Perspectives based on Korean AF and Clinical data with Apixaban

KHRS 2018 ELIUQIS luncheon

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A large proportion of strokes could be prevented

Strokes are the cause of ~140 million deaths worldwide every year[1]

15–20% are AF-related[2]

~28 million are due to AF

RRR of **64%** with warfarin vs no treatment[3]

250,000 are preventable with warfarin therapy

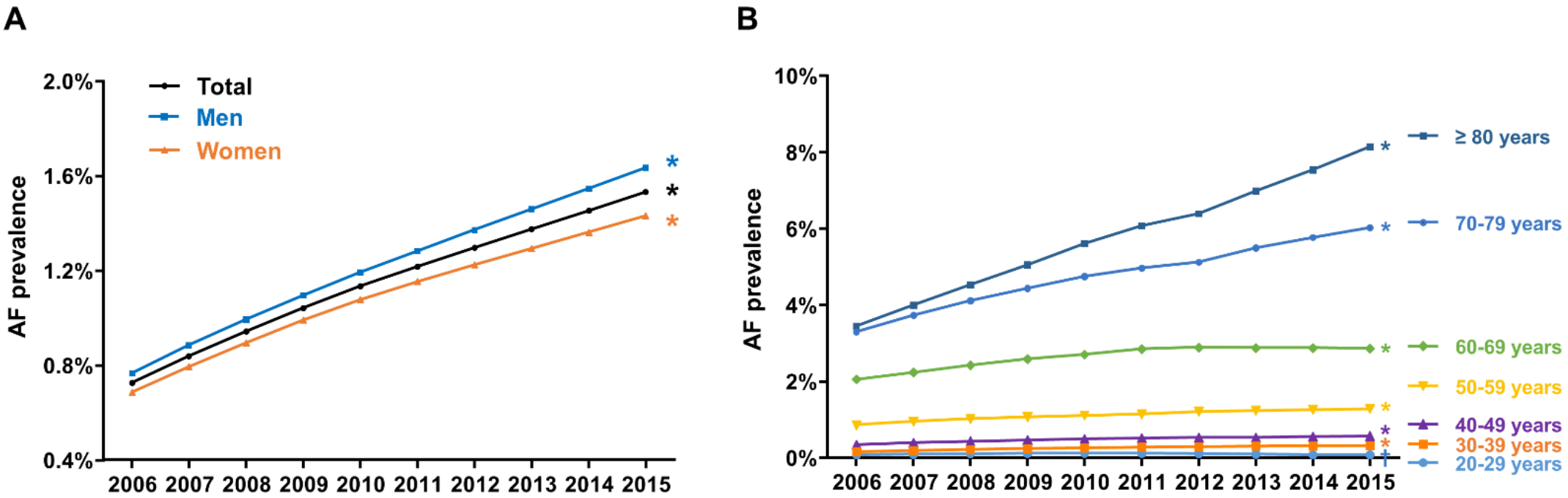
62% of eligible patients are treated with OAC[4]

~95,000 strokes could potentially have been prevente d

RRR: relative risk reduction.

Prevalence, incidence, and projected number of AF

Annual prevalence of AF between 2006 and 2015 stratified according to sex (A) and age (B)

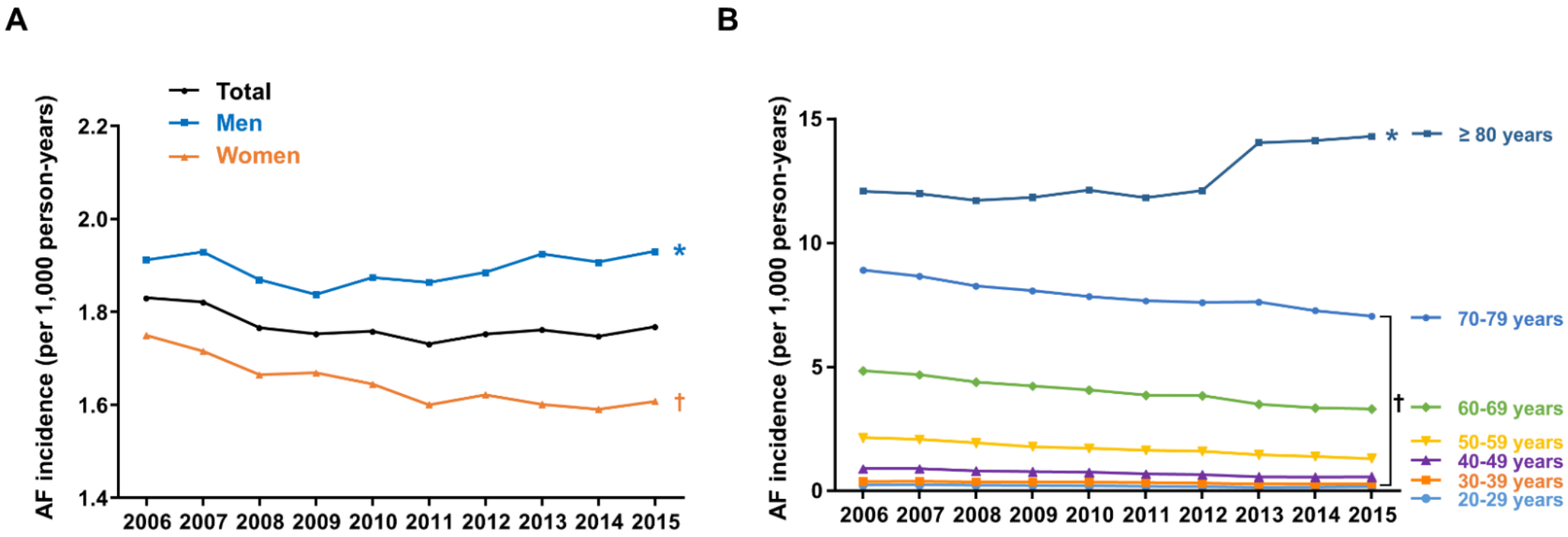


*P value for increasing trends <0.001. †P value for decreasing trends <0.001. AF, atrial fibrillation.

DH, Kim et al. S0002-8703(18)30140-6

Prevalence, incidence, and projected number of AF

Annual incidence of AF between 2006 and 2015 stratified according to sex (A) and age (B)

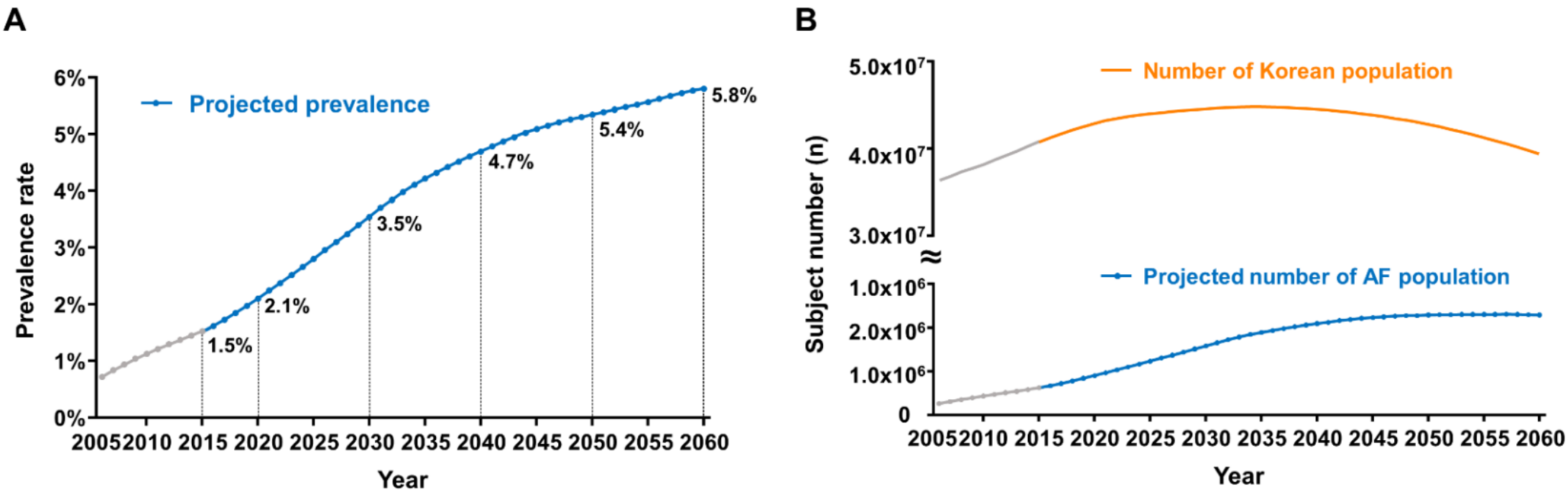


*P value for increasing trends <0.001. †P value for decreasing trends <0.001. AF, atrial fibrillation.

DH, Kim et al. S0002-8703(18)30140-6

Prevalence, incidence, and projected number of AF

Projected prevalence rate (A) and number (B) of AF

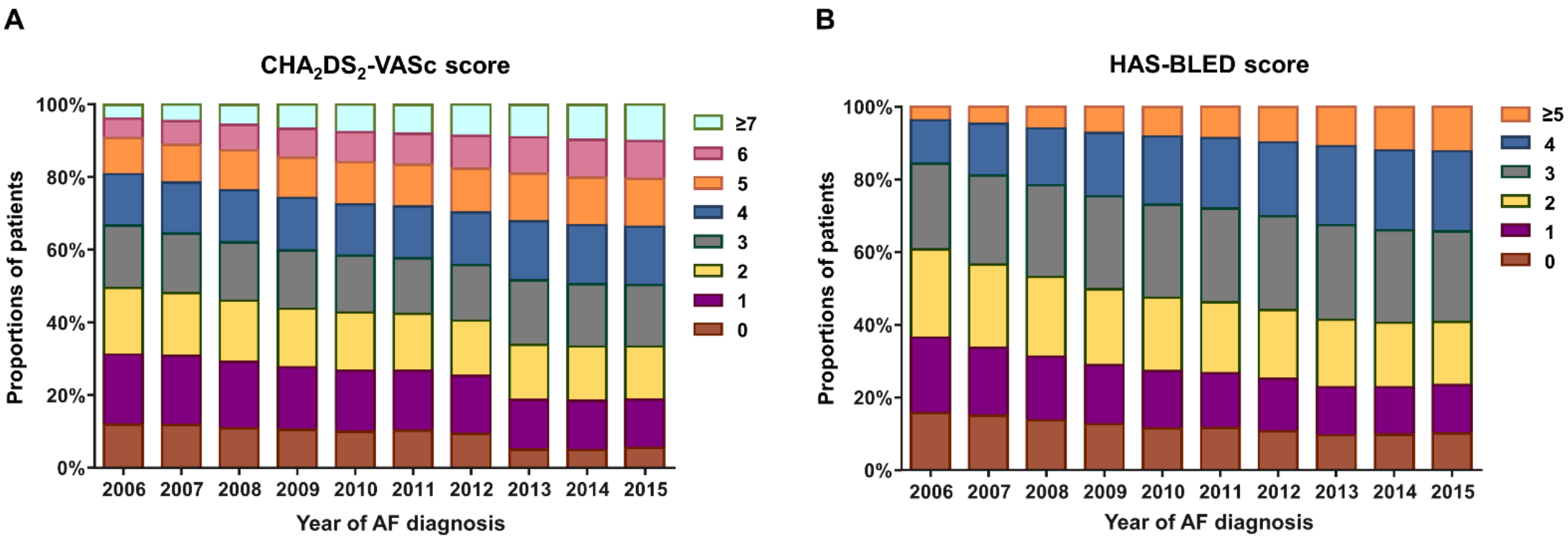


AF, atrial fibrillation.

DH, Kim et al. S0002-8703(18)30140-6

Trends of the CHA2DS2-VASc and HAS-BLED scores

Temporal trends of the distribution of the patients with newly diagnosed AF according to the CHA2DS2-VASc and HAS-BLED scores between 2006 and 2015

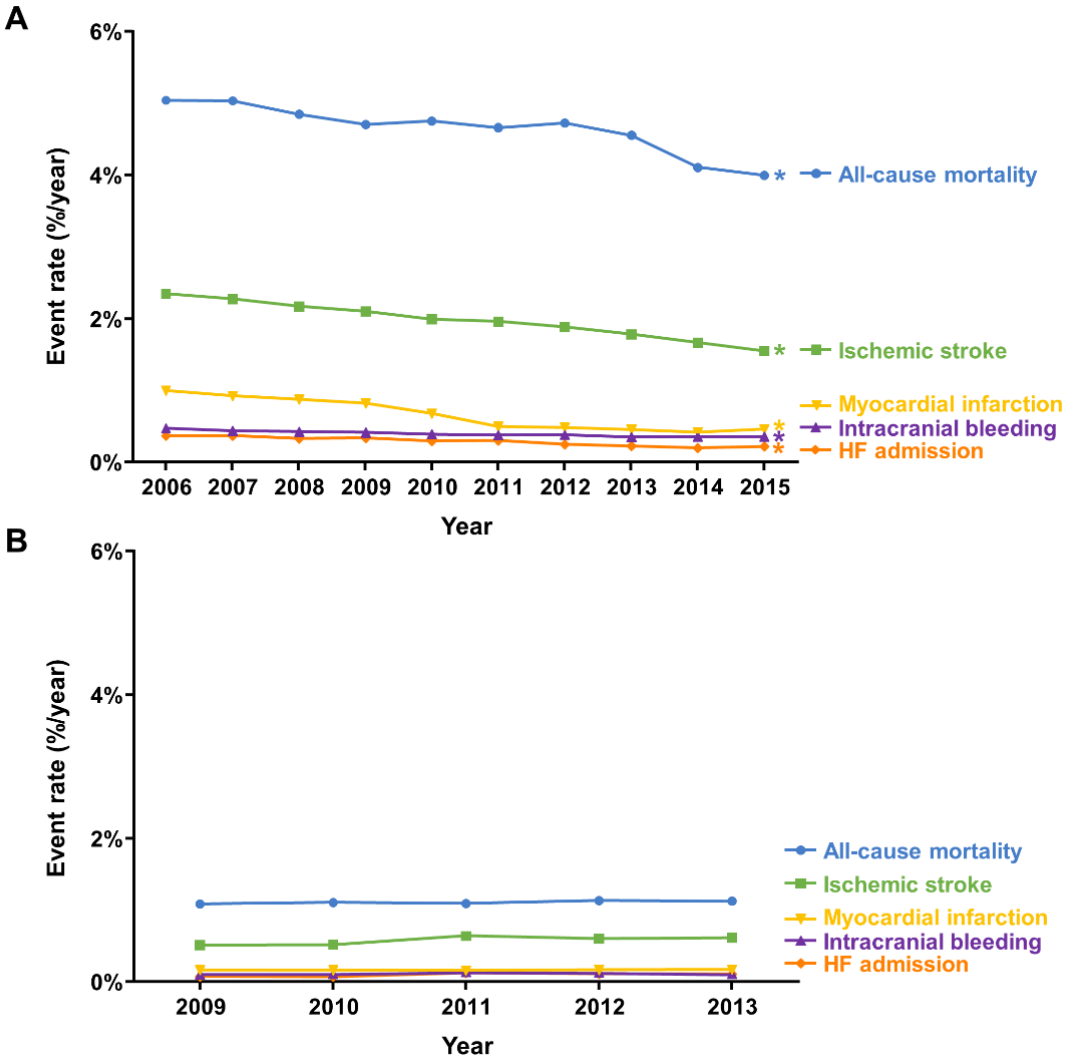


AF, atrial fibrillation.

DH, Kim et al. S0002-8703(18)30140-6

Trends of the adverse outcomes among the patients with AF

Temporal trends of the 1-year adverse event rates of the (A) patients with prevalent AF and (B) non-AF Korean population in each year

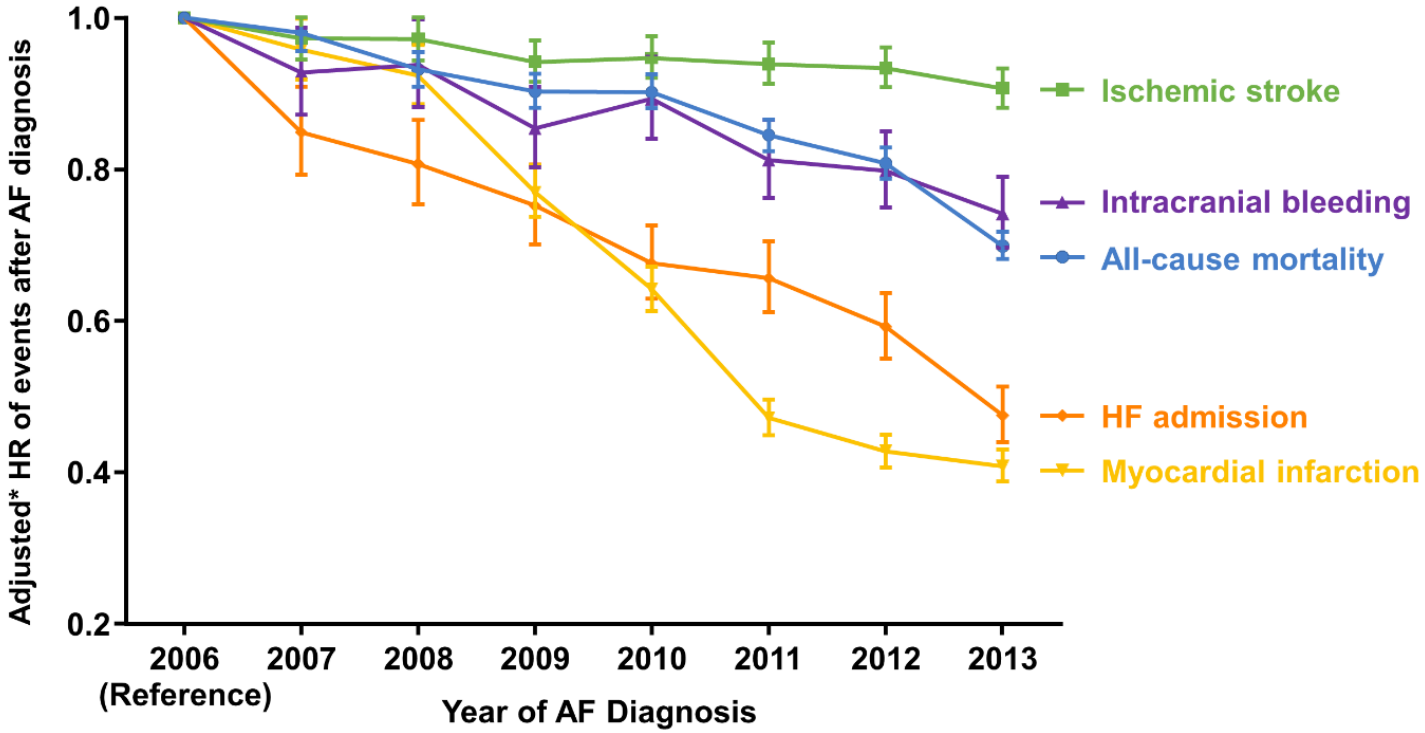


*P value for trends <0.001. The 1-year
the number of the first lifetime event t
the start of the year who had not expe
failure.

DH, Kim et al. S0002-8703(18)30140-6

Trends of the adverse outcomes among the patients with AF

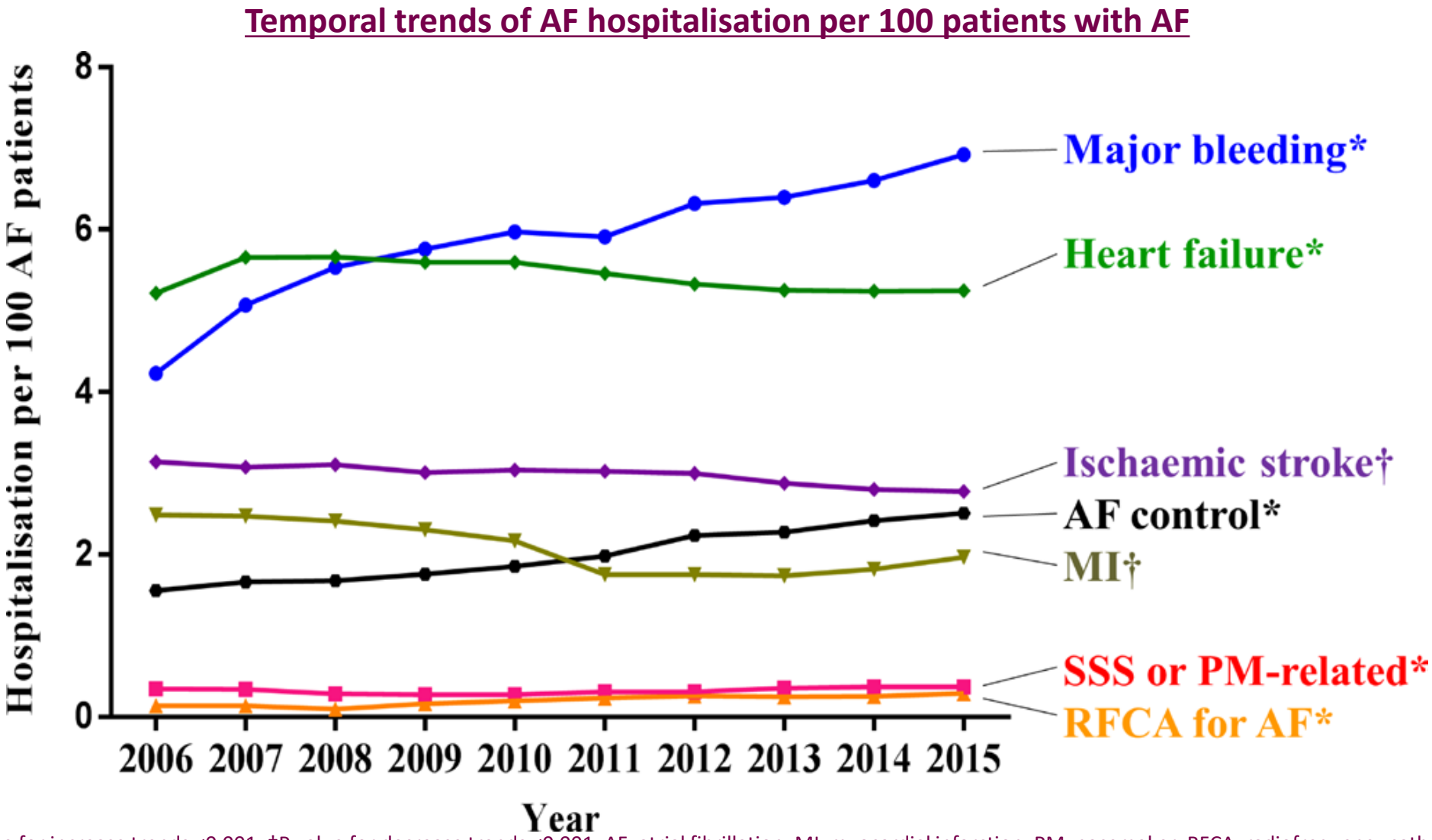
Temporal trends of the adjusted HRs of the adverse outcomes in the 2-year follow-up after AF diagnosis



The HR was adjusted for age, sex, economic status, and comorbidities. AF, atrial fibrillation; HF, heart failure; HR, hazard ratio

DH, Kim et al. S0002-8703(18)30140-6

Trends of AF hospitalisations

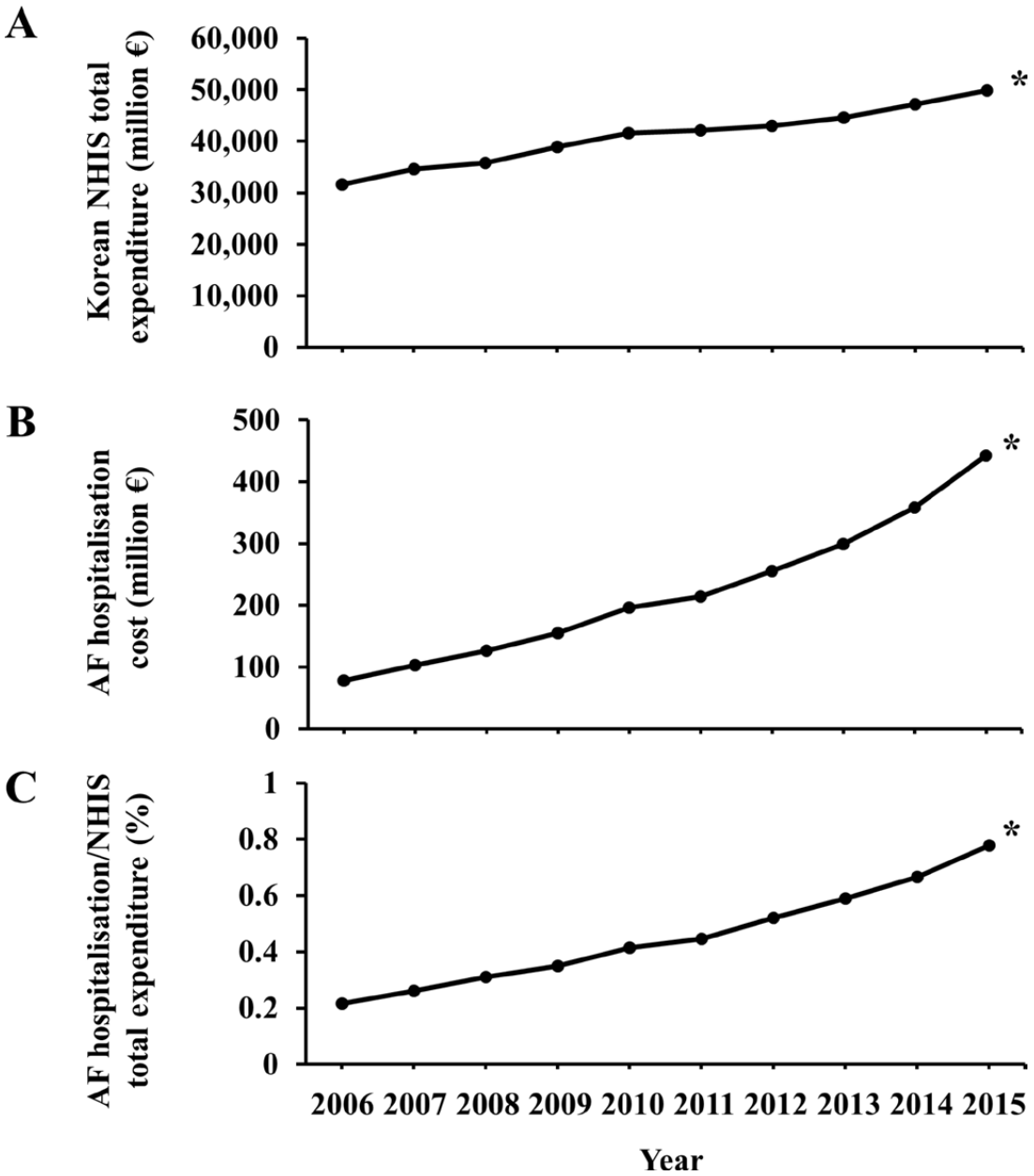


*P value for increase trends <0.001. †P value for decrease trends <0.001. AF, atrial fibrillation; MI, myocardial infarction; PM, pacemaker; RFCA, radiofrequency catheter ablation; SSS, sick sinus syndrome.

Kim D, et al. Heart 2018;0:1–8. doi:10.1136/heartjnl-2017-312930

Trends of AF hospitalisation costs

Temporal trends of medical cost between 2006 and 2015



(A) Korean NHIS total expenditure (million €), (B) total AF hospitalisation cost (million €) and (C) the proportion of total AF hospitalisation cost to Korean NHIS total expenditure (%). *P value for trends <0.001. AF, atrial fibrillation; NHIS, National Health Insurance Service.

Kim D, et al. Heart 2018;0:1–8. doi:10.1136/heartjnl-2017-312930

Increasing trends in hospital care burden of atrial fibrillation in Korea, 2006 through 2015

What is already known on this subject?

- The healthcare burden of atrial fibrillation (AF) is growing considerably, and is mainly related to hospitalisations. However, the impact of AF on hospitalisations and mortality, and the economic burden of AF is less understood in Asian populations.

What might this study add?

- AF hospitalisations have increased exponentially among Korean adults from 2006 to 2015, in association with an increase in comorbid chronic diseases. Mortality associated with AF hospitalisations decreased during the last decade, but hospitalisation costs have markedly increased.

How might this impact on clinical practice?

- Prevention of AF hospitalisations and streamlined integrated AF management should be pursued in a holistic manner to lessen the healthcare burden of AF.

Kim D, et al. Heart 2018;0:1–8. doi:10.1136/heartjnl-2017-312930

Anticoagulation in NVAF: The VKA era

VKA properties[1]

Established efficacy/safety profile[2]

Unpredictable anticoagulant effect

Narrow therapeutic window

Routine visits to clinic/hospital to monitor INR

Food and drug interactions

Diet and drug restrictions

Slow onset and offset of action

Difficult perioperative management

VKA superior to ASA for stroke prevention in AF[2]

VKA reduces stroke in AF by two-thirds versus placebo[2]

1995

2000

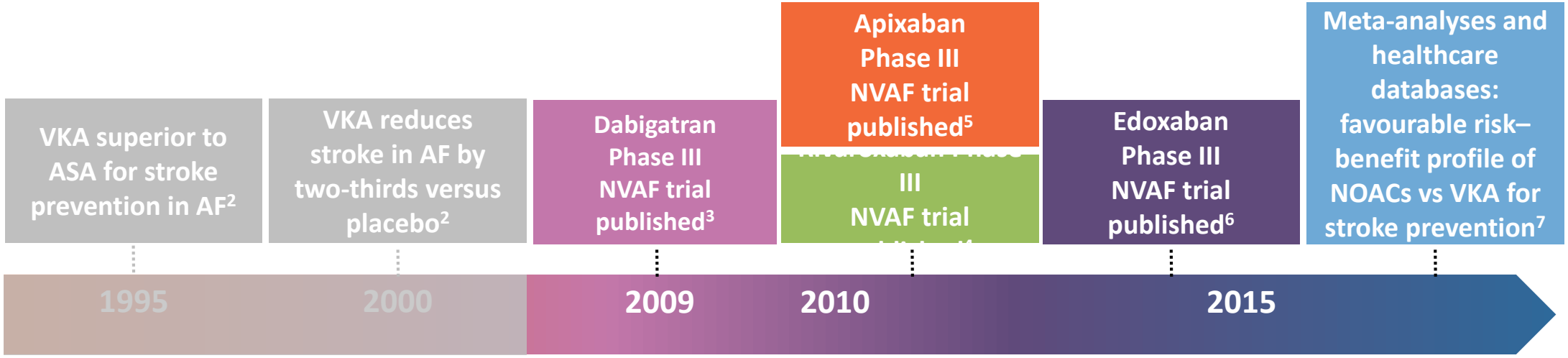
ASA: acetylsalicylic acid; INR: international normalised ratio; VKA: vitamin K antagonist.

1. Lin YP, et al. *Medicine* 2015;94:e1627;
2. Kirchhof P, et al. *Eur Heart J* 2016;37:2893–2962.

Anticoagulation in NVAF: NOACs in the current era

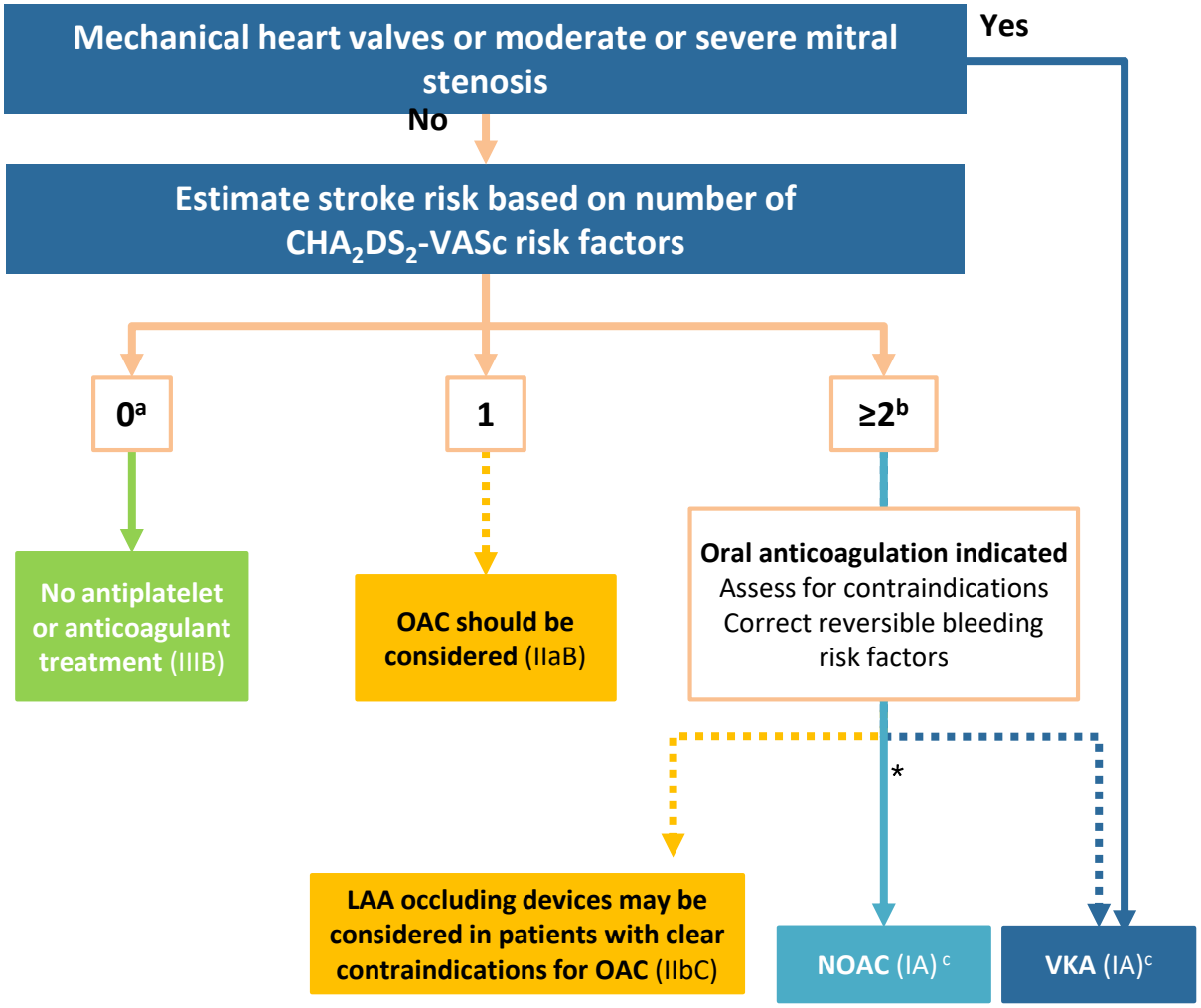
NOAC properties[1]

- Good efficacy and safety profile vs VKA[2–6]
- Fixed dose
- No need for monitoring
- Few drug and food interactions
- Few drug and diet restrictions
- Fast onset and offset of action
- Simpler perioperative management



1. Lin YP, et al. *Medicine* 2015;94:e1627; 2. Kirchhof P, et al. *Eur Heart J* 2016;37:2893–2962; 3. Connolly SJ, et al. *N Engl J Med* 2009;361:1139–1151;
4. Patel MR, et al. *N Engl J Med* 2011;365:883–891; 5. Granger CB, et al. *N Engl J Med* 2011;365:981–992;
6. Giugliano RP, et al. *N Engl J Med* 2013;369:2093–2104; 7. Ruff CT, et al. *Lancet* 2014;383:955–962.

2016 ESC Guidelines: Most patients with NVAF should be managed with NOACs as first-line anticoagulant



NOACs recommended as first-line anticoagulant (IA) **1**

Patients with moderate–severe mitral stenosis or mechanical heart valves should be treated with VKA (IB) **2**

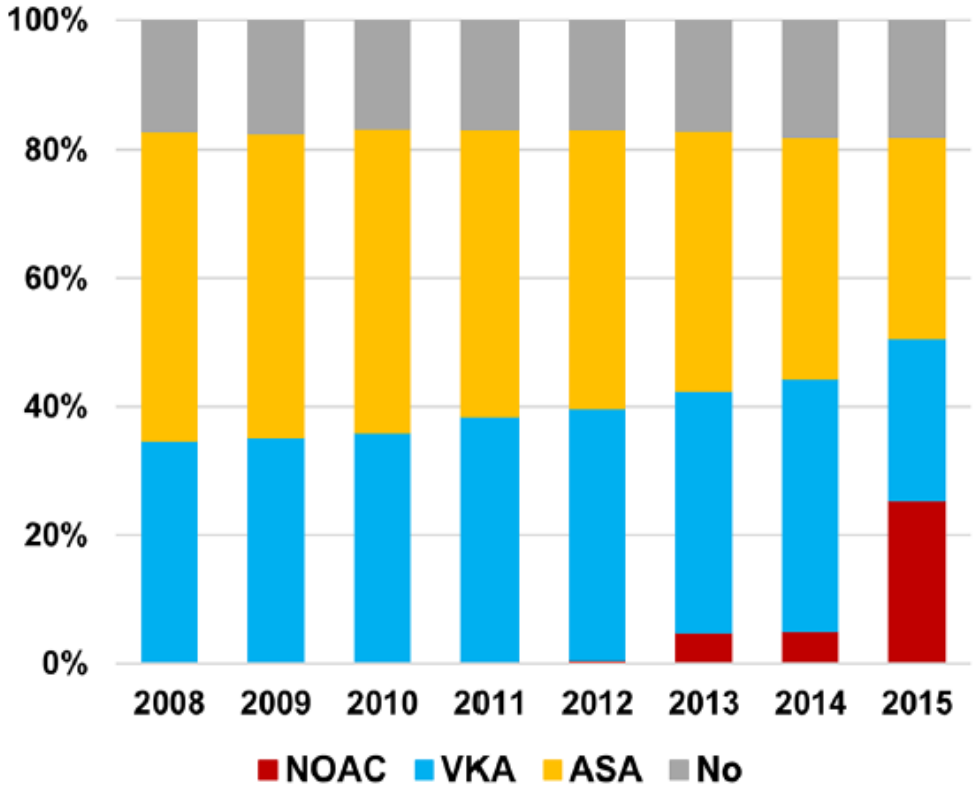
ASA and other antiplatelets have no role in stroke prevention (IIIA) **3**

**Solid arrow indicates preference; a. Includes women without other stroke risk factors; b. IIaB for women with only one additional stroke risk factor; c. IB for patients with mechanical heart valves or mitral stenosis. LAA: left atrial appendage; OAC: oral anticoagulant.*

Kirchhof P, et al. *Eur Heart J* 2016;37:2893–2962.

Trend of antithrombotic therapy in Korea

- OAC prescription increased from 34.7% to 50.6% between 2008 and 2015 (p for trend < 0.001)
- **Aspirin** prescription consistently **decreased** from 48.2% to 31.5%,
- **NOAC prescription increased** with wider approval of NOACs in 2015 (25.4% of total patients with CHA2DS2-VASc score 2 and 50.2% of OAC prescriptions).

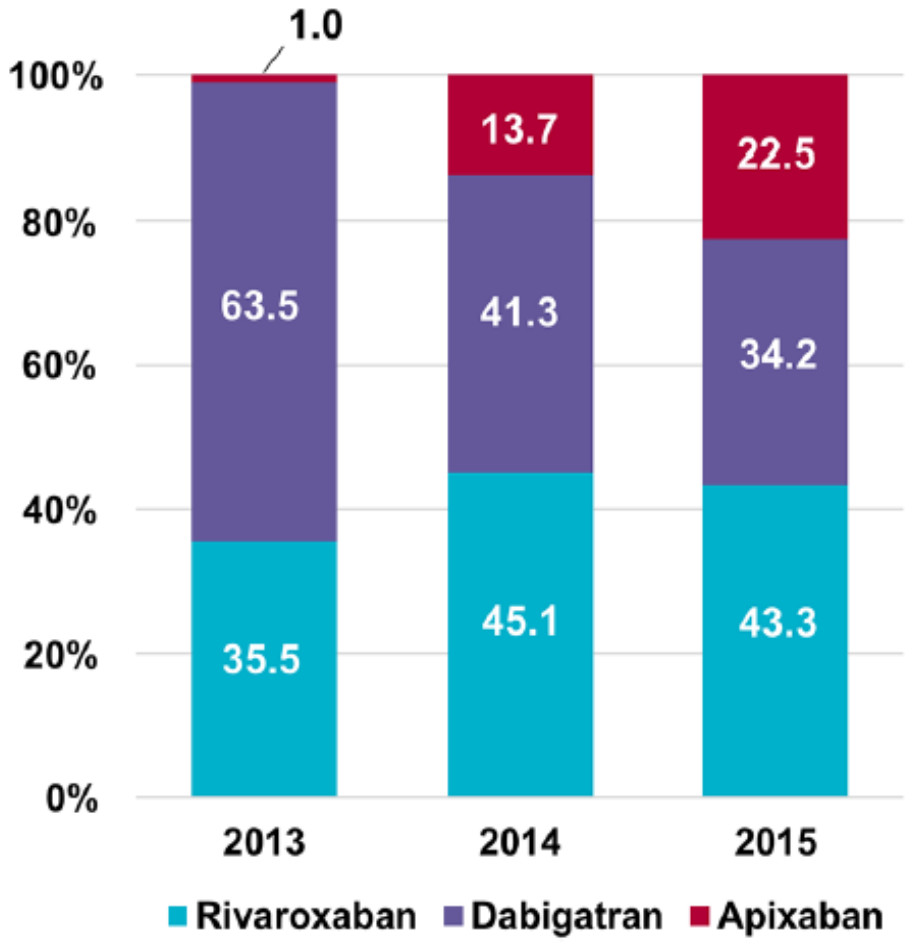


Temporal trends of antithrombotic therapy prescription. A. Temporal trends of antithrombotic therapy prescription in patients with CHA2DS2-VASc score 2. Abbreviation: ASA, aspirin; NOAC, non-vitamin K oral anticoagulants; VKA, vitamin K antagonists.

Lee, S. R., Choi, E. K., Han, K. D., Cha, M. J., Oh, S., & Lip, G. Y. (2017). Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: A nationwide population-based study. PloS one, 12(12), e018

Distribution of NOACs in Korea

- The use of Apixaban is getting more and more.
- Among patients on NOACs, 43.3% received rivaroxaban, 34.2% received dabigatran and 22.5% received apixaban in 2015.



Temporal trends of antithrombotic therapy prescription. Distribution of three NOACs use since 2013 in patients with CHA2DS2-VASc score 2. Abbreviation: ASA, aspirin; NOAC, non-vitamin K oral anticoagulants; VKA, vitamin K antagonists.

Lee, S. R., Choi, E. K., Han, K. D., Cha, M. J., Oh, S., & Lip, G. Y. (2017). Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with non-valvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: A nationwide population-based study. PloS one, 12(12), e018

Warfarin has a long onset of action and long half-life compared with NOACs

	Warfarin[1,2]	Dabigatran[3]	Rivaroxaban[4]	Apixaban[5]	Edoxaban[6]
Mechanism of action	Inhibitor of vitamin K-dependent factors	Direct thrombin inhibitor	Direct FXa inhibitor	Direct FXa inhibitor	Direct FXa inhibitor
Oral bioavailability	>95%	~6.5%	80–100%	~50%	~62%
Pro-drug	No	Yes	No	No	No
Food effect	Yes (foods high in vitamin K)	No*	Yes (20 mg and 15 mg doses need to be taken with food)	No	No
T_{max}	Within 4 hours†	0.5–2 hours	2–4 hours	3–4 hours	1–2 hours
Renal clearance	8%	85%	~33%‡	~27%	50%
Mean half-life ($t_{1/2}$)	40 hours	12–14 hours§	5–9 hours (young) 11–13 hours (elderly)	12 hours	10–14 hours

The information in this table is based on the SmPCs for apixaban, rivaroxaban, dabigatran and edoxaban. Please refer to the SmPCs for further information.[3–6]
**Food does not affect the bioavailability of dabigatran etexilate, but delays the time to peak plasma concentrations by 2 hours; †Time to peak effect is up to 3–5 days;[2]*
‡Direct renal excretion as unchanged active substance; §Prolonged in patients with impaired renal function.
FXa: factor Xa; SmPC: summary of product characteristics; T_{max}: time to reach peak plasma concentration; $t_{1/2}$: half-life.

1. Warfarin SmPC. Available at: http://www.medicine.org; 2. Weitz JI, Gross PL. *Hematology Am Soc Hematol Educ Program* 2012;2012:536–540; 3. Dabigatran SmPC. Available at: http://www.ema.europa.eu; 4. Rivaroxaban SmPC. Available at: http://www.ema.europa.eu; 5. Apixaban SmPC. Available at: http://www.ema.europa.eu; 6. Edoxaban SmPC. Available at: http://www.ema.europa.eu.

NOACs in NVAF: Study design of randomised trials

	RE-LY (dabigatran)[1]	ROCKET AF (rivaroxaban)[2]	ARISTOTLE (apixaban)[3]	AVERROES (apixaban)[4]	ENGAGE AF-TIMI 48 (edoxaban)[5]
n	18,113	14,264	18,201	5,599	21,105
Design	Blinded (dabigatran) Open-label (warfarin)	Double-blind, double-dummy	Double-blind, double-dummy	Double-blind, double-dummy	Double-blind, double-dummy
Treatments	• **Dabigatran 150 mg BID** • Dabigatran 110 mg BID*	• **Rivaroxaban 20 mg OD†**	• **Apixaban 5 mg BID‡**	• **Apixaban 5 mg BID‡**	• **Edoxaban 60 mg OD** • Edoxaban 30 mg OD§
	• Warfarin (INR target: 2.0–3.0)	• Warfarin (INR target: 2.0–3.0)	• Warfarin (INR target: 2.0–3.0)	• ASA (81–324 mg/day)	• Warfarin (INR target: 2.0–3.0)
Objective	Non-inferiority	Non-inferiority	Non-inferiority	Superiority	Non-inferiority

**Per the dabigatran SmPC, the recommended dose is 150 mg BID. A dose of 110 mg BID is recommended in selected patients. Please refer to the SmPC for further details;[6] †15 mg OD in selected patients; Patients with CrCl between 30–49 mL/min;[7] ‡2.5 mg BID in selected patients; Patients with more than two of the following criteria: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL (133 µmol/L). Per the apixaban SmPC, patients with NVAF and the exclusive criterion of severe renal impairment (CrCl 15–29 mL/min) should also receive the lower dose of apixaban 2.5 mg BID. This criterion differs from the trial conduct;[8] §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.[9] A dose of 30 mg OD is recommended in selected patients. Please refer to the SmPC for further details.[9]*
ASA: acetylsalicylic acid; INR: international normalised ratio.

1. Connolly SJ, et al. *N Engl J Med* 2009;361:1139–1151; 2. Patel MR, et al. *N Engl J Med* 2011;365:883–891; 3. Granger CB, et al. *N Engl J Med* 2011;365:981–992; 4. Connolly SJ, et al. *N Engl J Med* 2011;364:806–817; 5. Giugliano RP, et al. *N Engl J Med* 2013;369:2093–2104; 6.Dabigatran SmPC. Available at: http://www.ema.europa.eu; 7. Rivaroxaban SmPC. Available at: http://www.ema.europa.eu; 8. Apixaban SmPC. Available at: http://www.ema.europa.eu; 9. Edoxaban SmPC. Available at: http://www.ema.europa.eu.

NOAC Phase III trials in NVAF: Study characteristics

	RE-LY (dabigatran)[1,2]	ROCKET AF (rivaroxaban)[3]	ARISTOTLE (apixaban)[4]	AVERROES (apixaban)[5]	ENGAGE AF-TIMI 48 (edoxaban)[6,7]
Age (mean)*	72	73†	70†	70	72†
Gender (men)	64%	60%	65%	59%	62%
Type of AF*					
Persistent/permanent	67.2%	81.1%	84.7%	73%	74.6%
Paroxysmal	32.8%	17.6%	15.3%	27%	25.4%
Newly diagnosed	–	1.4%	–	–	–
$CHADS_2$ score, mean*	2.1	3.5	2.1	2.0	2.8
0 or 1	31.9%	0%	34.0%	36.5%	–
2	36%	13.0 %	35.8%	35.5%	77.4%ǂ
3–6	32.5%	86.9%	30.2%	28.0%	22.6%ǂ
TTR in the warfarin group (mean % of the study period)	64.4%	55.0%	62.2%	N/A	68.4%

**Data calculated for the entire study group; †Median age; ǂ77.4% for $CHADS_2$ score of ≤3 of 77.4%; 4–6 of 22.6%.*
AF: atrial fibrillation; N/A: not applicable; TTR: time in therapeutic range.

1. Connolly SJ, et al. *N Engl J Med* 2009;361:1139–1151; 2. Connolly SJ, et al. *N Engl J Med* 2010;363:1875–1876; 3. Patel MR, et al. *N Engl J Med* 2011;365:883–891; 4. Granger CB, et al. *N Engl J Med* 2011;365:981–992; 5. Connolly SJ, et al. *N Engl J Med* 2011;364:806–817; 6. Giugliano RP, et al. *N Engl J Med* 2013;369:2093–2104; 7. EMA Lixiana assessment report, 23 April 2015.

Meta-analysis of NOAC randomised clinical trials[1]

Objective: To assess the relative benefit of NOACs in the prevention of stroke in patients with NVAF

Method:

- Prespecified meta-analysis of all 71,683 participants included in the following Phase III trials:
  - RE-LY, ROCKET AF, ARISTOTLE and ENGAGE AF-TIMI 48
- RRs and 95% CIs were calculated for each of the main efficacy and safety outcomes of each study
- Outcomes were pooled and compared with a random effects model and tested for heterogeneity

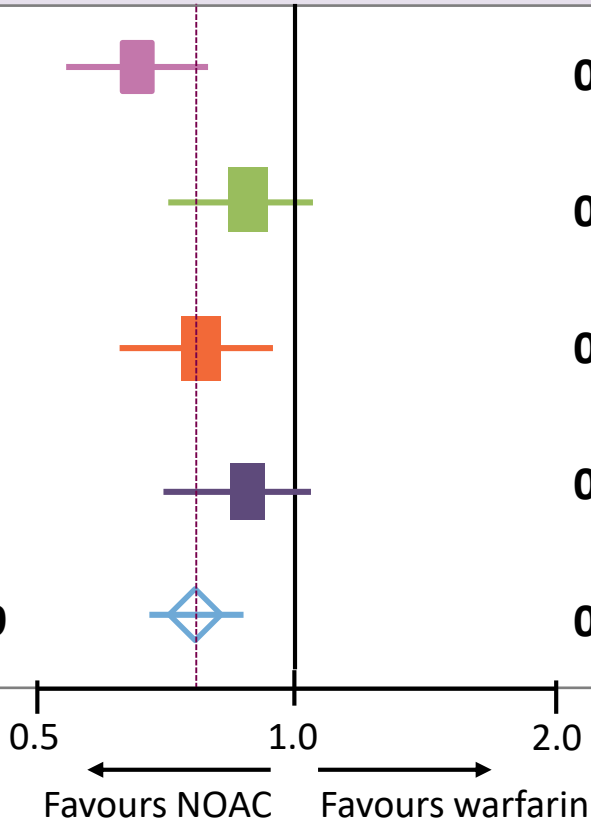
CI: confidence interval; RR: relative risk.

1. Ruff CT, et al. *Lancet* 2014;383:955–962.

Meta-analysis: Efficacy of NOACs versus warfarin for stroke prevention in patients with NVAF[1]

Stroke or SE

Study	NOAC (events)	Warfarin (events)	RR (95% CI)	*P* value
RE-LY (dabigatran)*	134/6,076	199/6,022	**0.66** (0.53–0.82)	0.0001
ROCKET AF (rivaroxaban)†	269/7,081	306/7,090	**0.88** (0.75–1.03)	0.12
ARISTOTLE (apixaban)‡	212/9,120	265/9,081	**0.80** (0.67–0.95)	0.012
ENGAGE AF-TIMI 48 (edoxaban)§	296/7,035	337/7,036	**0.88** (0.75–1.02)	0.10
Combined (random)	**911/29,312**	**1,107/29,229**	**0.81** (0.73–0.91)	<0.0001



Data are n, unless otherwise indicated
Heterogeneity: I^2=47%, *P*=0.13

Ruff et al. 2014[1]

**150 mg BID; †20 mg OD; ‡5 mg BID; §60 mg OD.*
SE: systemic embolism.

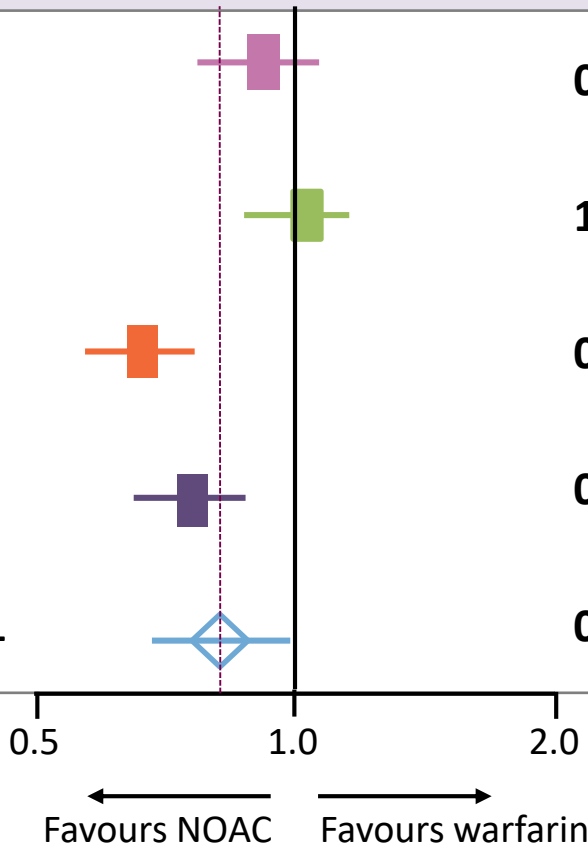
There are no head-to-head randomised clinical trials comparing the NOACs. Comparisons cannot be made between individual NOACs based on these data

1. Ruff CT, et al. *Lancet* 2014;383:955–962.

Meta-analysis: Safety of NOACs versus warfarin for stroke prevention in patients with NVAF[1]

Major bleeding

Study	NOAC (events)	Warfarin (events)	RR (95% CI)	*P* value
RE-LY (dabigatran)*	375/6,076	397/6,022	**0.94** (0.82–1.07)	0.34
ROCKET AF (rivaroxaban)†	395/7,111	386/7,125	**1.03** (0.90–1.18)	0.72
ARISTOTLE (apixaban)‡	327/9,088	462/9,052	**0.71** (0.61–0.81)	<0.0001
ENGAGE AF-TIMI 48 (edoxaban)§	444/7,012	557/7,012	**0.80** (0.71–0.90)	0.0002
Combined (random)	**1,541/29,287**	**1,802/29,211**	**0.86** (0.73–1.00)	0.06



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Ruff et al. 2014[1]

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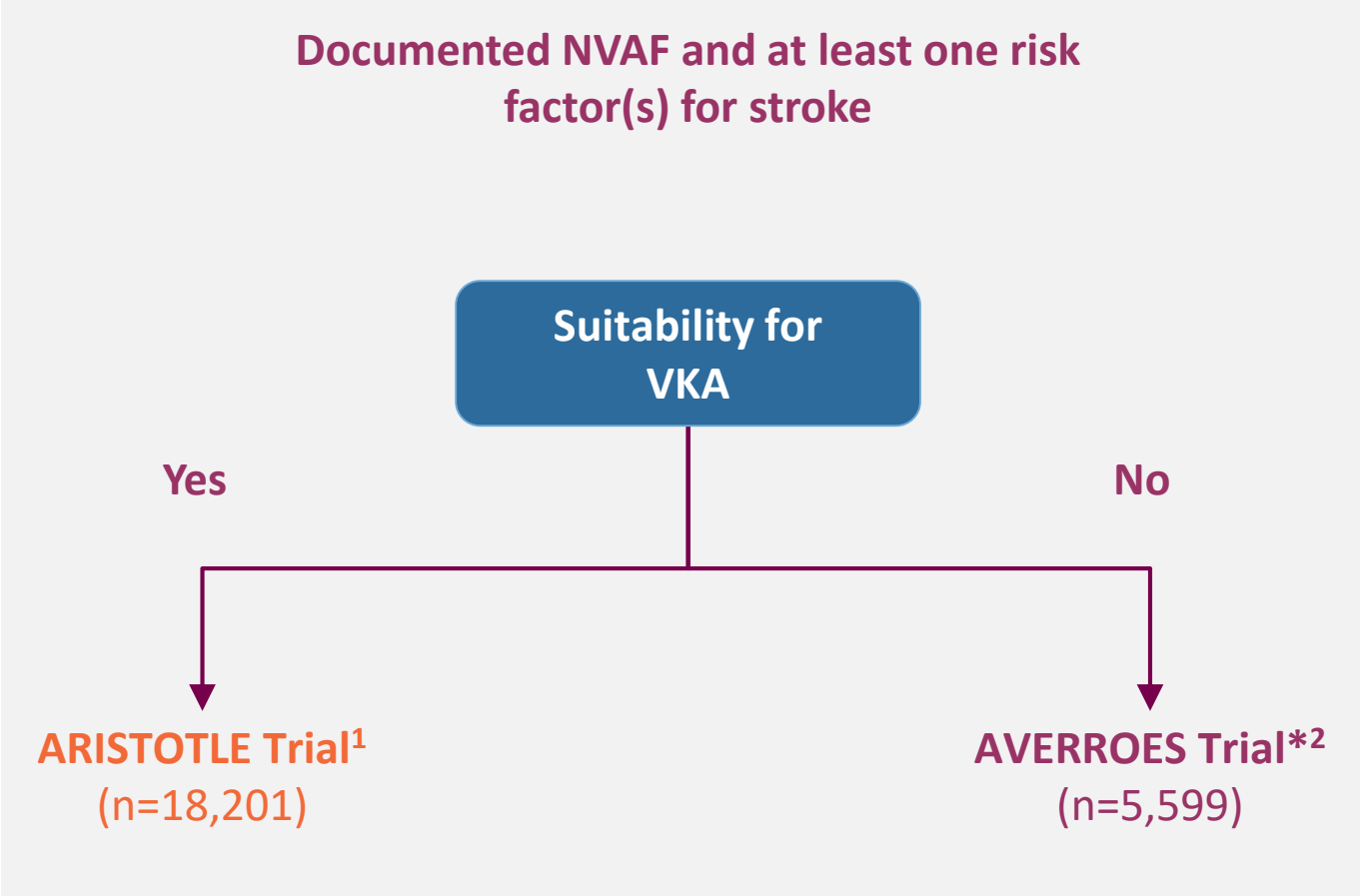
1. Ruff CT, et al. *Lancet* 2014;383:955–962.

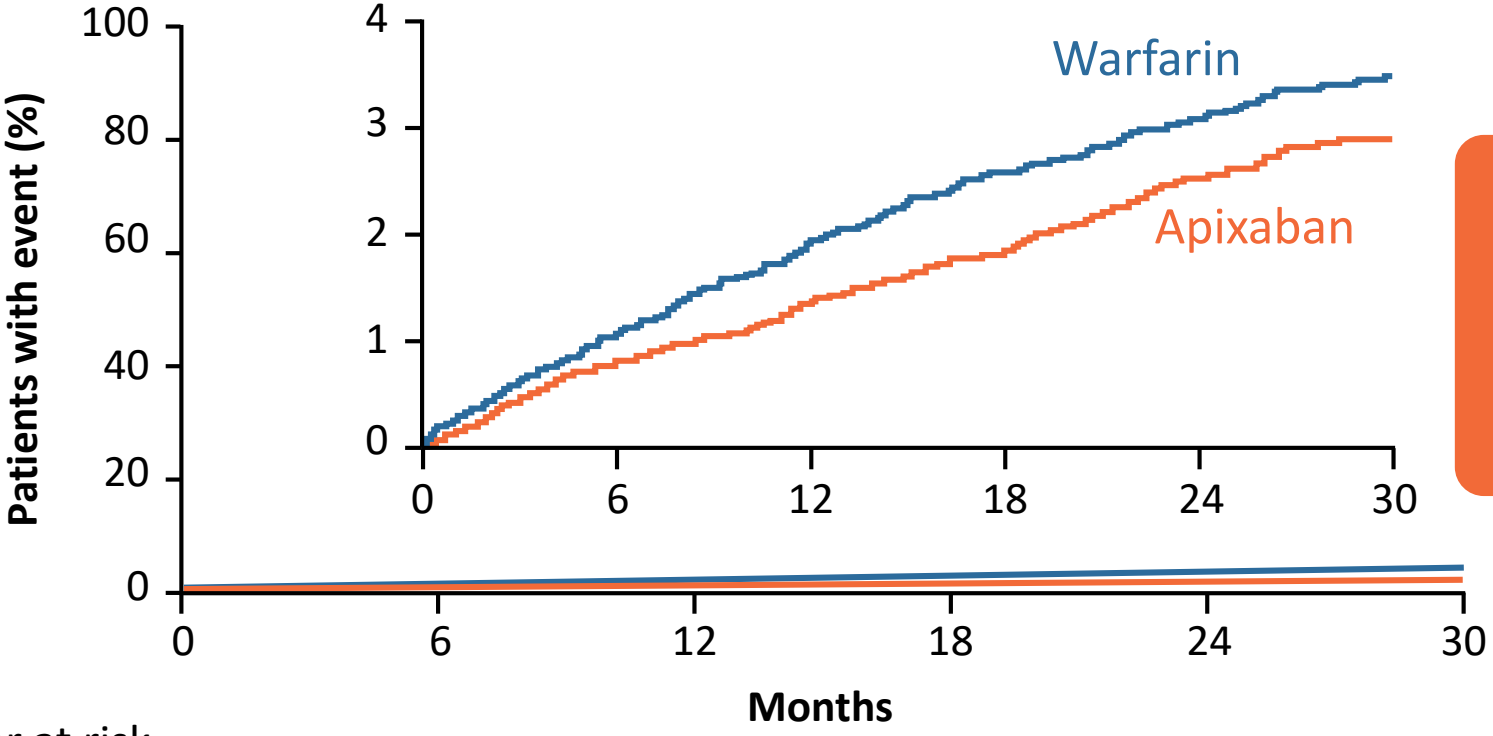
The apixaban trial programe for NVAF covers a broad patient population



**Some reasons for VKA unsuitability: INR could not be maintained in therapeutic range or patient preference against VKA. The non-suitability was not because of a high bleeding risk, since such patients were excluded.*
VKA: vitamin K antagonist.

1. Granger CB, et al. *N Engl J Med* 2011;365:981–992;
2. Connolly SJ, et al. *N Engl J Med* 2011;364:806–817.

ARISTOTLE: Apixaban was superior to warfarin in preventing stroke or SE[1]



RRR 21%

ARR 0.33%

HR=0.79 (95% CI: 0.66–0.95)
***P*<0.001 for non-inferiority**
***P*=0.01 for superiority**

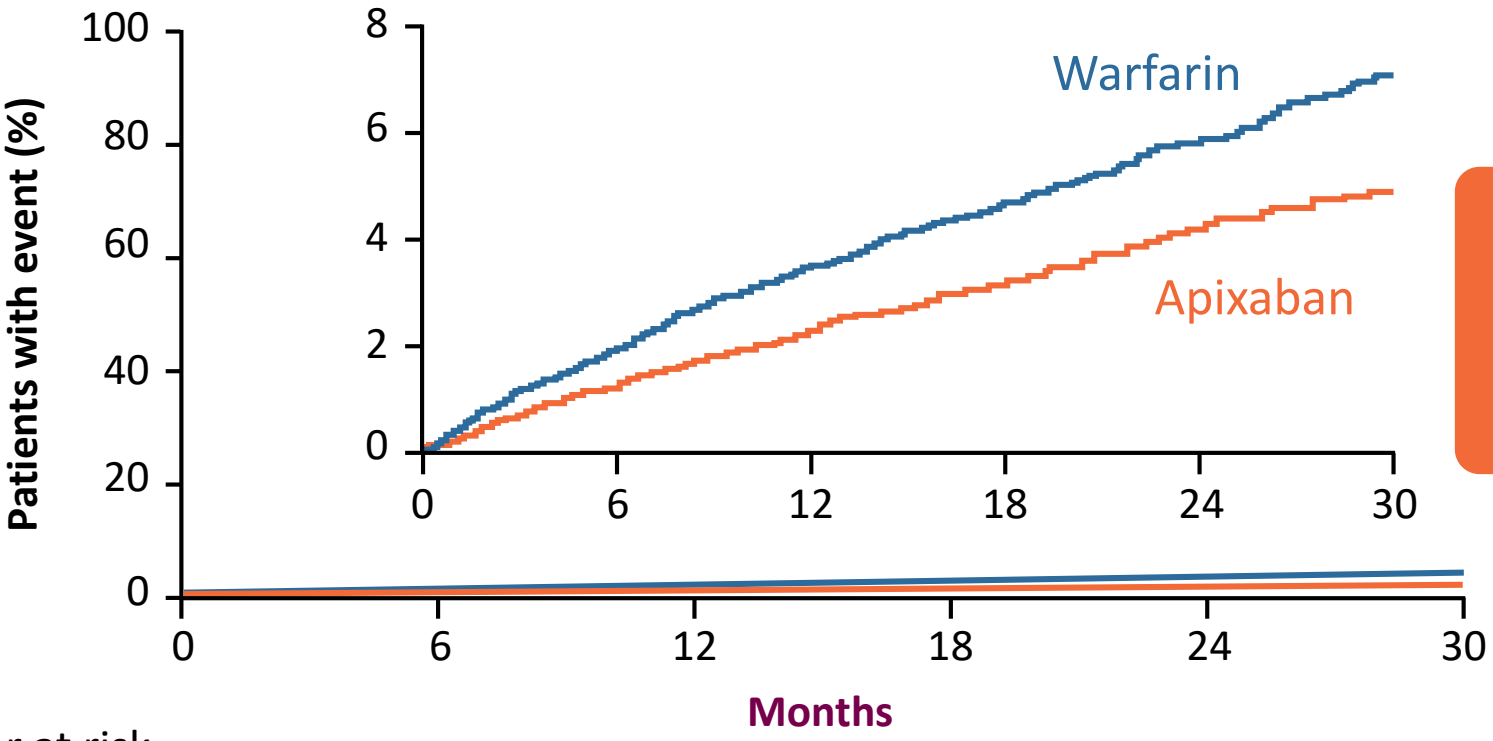
Number at risk						
Apixaban	9,120	8,726	8,440	6,051	3,464	1,754
Warfarin	9,081	8,620	8,301	5,972	3,405	1,768

ARR: absolute relative risk; HR: hazard ratio; RRR: relative risk reduction.

Reproduced from Granger et al. 2011[1]

1. Granger CB, et al. *N Engl J Med* 2011;365:981–992.

ARISTOTLE: Apixaban significantly reduced the risk of major bleeding versus warfarin[1]



RRR 31%
ARR 0.96%
HR=0.69 (95% CI: 0.60–0.80)
P<0.001

Number at risk						
Apixaban	9,088	8,103	7,564	5,365	3,048	1,515
Warfarin	9,052	7,910	7,335	5,196	2,956	1,491

Major bleeding defined by ISTH criteria.
ISTH: International Society for Thrombosis and Haemostasis.

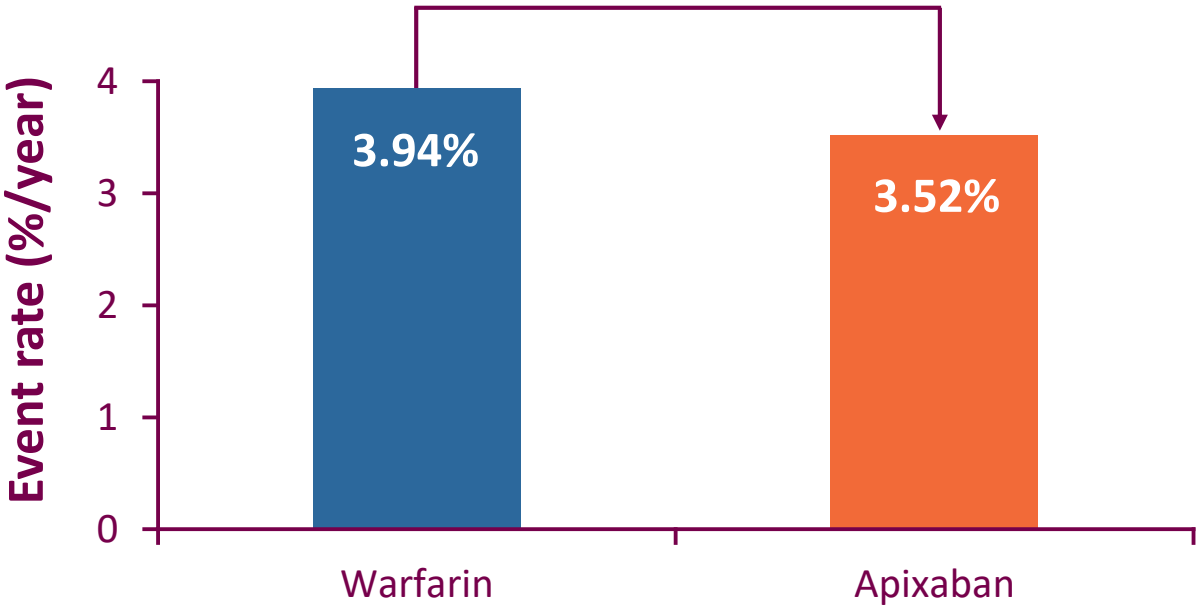
Reproduced from Granger et al. 2011[1]

1. Granger CB, et al. *N Engl J Med* 2011;365:981–992.

ARISTOTLE: Statistically significant reduction for apixaban compared with warfarin in all-cause death[1]

Key secondary efficacy endpoint: all-cause mortality

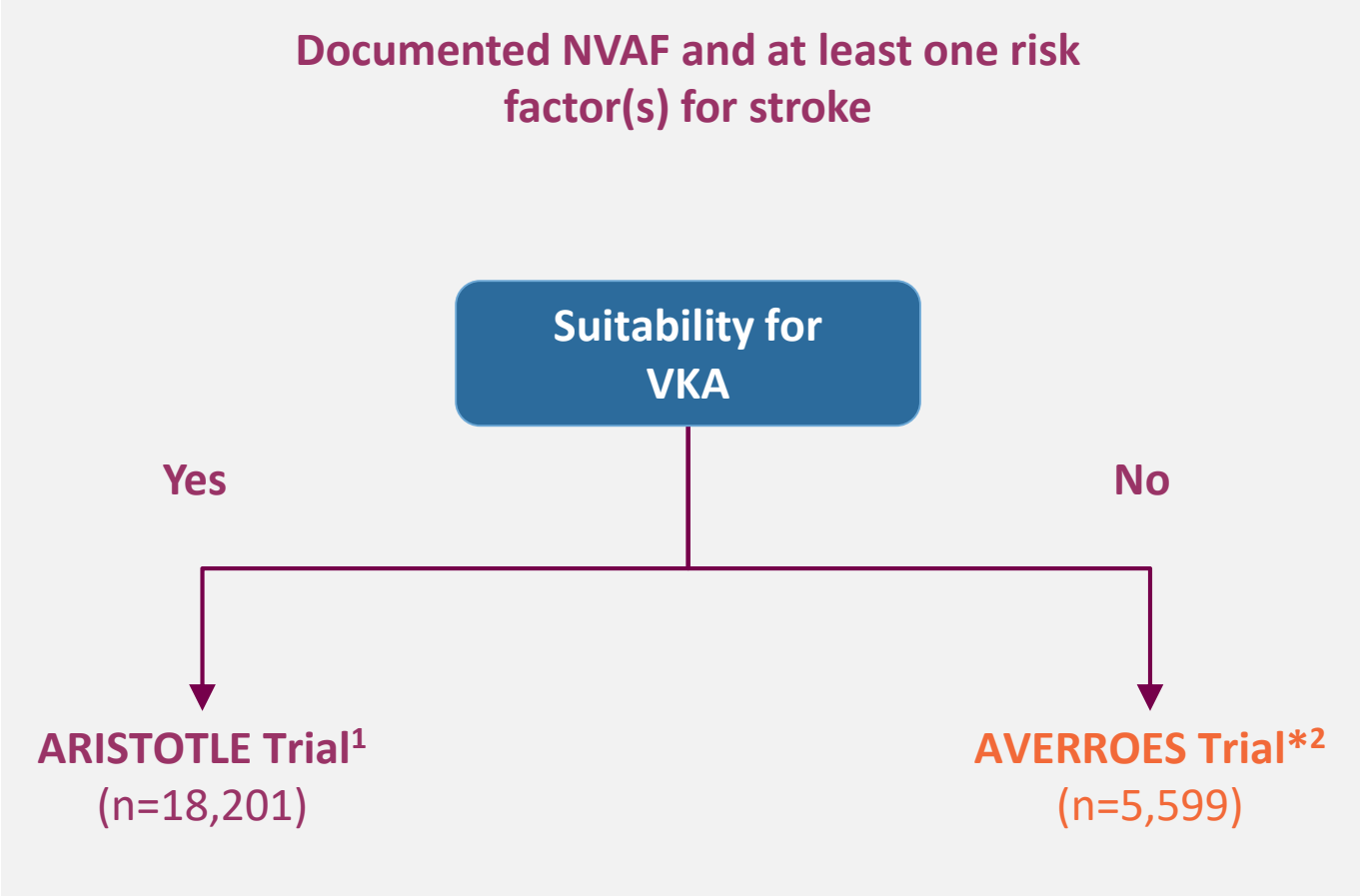
HR=0.89
(95% CI: 0.80–0.99; *P*=0.047)
RRR 11%, ARR 0.42%



Created from Granger et al. 2011[1]

1. Granger CB, et al. *N Engl J Med* 2011;365:981–992.

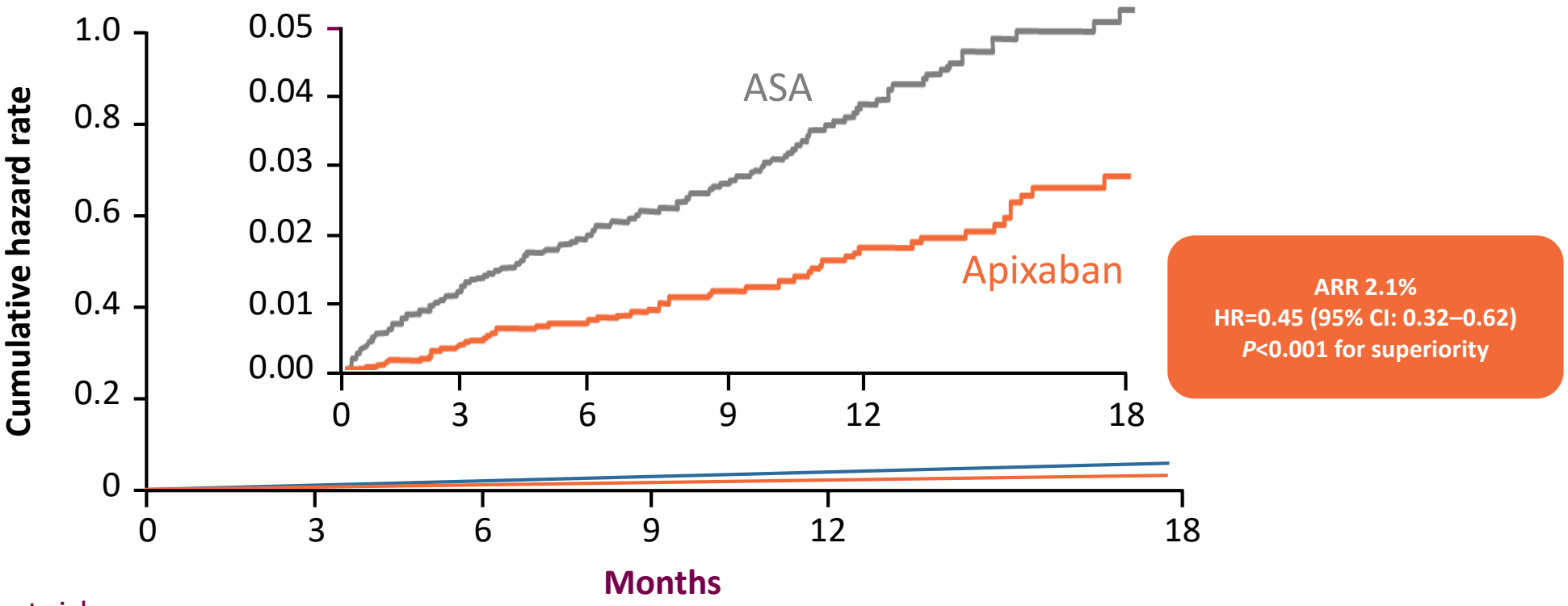
The apixaban trial programe for NVAF covers a broad patient population



**Some reasons for VKA unsuitability: INR could not be maintained in therapeutic range or patient preference against VKA. The non-suitability was not because of a high bleeding risk, since such patients were excluded.*
VKA: vitamin K antagonist.

1. Granger CB, et al. *N Engl J Med* 2011;365:981–992;
2. Connolly SJ, et al. *N Engl J Med* 2011;364:806–817.

AVERROES: Apixaban versus ASA – significant reduction in stroke or SE[1]



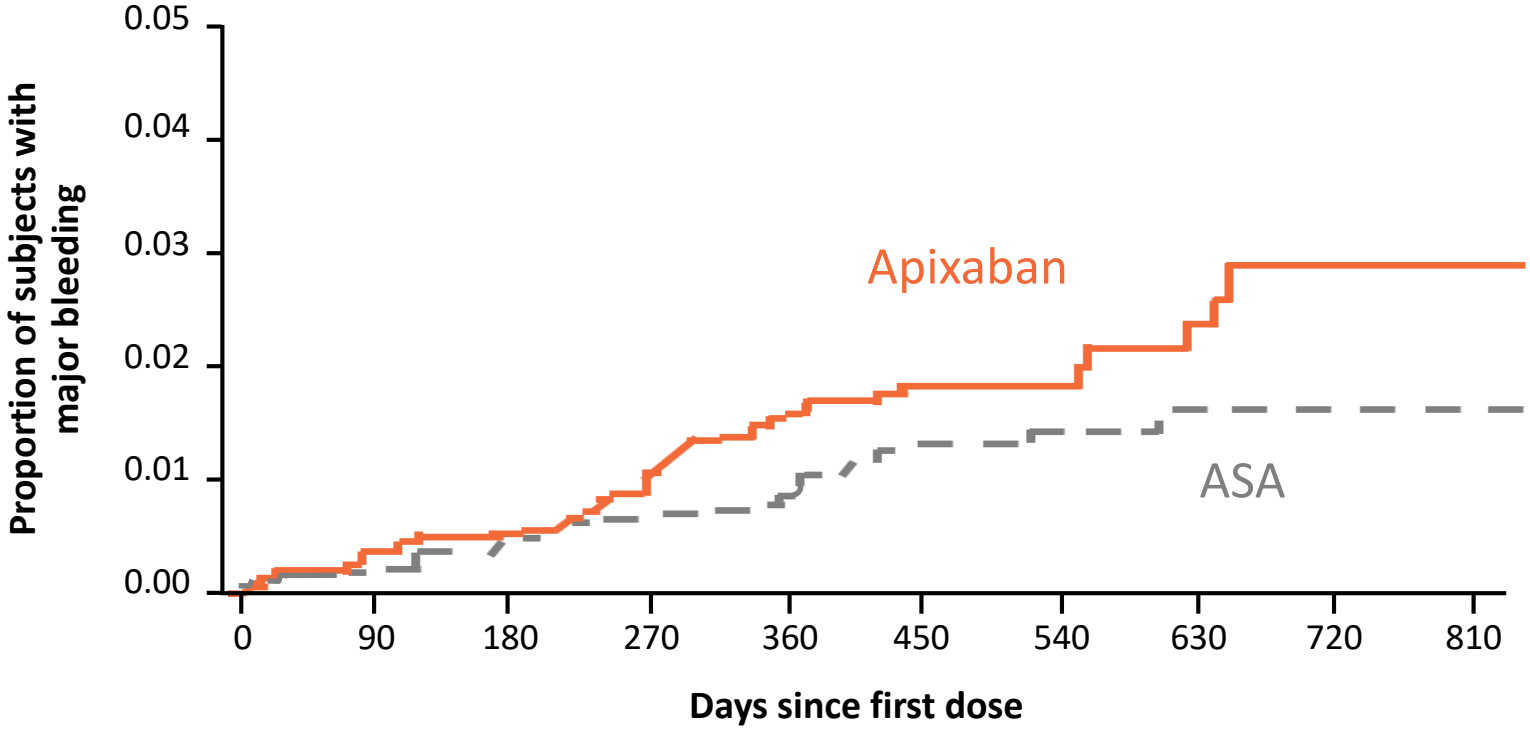
Number at risk						
ASA	2,791	2,716	2,530	2,112	1,543	628
Apixaban	2,808	2,758	2,566	2,125	1,522	615

Due to clear benefit in favour of apixaban the study was terminated early.[1]
ASA: acetylsalicylic acid.

Reproduced from Connolly et al. 2011[1]

1. Connolly SJ, et al. *N Engl J Med* 2011;364:806–817.

AVERROES: Apixaban versus ASA – comparable rates of major bleeding[1,2]



HR=1.54
(95% CI: 0.96–2.45)
***P*=0.0716 (NS)**

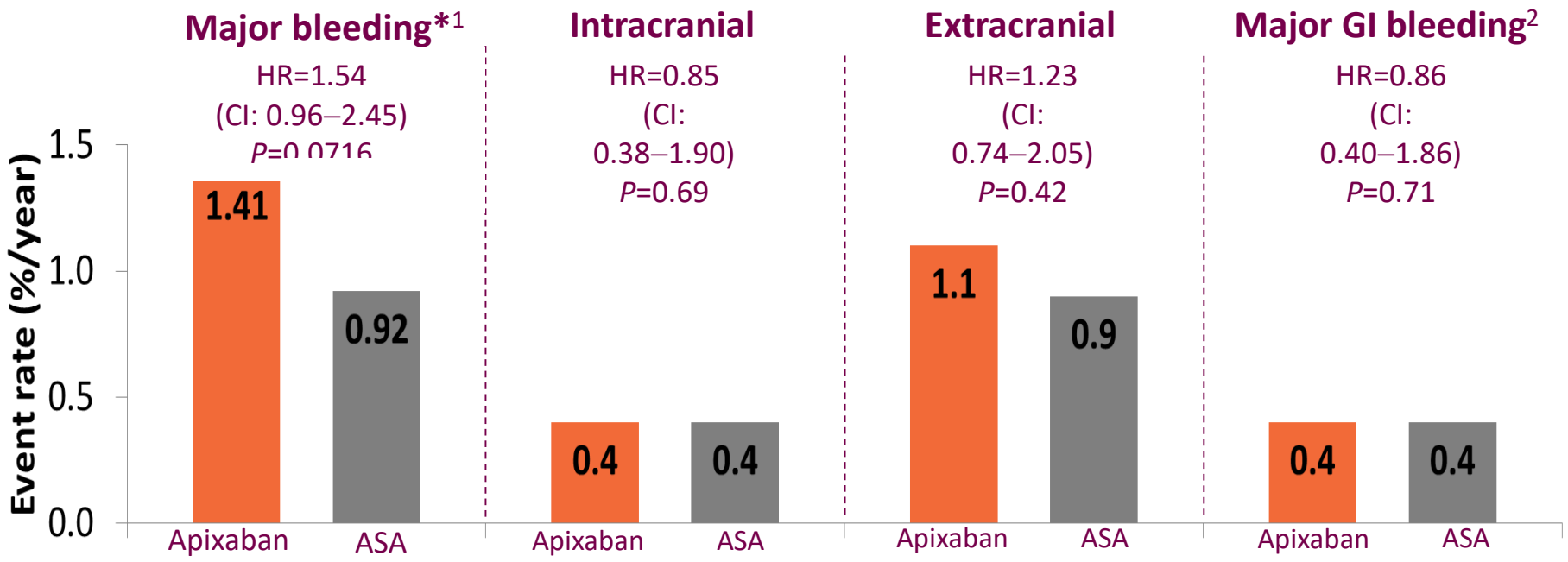
Number at risk										
ASA	2,780	2,569	2,446	2,116	1,722	1,215	773	452	205	71
Apixaban	2,798	2,618	2,496	2,154	1,715	1,207	763	453	237	66

Safety population patients who had been randomised to treatment and received at least one dose of study drug.
NS: not significant.

Reproduced from Connolly et al. 2011[1]

1. Apixaban EPAR Assessment Report 2012. Available at: http://www.ema.europa.eu;
2. Apixaban SmPC. Available at: http://www.ema.europa.eu.

Bleeding data for apixaban versus ASA (AVERROES)[1,2]



- There were significantly higher rates of bleeding for apixaban versus ASA for the secondary safety endpoints of major/CRNM bleeding* (HR=1.38, 95% CI: 1.07–1.78; *P*=0.0144) and all bleeding (HR=1.30, 95% CI: 1.10–1.53; *P*=0.0017)[1]

HR shown with 95% CI.
**Major bleeding analysis based on safety population.*
†Extracranial bleeding also included unclassified bleeding.
CRNM: clinically relevant non-major.

Created from Apixaban SmPC and Connolly et al. 2011[1,2]

1. Apixaban SmPC. Available at: http://www.ema.europa.eu;
2. Connolly SJ, et al. *N Engl J Med* 2011;364:806–817.

Proven efficacy and safety of Apixaban

- NOACs are preferred over VKA for stroke prevention in NVAF according to the ESC guidelines[1]
- All NOACs have benefits over warfarin, but differ in pharmacological characteristics and efficacy and safety profiles versus warfarin[2]
  - Apixaban demonstrated superior efficacy versus warfarin, with a significant reduction in the risk of major bleeding in patients with NVAF[3]
- Apixaban is the only NOAC that has been studied versus ASA for stroke prevention in NVAF patients not suitable for warfarin[4]

1. Kirchhof P, et al. *Eur Heart J* 2016;37:2893–2962; 2. Schulman S. *Thromb Haemost* 2014;111:575-582;
3. Granger CB, et al. *N Engl J Med* 2011;365:981–992; 4. Connolly SJ, et al. *N Engl J Med* 2011;364:806–817.