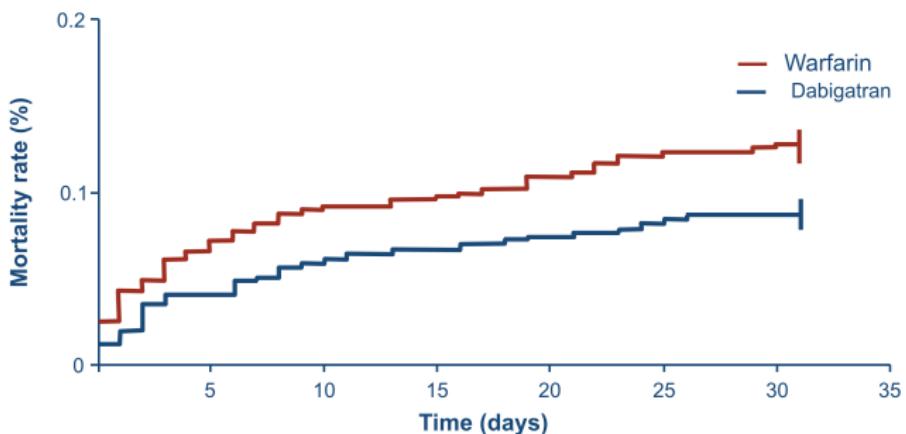
*Dabigatran patients received 150 mg BID or 110 mg BID according to EU label recommendations;
edoxaban patients received 60 mg QD dose

ICH, intracranial haemorrhage; TTR, time in therapeutic range

1. Lip et al. Thromb Haemost 2014; 2. Connolly et al. N Engl J Med 2009; 3. Granger et al. N Engl J Med 2011;

4. Patel et al. N Engl J Med 2011; 5. Giugliano et al. N Engl J Med 2013

In patients who experience a major bleed, dabigatran is associated with improved outcomes vs warfarin



Reduced risk for death with dabigatran vs warfarin during 30 days after the bleeding
($P=0.052$) in the absence of a specific reversal agent*

*Combined data from dabigatran 150 mg and 110 mg BID treatment groups. Only first major bleed included.

Analysis not adjusted for covariates

Majeed et al. Circulation 2013

17

Only dabigatran offers an option to remove the anticoagulant in emergency cases (life-threatening bleeding events or urgent invasive procedures)

RE-VERSE AD™: in a cohort of multi-morbid, elderly patients taking dabigatran who presented with life-threatening bleeding or urgent procedures



Immediate and complete reversal of dabigatran anticoagulation (dTT) in 99% of patients¹

Secondary clinical endpoints confirmed effective reversal^{1,2}

No safety concerns identified to date in the analysis^{1,2}

Now approved for use in many countries for patients treated with dabigatran when rapid reversal of anticoagulation is required:

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding^{3,4}

dTT, diluted thrombin time

1. Pollack et al. AHA 2016; 2. Pollack et al. N Engl J Med 2015; 3. Praxbind®: EU SPC; 4. Praxbind®: US PI

29

Section 3

Summary

	Dabigatran 150 mg	Dabigatran 110 mg	Apixaban 5/2.5 mg	Rivaroxaban 20/15 mg	Edoxaban 60/30 mg
Dosing frequency	BID		BID	OD	OD
RCTs: major bleeding vs warfarin ¹⁻⁴	Not significant	20%	31%	Not significant	20%
RCTs: stroke/SE vs warfarin ¹⁻⁴	35%	Not significant	21%	Not significant	Not significant
RCTs: ischaemic stroke vs warfarin ³⁻⁶	24%	Not significant	Not significant	Not significant	Not significant
RCTs: haemorrhagic stroke vs warfarin ¹⁻⁵	74%	69%	49%	41%	46%
Superior safety profile reinforced by comparative real-world data ^{7,8}					
Specific reversal agent available					

No head-to-head RCT comparison. Head-to-head data available from observational studies

SE, systemic embolism

1. Connolly et al. N Engl J Med 2014; 2. Granger et al. N Engl J Med 2011; 3. Patel et al. N Engl J Med 2011; 4. Giugliano et al. N Engl J Med 2013; 5. Pradaxa®: EU SPC, 2016; 6. Lopes et al. Lancet 2012; 7. Larsen et al. BMJ 2016; 8. Lin et al. ESC 2015

Take-Home Message

- In Asian countries, the rate of stroke mortality and the risk of hemorrhagic stroke are higher than Western countries.
- NOAC has been proven to be more effective and safer treatment than warfarin in patients with NVAF in several RCTs.
- Dabigatran 150 mg BID is the only NOAC to provide superior protection from ischaemic and haemorrhagic stroke vs warfarin.