

Master Class Web Symposium NVAF

Consistent Superior Dual Risk Reduction of Apixaban from RCT to Real World Practice



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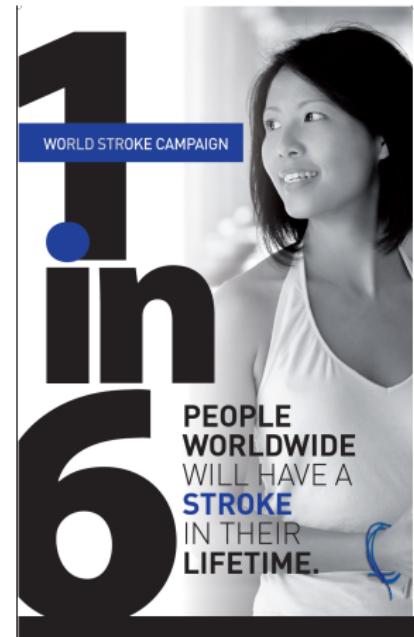
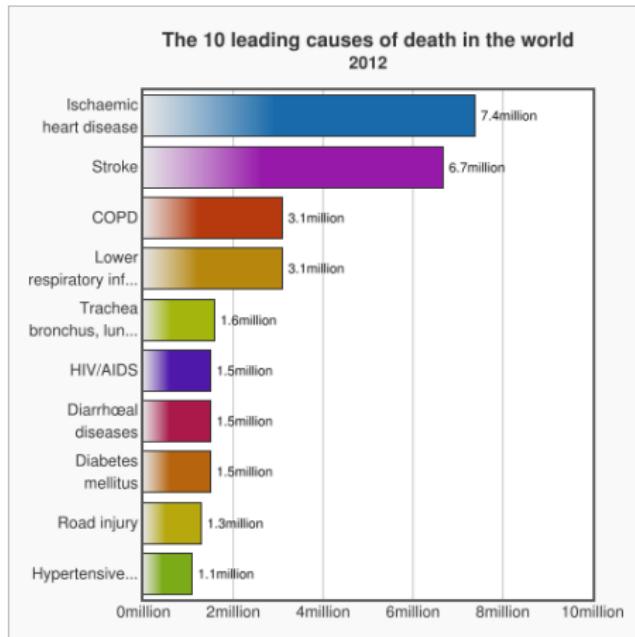
- Vit. K antagonist

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- Apixaban in RCT
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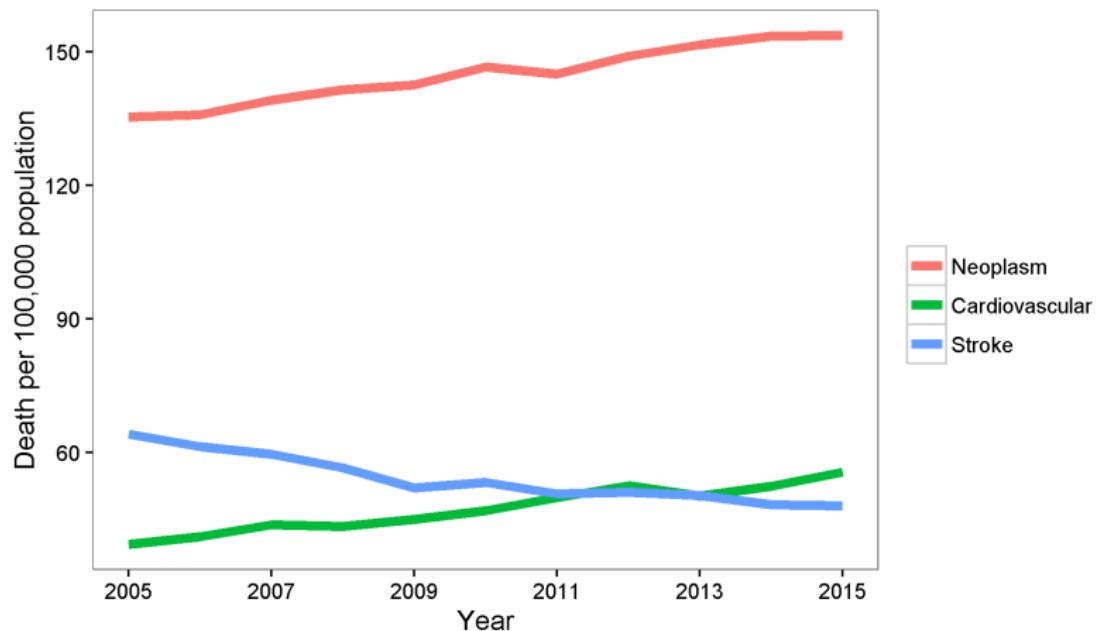
Global burden of stroke



<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>

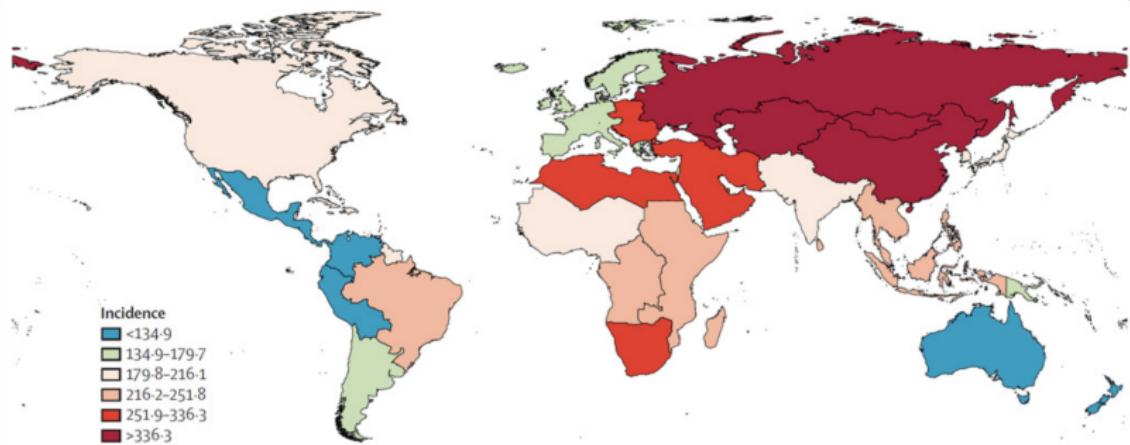
Secular trend of mortality in Korea



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

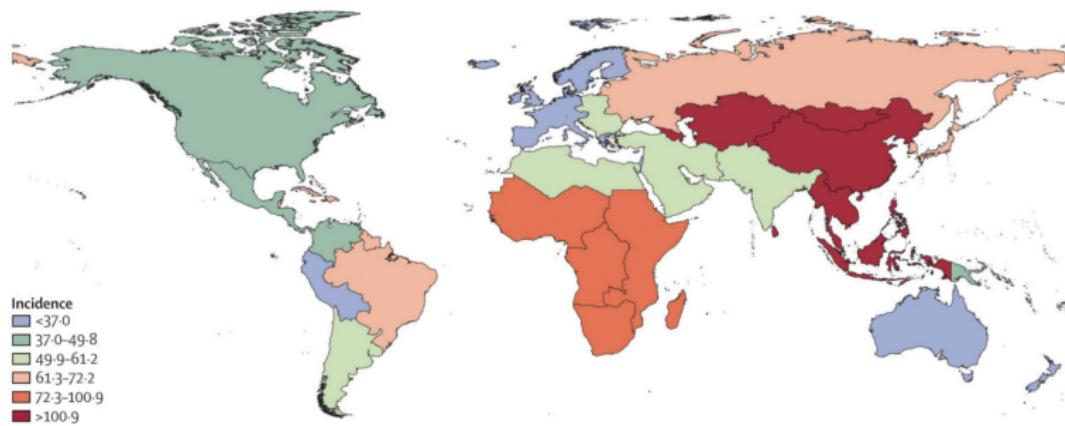
Age-standardised stroke incidence

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.

Stroke in Asian

Ischemic Stroke

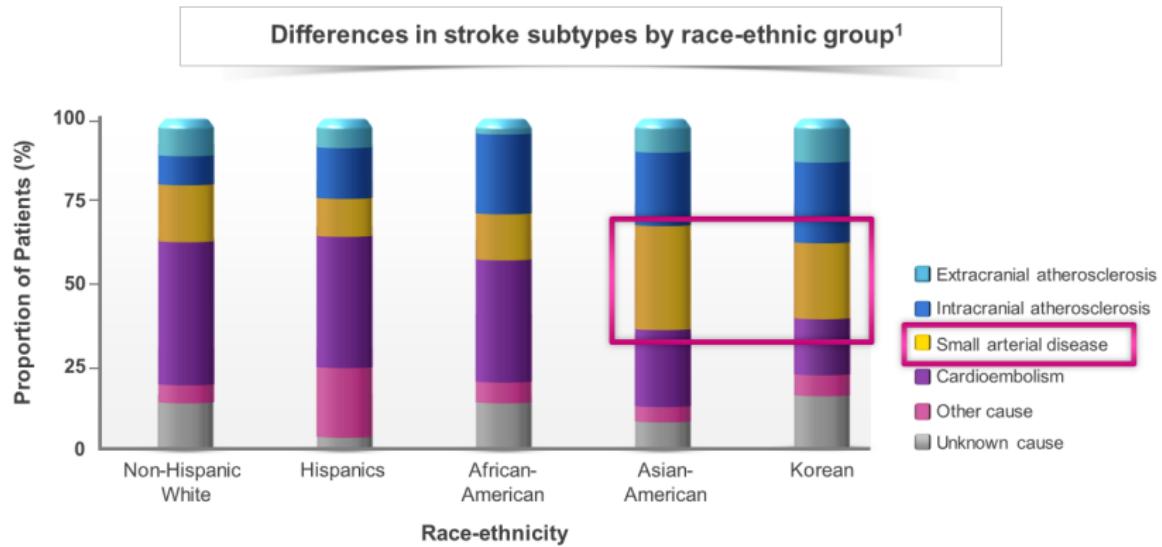
- Atherosclerosis
- Small artery occlusion
- Cardiac disease causing embolism
- Other causes such as moyamoya disease

Hemorrhagic Stroke

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

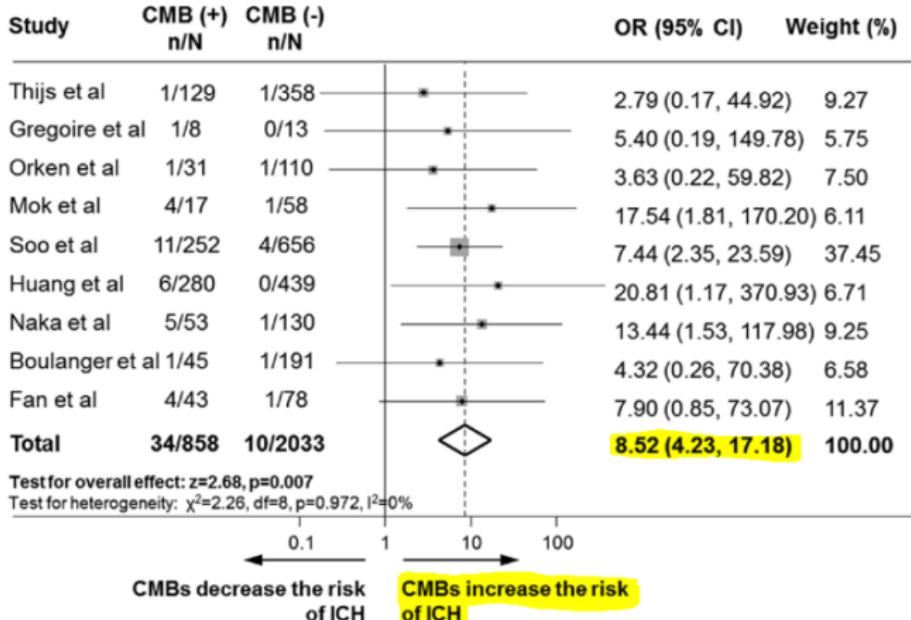
Higher risk of hemorrhagic stroke should be considered when choosing the anti-thrombotic medication in Asians.

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

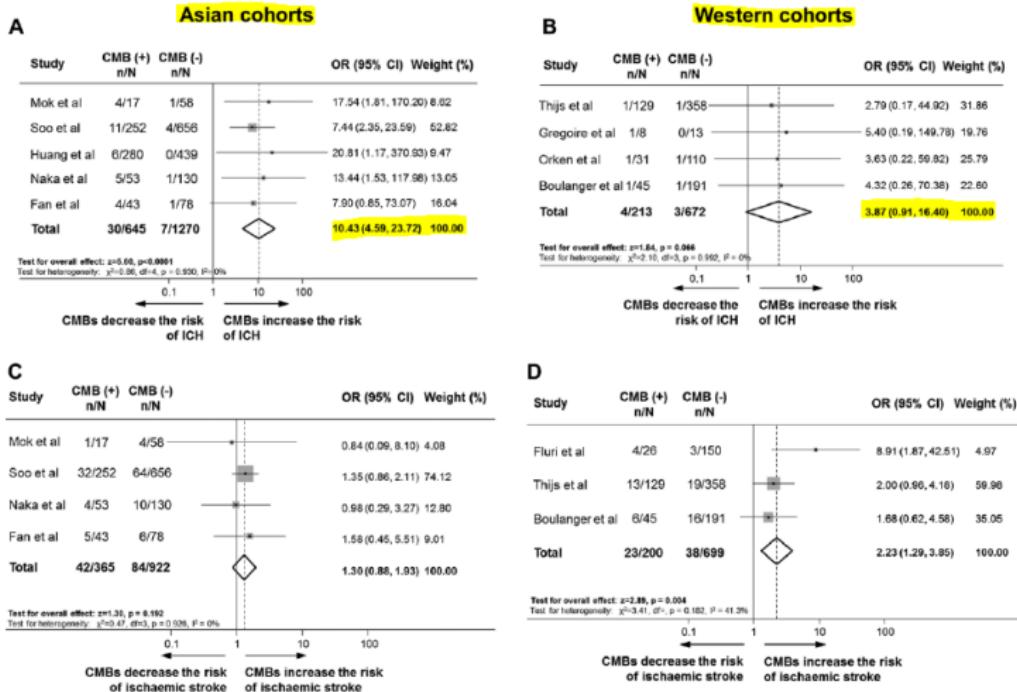
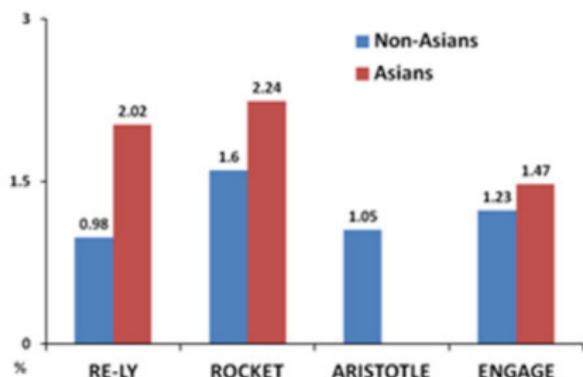
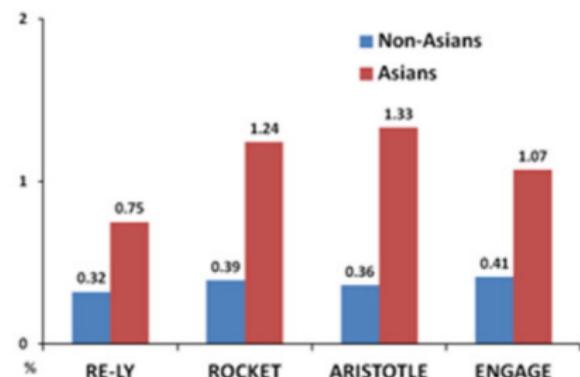


Figure 4. Meta-analysis of the risk of spontaneous intracerebral hemorrhage (ICH; A and B) and ischemic stroke (C and D) stratified by the dominant ethnicity of subjects included in each cohort as Asian or Western (white), with and without cerebral microbleeds (CMBs).

Stroke on warfarin

B

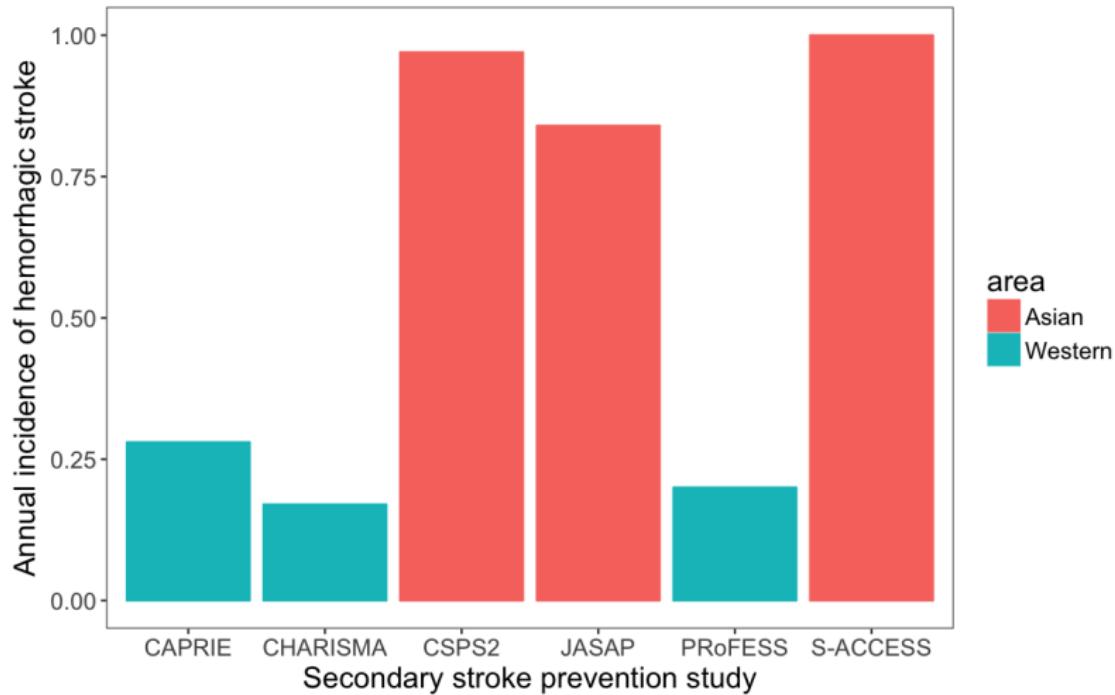
Ischemic stroke

C

Hemorrhagic stroke

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

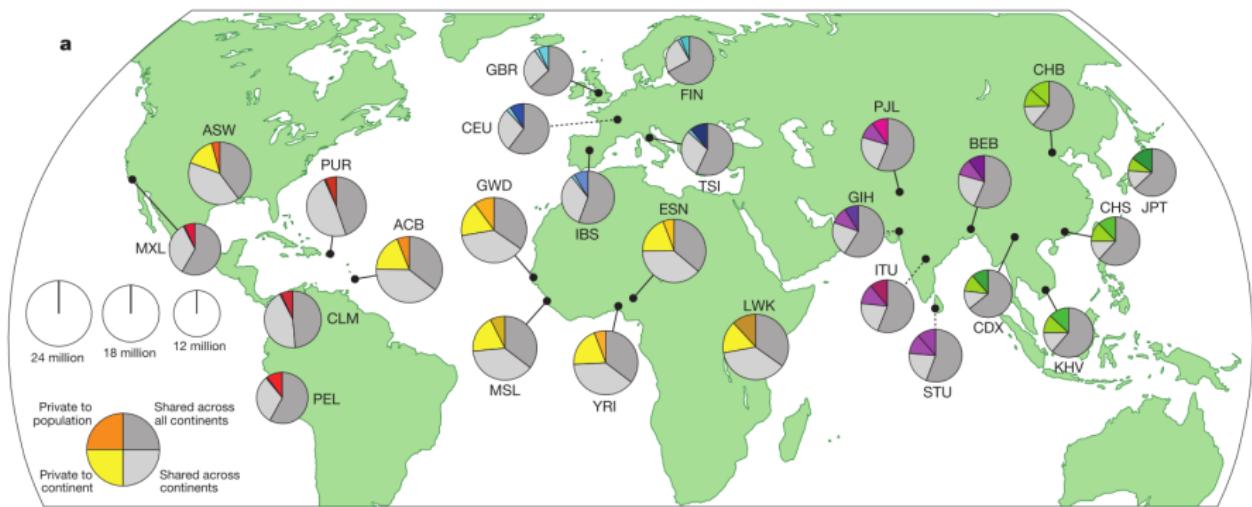


Populations: ● - African; ● - American; ● - East Asian; ● - European; ● - South Asian;

2,504 individuals from 26 populations

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

A global reference for human genetic variation



The 1000 Genomes Project. Nature 2015

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

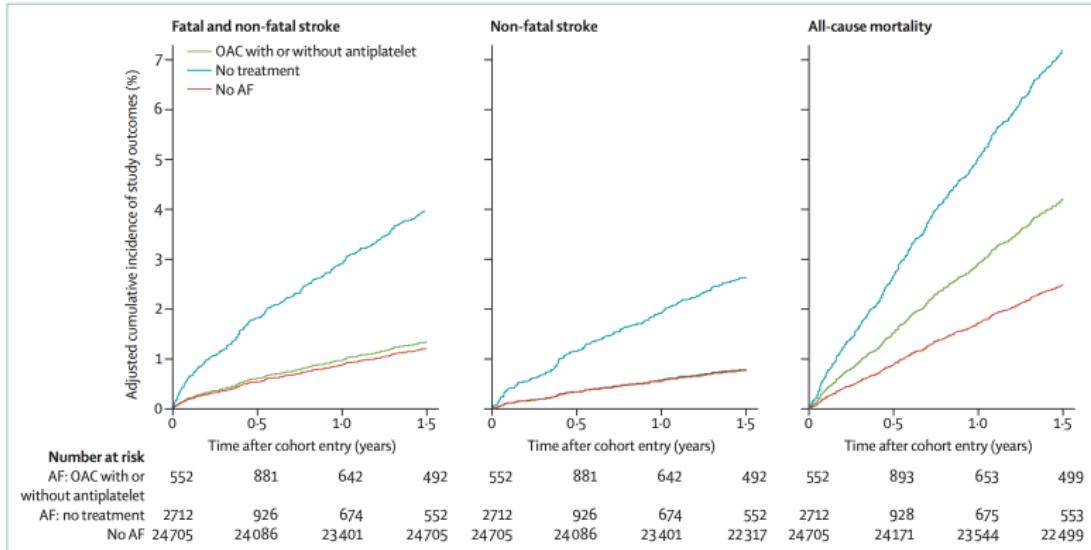
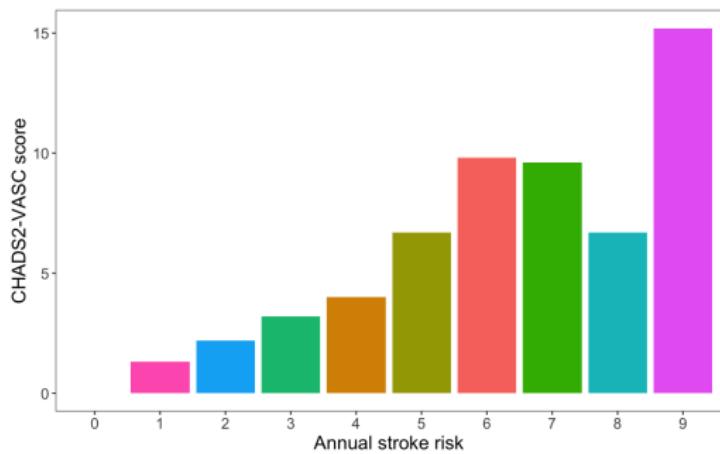


Figure 2: Effect of treatment on incidentally detected atrial fibrillation

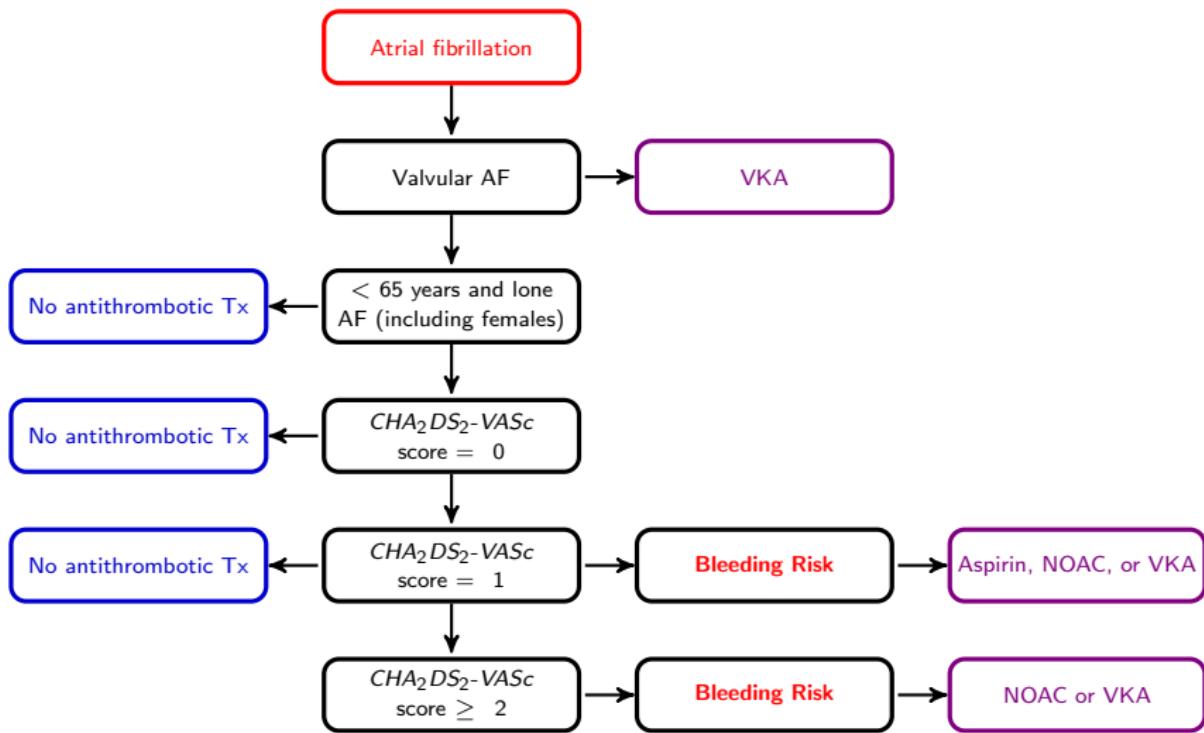
AF=atrial fibrillation. OAC=oral anticoagulant. Reproduced with permission from Freedman and colleagues.²¹

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

VKA is effective in preventing embolism when INR is > 2.0

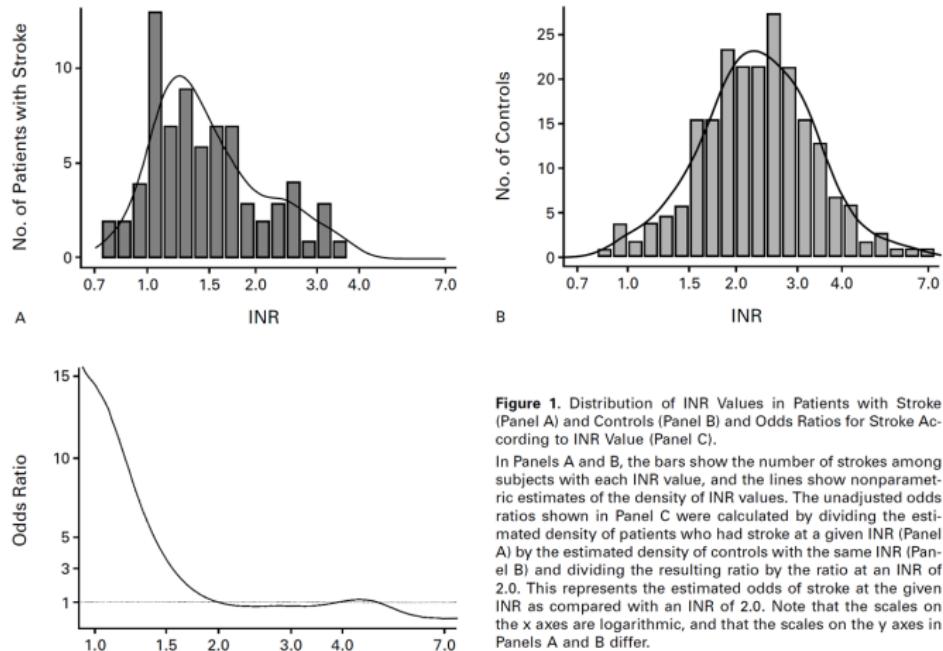


Figure 1. Distribution of INR Values in Patients with Stroke (Panel A) and Controls (Panel B) and Odds Ratios for Stroke According to INR Value (Panel C).

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

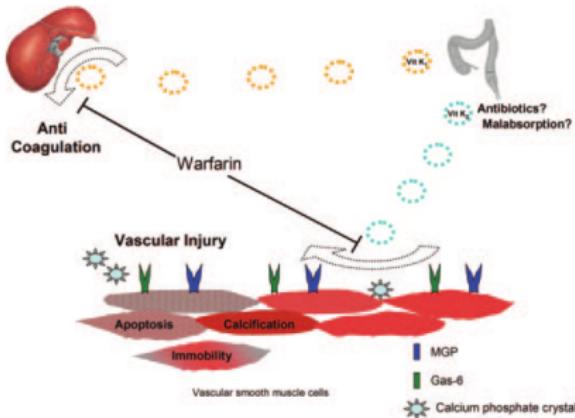
Vitamin K-dependent Proteins, Warfarin, and Vascular Calcification

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.

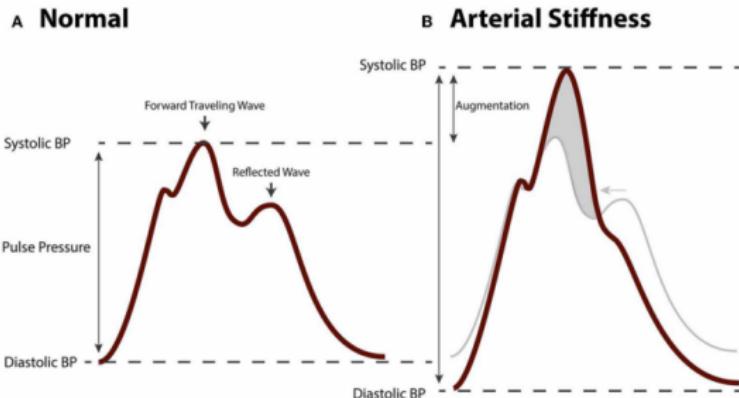
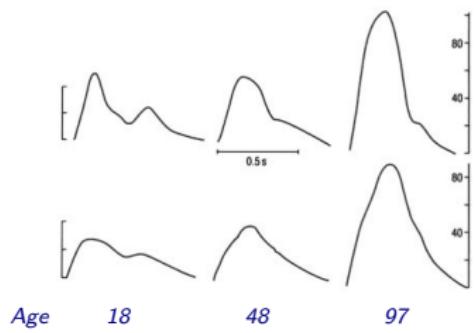


FIGURE 4 | Hemodynamic changes in arterial stiffening. (A) Aortic blood pressure waveform of a healthy, normotensive person. The forwards traveling wave precedes the (backwards traveling) reflected wave. **(B)** Aortic pressure

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



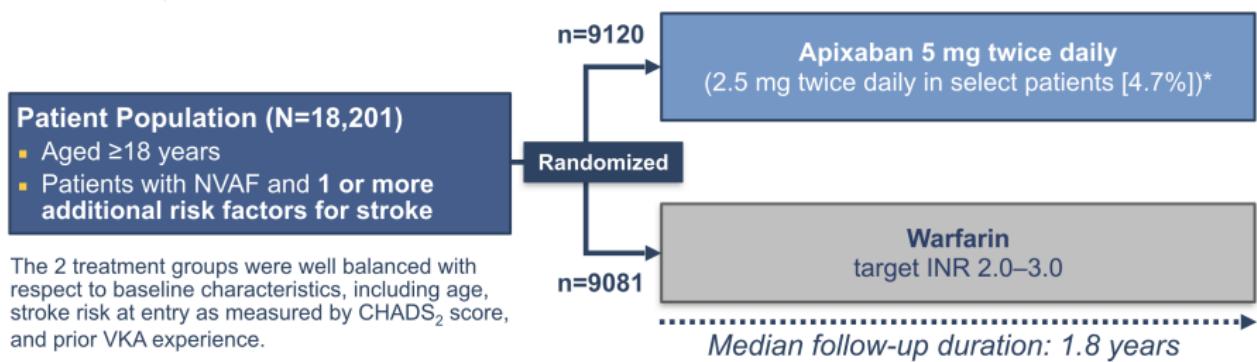
these organs while mean flow is maintained.³⁶ Brain and kidney arteries of all sizes are thus subjected to higher pulsatile circumferential stress and higher longitudinal shear stress. Their ability to withstand increased stresses depends on their resilience, and this is markedly decreased in a number 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 lipohyalinosis and of fibrinoid necrosis as seen in the brains and kidneys of

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

ARISTOTLE: Apixaban vs Warfarin in Patients With NVAF



PRIMARY EFFICACY ENDPOINT

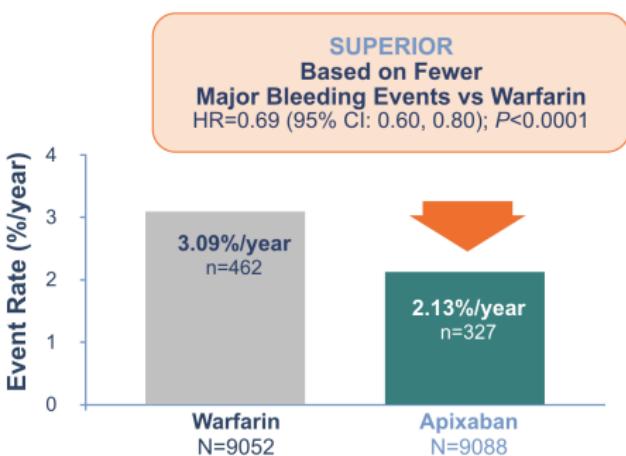
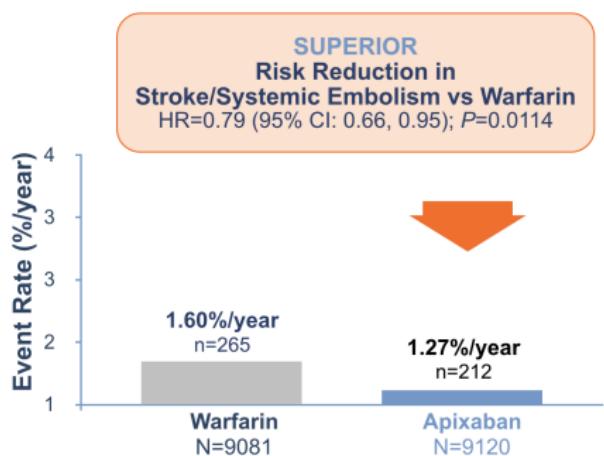
- Stroke and systemic embolism

PRIMARY SAFETY ENDPOINT

- Major bleeding

Granger CB et al. N Engl J Med. 2011;365:981-992.

ARISTOTLE



Granger CB et al. N Engl J Med. 2011;365:981-992.

NOAC trials

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF-TIMI 48
Number of Pts	18,113	14,264	18,201	21,105
Design	Blinded (dabigatran) Open-label (warfarin)	Double-blind, double-dummy	Double-blind, double-dummy	Double-blind, double-dummy
Treatments	<ul style="list-style-type: none"> • Dabigatran: 110 mg/150 mg BID • Warfarin (INR target: 2–3) 	<ul style="list-style-type: none"> • Rivaroxaban 20 mg OD 15 mg OD in selected patients[†] • Warfarin (INR target: 2–3) 	<ul style="list-style-type: none"> • Apixaban 5 mg BID 2.5mg BID in selected patients* • Warfarin (INR target: 2–3) 	<ul style="list-style-type: none"> • Edoxaban 60 mg OD 30 mg OD in selected patients‡ • Warfarin (INR target: 2–3)

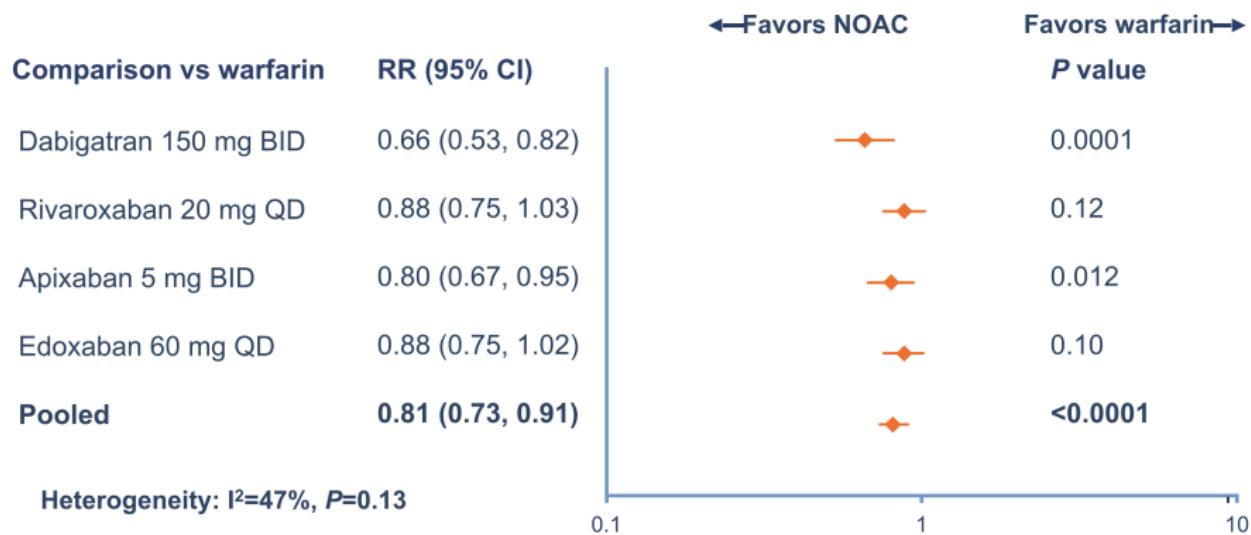
*Patients with CrCl between 30–49 mL/min;

[†]Patients with ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 µmol/L). Note: Per the apixaban SmPC, patients with the exclusive criterion of severe renal impairment (CrCl 15–29 mL/min) should also receive the lower dose of apixaban 2.5 mg BD. This criterion differs from the trial conduct.

[‡]Patients with any of the following: CrCl 30–50 mL/min, body weight ≥60 kg or concomitant use of specific P-gp inhibitors. Per the edoxaban SmPC, the recommended dose is 60 mg OD. A dose of 30 mg OD is recommended in selected patients. Please refer to the SmPC for further details.

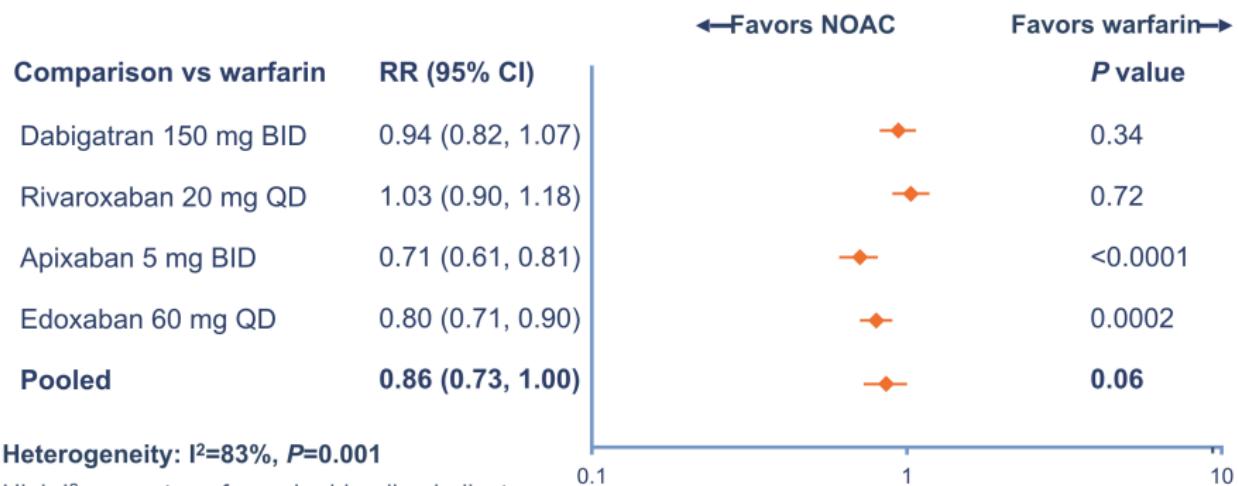
Connolly SJ et al. *N Engl J Med.* 2009;361:1139–1151; Patel MR et al. *N Engl J Med.* 2011;365:883–891 ; Granger CB et al. *N Engl J Med.* 2011;365:981–992; Giugliano RP et al. *N Engl J Med.* 2013;369(22):2093–2104

NOAC trials: systemic embolism/stroke



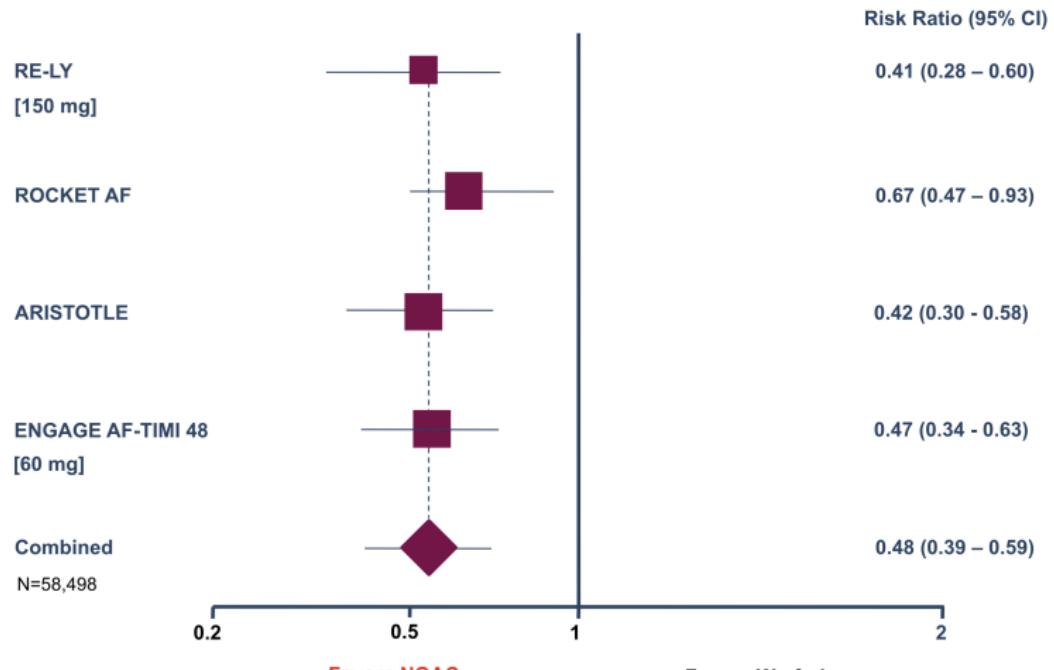
Ruff CT et al. Lancet. 2014;383:955-962

NOAC trials: major bleeding



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

NOAC trials: ICH

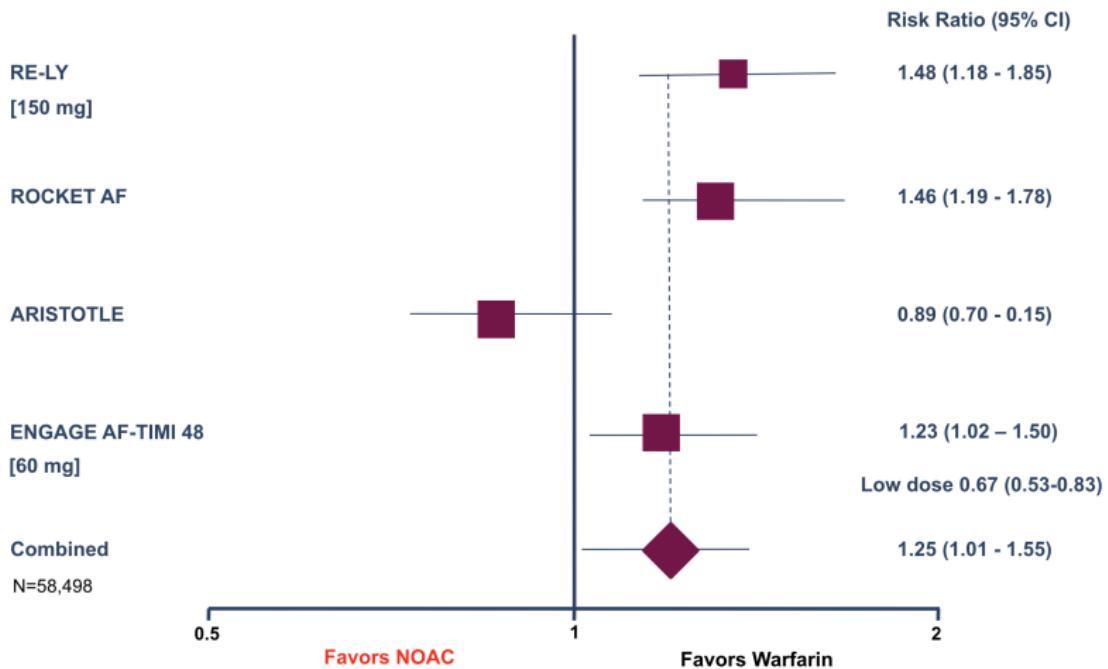


Lancet 2015; 383:955

Favors NOAC

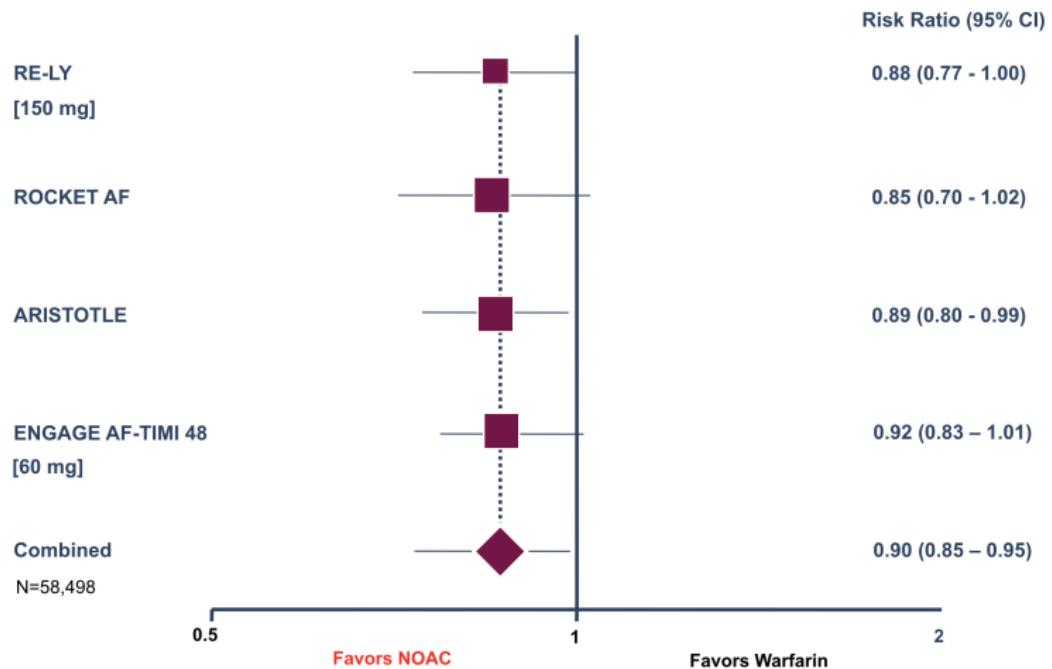
Favors Warfarin

NOAC trials: GI bleeding



Lancet 2015; 383:955

NOAC trials: total death



Lancet 2015; 383:955

Eligibility and Preference of New Oral Anticoagulants in Patients With Atrial Fibrillation

Comparison Between Patients With Versus Without Stroke

Chang Hyo Yoon, MD; Yoon Kyung Park, MD; Suk Jae Kim, MD; Mi-ji Lee, MD; Sookyung Ryoo, MD; Gyeong-Moon Kim, MD, PD; Chin-Sang Chung, MD, PhD; Kwang Ho Lee, MD, PhD; June Soo Kim, MD, PhD; Oh Young Bang, MD, PhD

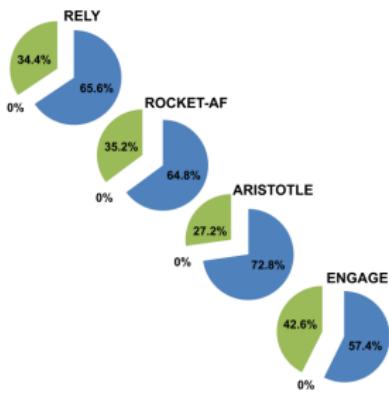
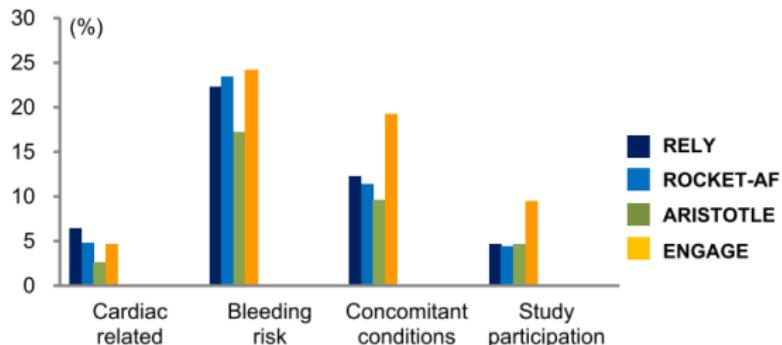
Background and Purpose—Recent randomized clinical trials (RCTs) have evaluated the benefit of new oral anticoagulants in reducing the risk of vascular events and bleeding complications in patients with atrial fibrillation (AF). However, abundant and strict enrollment criteria may limit the validity and applicability of results of RCTs to clinical practice. We estimated the eligibility for participation in RCTs of an unselected group of patients with AF. In addition, we compared features favoring new oral anticoagulant use between patients with versus without stroke. Randomized Evaluation of Long-Term Anticoagulation Therapy

Methods—We applied enrollment criteria of 4 RCTs (RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE-AF-TIMI 48) to 695 patients with AF taking warfarin, prospectively and consecutively collected at a university medical center; 500 patients with and 195 patients without stroke. Time in therapeutic range and bleeding risk scheme (anticoagulation and risk factors in atrial fibrillation) were also measured.

Results—The proportions of patients fulfilling the trial enrollment criteria varied, ranging from 39% to 72.8%, depending on the differences in indications/contraindications among studies and presence/absence of stroke. The main reasons for ineligibility for RCTs were hemorrhagic risk (anticoagulation and risk factors in atrial fibrillation [ATRIA] score) (10.8%–40.5%) and planned cardioversion (5.1%–7.7%) for nonstroke patients, and a low creatinine clearance (5.6%–9.2%) and higher risk of bleeding (15.2%–20.8%) for patients with stroke. When compared with nonstroke patients, patients with stroke showed a lower time in therapeutic range ($54.4\pm42.8\%$ versus $65.4\pm34.9\%$, especially with severe disability) and a high hemorrhagic risk (ATRIA score) (3.06 ± 2.30 versus 2.18 ± 2.16) ($P<0.05$ in both cases).

Conclusions—Patients enrolled in RCTs are partly representative of patients with AF in clinical practice. When time in therapeutic range and bleeding tendency with warfarin use were considered, the use of new oral anticoagulants was preferred in patients with stroke than in nonstroke patients, but they were more likely to be excluded in RCTs. (*Stroke*. 2014;45:2983-2988.)

- Eligible
- Not indicated
- Contraindicated

A-fib Stroke (n=500)**C**

The main reasons for ineligibility for RCTs were a low creatinine clearance (5.6%-9.2%) and higher risk of bleeding (15.2%-20.8%) for patients with stroke.

Table: Exclusion criteria due to hemorrhagic risk

	RE-LY	ROCKET	ARISTOTLE	ENGAGE
GI bleeding	Within 1y	Within 6m		Within 1y
GI ulcer	Within 1m	Within 6m		Within 1y
History of bleeding	Exclude	Exclude	Exclude	Exclude
Chronic hemorrhagic dis	Exclude	Exclude		Exclude
Intracranial neoplasm		Exclude		
Intracranial aneurysm		Exclude		
Major surgery or trauma	Exclude	Exclude	Exclude	Exclude
Thrombocytopenia or anemia	Exclude	Exclude	Exclude	Exclude
Uncontrolled HTN	Exclude	Exclude	Exclude	Exclude

Yoon CH et al. Stroke. 2014

Clinical studies offer:

- **High degree** of evidence
- **Controlled**, randomized conditions
- Basis for **regulatory approval**
- Basis for **treatment guidelines**

Real-world data offer:

- **Lower degree** of evidence
- Non-randomized; a **more heterogeneous environment from routine clinical practice**
- Help with **interpretation** of clinical practice
- Basis for new **hypotheses**

Real world data

	Tepper P et al ¹	Lip GYH et al ²	Lin I et al ³
Data source	<ul style="list-style-type: none"> ■ US Truven MarketScan® Earlyview insurance claims database 	<ul style="list-style-type: none"> ■ US Truven MarketScan® Commercial and Medicare supplemental databases 	<ul style="list-style-type: none"> ■ US Humedica de-identified EHR data
Study population	<ul style="list-style-type: none"> ■ Age ≥18 years ■ Switched from warfarin or newly prescribed a NOAC during study period 	<ul style="list-style-type: none"> ■ Age ≥18 years ■ Newly prescribed NOAC or warfarin with NVAF diagnosis 	<ul style="list-style-type: none"> ■ Age ≥18 years ■ Newly prescribed NOAC or warfarin with NVAF diagnosis
Study drug (n)	<ul style="list-style-type: none"> ■ Apixaban (n=8785) ■ Rivaroxaban (n=30,529) ■ Dabigatran (n=20,963) 	<ul style="list-style-type: none"> ■ Apixaban (n=2402) ■ Rivaroxaban (n=10,050) ■ Dabigatran (n=4173) ■ Warfarin (n=12,713) 	<ul style="list-style-type: none"> ■ Apixaban (n=2038) ■ Rivaroxaban (n=6407) ■ Dabigatran (n=2440) ■ Warfarin (n=24,872)
Study period	<ul style="list-style-type: none"> ■ 1/1/13–10/31/14 	<ul style="list-style-type: none"> ■ 1/1/12–12/31/13 (includes 1 year baseline) 	<ul style="list-style-type: none"> ■ 1/1/13–6/30/14
Follow-up	<ul style="list-style-type: none"> ■ Up to 6 months 	<ul style="list-style-type: none"> ■ Up to 1 year 	<ul style="list-style-type: none"> ■ Up to 180 days
Endpoints	<ul style="list-style-type: none"> ■ Major; CRNM; any bleeding 	<ul style="list-style-type: none"> ■ Major bleeding 	<ul style="list-style-type: none"> ■ Any bleeding
Bleeding definitions	<ul style="list-style-type: none"> ■ Based on ICD-9-CM diagnostics codes, CPT and HCPCS procedure codes 	<ul style="list-style-type: none"> ■ Inpatient major bleeding: bleeding requiring hospitalization with a bleeding diagnosis code as the first listed ICD-9-CM code 	<ul style="list-style-type: none"> ■ At least one encounter with an ICD-9-CM code indicative of a major or CRNM bleed in any setting

1. Tepper P et al. Presented at: ESC Congress; August 29-September 2, 2015; London, UK.

2. Lip GYH et al. Presented at: ESC Congress; August 29-September 2, 2015; London, UK.

3. Lin I et al. Presented at: ESC Congress; August 29-September 2, 2015; London, UK.

Real world data

Switched from warfarin to a NOAC or newly prescribed a NOAC¹

Tepper et al¹

Major bleeding

CRNM bleeding

Any bleeding

← Favors rivaroxaban Favors apixaban →



Newly anticoagulated^{2,3}

Lip et al²

Inpatient major bleeding

Inpatient/outpatient major bleeding

Lin et al³

Any bleeding



1. Tepper P et al. Presented at: ESC Congress; August 29-September 2, 2015; London, UK.

2. Lip GYH et al. Presented at: ESC Congress; August 29-September 2, 2015; London, UK.

3. Lin I et al. Presented at: ESC Congress; August 29-September 2, 2015; London, UK.

Take-Home Message

- Asian stroke is associated with higher risk of cerebral hemorrhage
- Atrial fibrillation increases the risk of embolic stroke and bleeding
- Apixaban demonstrated superiority versus warfarin in reducing the risk of both stroke/SE and major bleeding in the ARISTOTLE randomized controlled trial of patients with NVAF
- Meta analysis and Real-world data add additional information about the efficacy and safety profile of Apixaban