

# Apixaban to prevent stroke in patients with atrial fibrillation: a review

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**Abstract:** Atrial fibrillation is a common, costly and morbid cardiovascular arrhythmia. Stroke prevention remains the mainstay of treatment for atrial fibrillation, and the recent advent of novel oral anticoagulants with direct factor IIa or factor Xa inhibition has significantly revolutionized this aspect of treatment for atrial fibrillation patients. This review focuses on the tolerability and efficacy of apixaban and tackles the generalizability of the findings with apixaban to broader patient populations than those primarily enrolled in the clinical trials, drawing from the AVERROES and ARISTOTLE trials and their subsequent secondary analyses. Taken together, findings from these trials show that apixaban is superior to warfarin in preventing stroke with a lower risk of major bleeding in the general population of patients with atrial fibrillation as well as in several key high-risk patient subgroups.

**Keywords:** anticoagulation, atrial fibrillation, stroke

## Introduction

Atrial fibrillation is the most common cardiac arrhythmia, affecting 2.7–6.1 million US adults in 2015 [Mozaffarian *et al.* 2015; National Center for Health Statistics – CDC, 2014], and even more if one includes clinically undetected atrial fibrillation. Each year, approximately 750,000 hospitalizations, 130,000 deaths, and over US\$6 billion dollars of healthcare spending are attributed to atrial fibrillation [Agency for Healthcare Research and Quality, 2012; National Center for Health Statistics – CDC, 2014]. Atrial fibrillation has been associated with increased all-cause mortality [hazard ratio (HR) of 9.62 in the first 4 months of diagnosis and 1.66 afterwards] [Miyasaka *et al.* 2007]. Women are more likely to die from atrial fibrillation than men, and Americans of European descent are more likely to die from atrial fibrillation than those of African or Asian descent [Benjamin *et al.* 1998; Novaro *et al.* 2008]. Patients with atrial fibrillation are at a 5–7 times increased risk of developing a stroke than the general population [Wolf *et al.* 1978; Flegel *et al.* 1987]. Strokes associated with atrial fibrillation are more disabling than other strokes, with the majority being either fatal or of moderate-to-high severity [Lin *et al.* 1996].

While oral anticoagulation has been a challenging aspect of atrial fibrillation treatment for years, the

relatively recent advent of direct oral anticoagulants (DOACs) has provided improved options for patients. At the same time, the aging and highly morbid population with atrial fibrillation has posed a number of important clinical questions related to DOAC use. Atrial fibrillation disproportionately affects the elderly; while the prevalence of atrial fibrillation in the general population is approximately 1%, 4.1–8.6% of adults 65–74 and 21.6–22.7% of adults 75–84 have atrial fibrillation [Psaty *et al.* 1997; Mozaffarian *et al.* 2015]. Thus, with the aging US population, atrial fibrillation has increasingly become a disease of the elderly, with over 50% of all cases occurring in patients aged over 80 years [Feinberg *et al.* 1995]. Some 36% of all strokes in patients over 80 years are related to atrial fibrillation [Psaty *et al.* 1997]. Furthermore, atrial fibrillation is a disease of the multimorbid. Patients with atrial fibrillation are more likely to have other cardiovascular diseases such as ischemic heart disease, congestive heart failure, hypertension and valvular disease, as well as diabetes, chronic obstructive lung disease, chronic kidney disease, obesity and alcoholism [Furberg *et al.* 1994; Benjamin *et al.* 1994]. Therefore, it is critically important to examine the efficacy and tolerability profiles of any oral anticoagulant in these diverse groups of patients.

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Apixaban is currently approved in the US to prevent stroke in patients with atrial fibrillation. Major trials excluded patients with serum creatinine greater than  $\text{Cr} = 2.5 \text{ mm/dL}$ , or glomerular filtration rate of less than  $25 \text{ ml/min/1.73 m}^2$  (as derived from the Cockcroft–Gault equation) [Agnelli *et al.* 2013]. Also, apixaban has been dose reduced to 2.5 mg twice daily from the usual 5 mg twice daily in patients with at least two of the following criteria: age greater than 80 years, serum creatinine greater than 1.5, and weight less than 60 kg [Lopes *et al.* 2010; Eikelboom *et al.* 2010]. Understanding the role of apixaban in patients with different chronic kidney disease (CKD) stages is important. Likewise, a better understanding of how apixaban fares in relation to different scoring systems for stroke (such as  $\text{CHA}_2\text{DS}_2\text{-VASc}$ ) and major bleeding (such as HAS-BLED) is equally important. A number of decision tools have been developed to identify patients who may benefit most from oral anticoagulation. In a large prospective study of over 60,000 patients with atrial fibrillation, the CHADS<sub>2</sub>,  $\text{CHA}_2\text{DS}_2\text{-VASc}$  and ATRIA stroke scores had *C* statistics of 0.68–0.70 for full-point scores, with a slight advantage in using the ATRIA score over the other two [van den Ham *et al.* 2015]. The HAS-BLED score has been used to predict 1-year major bleeding risk in patients on oral anticoagulants [Pisters *et al.* 2010], although it has poor ability to discriminate and it may potentiate underuse of anticoagulation, including among those at high risk of stroke who also tend to have high risk of bleeding. Moreover, bleeding risk-stratification tools are largely generated from patients treated with warfarin. In this paper, we will discuss the emerging evidence supporting the use of apixaban to treat patients with atrial fibrillation.

### Prevention of stroke and systemic embolism

#### *AVERROES trial*

In early 2011, the apixaban *versus* acetyl-salicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment (AVERROES) trial was published. It was a double-blind, randomized-controlled trial comparing the use of apixaban with aspirin (two thirds received low-dose aspirin) for prevention of stroke or systemic embolism among 5599 patients who had previously failed warfarin (poor compliance, refusal or prior bleeding) and who were deemed to be unsuitable for warfarin (like a CHADS<sub>2</sub> score of 1) [Eikelboom

*et al.* 2010]. The trial was stopped early in 2010 because of a clear benefit of apixaban over aspirin in preventing stroke. Mean follow up was approximately 1.1 years. Overall, the primary outcome of stroke or systemic embolism occurred in 1.6% of patients per year treated with apixaban and in 3.7% of patients per year treated with aspirin [Connolly *et al.* 2011]. There was no significant difference between the groups in all-cause mortality, but subsequent analysis revealed that there was a significant reduction in cardiovascular hospitalizations in the apixaban group (12.3% per year) compared with the aspirin group (15.4% per year), and that cardiovascular hospitalization was predictive of mortality (HR 3.95) [Hohnloser *et al.* 2013]. Apixaban was less often discontinued than was aspirin, showing its favorable tolerability. Importantly, the risk of major bleeding was only modestly higher with apixaban (HR 1.13), as was the risk of minor bleeding (HR 1.24). The rates of intracranial hemorrhage were the same. Given the smaller sample size and shorter follow-up period in AVERROES, results have been interpreted with more caution, especially where they may differ from other larger trials, such as ARISTOTLE.

#### *ARISTOTLE trial*

Later in 2011, the apixaban for reduction in stroke and other thrombotic events in atrial fibrillation (ARISTOTLE) trial was published. It was a double-blinded, double-dummy noninferiority trial comparing the use of apixaban *versus* warfarin to prevent stroke and systemic embolism among 18,201 patients with atrial fibrillation; eligible patients had two or more episodes of atrial fibrillation within the previous 12 months, as well as at least one of the following risk factors: age greater than 75, prior stroke or systemic embolism, symptomatic heart failure within the previous 3 months, or diabetes or hypertension requiring pharmacologic treatment. Median age at enrollment was 70 years with 35% of the patients being female [Lopes *et al.* 2010; Granger *et al.* 2011]. At the conclusion of the study, apixaban was not only noninferior based on predefined specifications, but actually superior to warfarin in terms of the primary outcome (stroke or systemic embolism), major bleeding, and all-cause mortality (see Table 1). Stroke or systemic embolism occurred in 1.27% per year of patients treated with apixaban and in 1.6% per year of patients treated with warfarin (HR 0.79,  $p < 0.001$ ). All-cause mortality was lower in patients treated with

**Table 1.** Comparison of study designs and key findings of the AVERROES and ARISTOTLE trials [Connolly *et al.* 2011; and Granger *et al.* 2011].

Trial	AVERROES	ARISTOTLE
<b>Design</b>	RCT, double blind	Noninferiority RCT, double blind, double dummy, placebo controlled.
<b>Patient population</b>	Patients 'unsuitable' for VKA based on being unacceptable or prior failure	Patients with AFib and at least one other stroke risk factor
<b>Treatment versus comparison</b>	Apixaban <i>versus</i> aspirin	Apixaban <i>versus</i> warfarin
<b>Number of subjects</b>	5599	18,201
<b>Primary outcome:</b>	Stroke or systemic embolism: 1.6% per year in the apixaban group and 3.7% per year in the ASA group ( $p < 0.001$ )	Stroke or systemic embolism: 1.27% per year in the apixaban group, 1.60% per year in the warfarin group ( $p < 0.001$ )
<b>Secondary outcomes:</b>	Major bleeding: 1.4% per year in the apixaban group, 1.2% per year in the ASA group ( $p = 0.57$ ). All-cause mortality: 3.5% per year in the apixaban group, 4.4% per year in the ASA group ( $p = 0.07$ ).	Major bleeding: 2.13% per year in the apixaban group, 3.09% per year in the warfarin group ( $p < 0.001$ ). All-cause mortality: 3.52% per year in the apixaban group, 3.94% per year in the warfarin group ( $p = 0.047$ )
AFib, atrial fibrillation; ASA, aspirin at randomization; VKA, vitamin K antagonist; RCT, randomized-controlled trial.		

apixaban (3.52% per year) compared with patients treated with warfarin (3.94% per year) (HR 0.89,  $p = 0.047$ ) [Granger *et al.* 2011]. (See Figure 1 for comparison of results of the AVERROES and ARISTOTLE trials). With the other DOACs, there were also consistent modest (about 10%) reductions in mortality in each of the trials [Rao *et al.* 2014; Connolly *et al.* 2009; Patel *et al.* 2011; Giugliano *et al.* 2013] and a highly significant and consistent reduction in mortality with DOACs *versus* warfarin in the overview [Ruff *et al.* 2015].

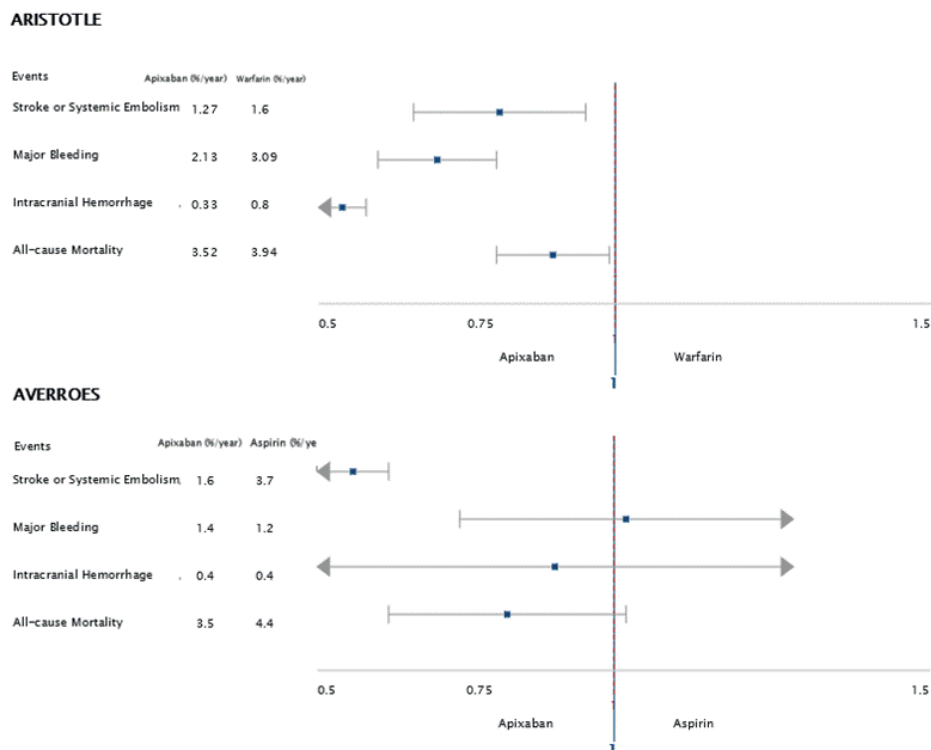
It should be noted that when the ARISTOTLE trial ended, there was a 2-day bridging period, such that patients on apixaban had a 2-day overlap of continuing apixaban while being transitioned to vitamin K antagonist (VKA). Following this, there was an excess in both thrombosis and bleeding events. This was largely attributed to the liability of initiating VKA rather than an adverse effect of apixaban [Granger *et al.* 2015]. In the edoxaban *versus* warfarin in subjects with atrial fibrillation—effective anticoagulation with factor Xa next generation in atrial fibrillation (ENGAGE AF-TIMI 48 trial), which had a more careful overlap of half-dose edoxaban until the INR was at least 2.0, the transition to warfarin was not associated with higher risk [Ruff *et al.* 2014].

### Major bleeding

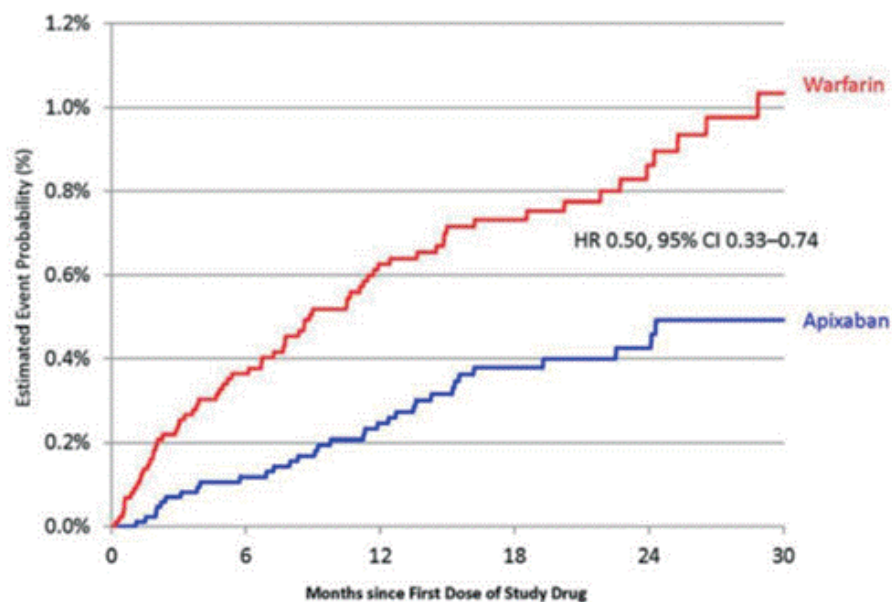
As with warfarin, major bleeding remains the most serious adverse effect of apixaban. Despite

this being of special concern, given the lack of a reversal agent, patients in ARISTOTLE taking apixaban had a significantly lower risk of death within 30 days of a major bleeding event than patients taking warfarin (HR 0.5, 95% CI 0.33–0.74) (see Figure 2) [Hyleck *et al.* 2014]. Patients in ARISTOTLE with both intracranial and nonintracranial hemorrhage had higher mortality, higher risk of stroke and higher risk of myocardial infarction [Held *et al.* 2015]. Apixaban was associated with a significantly lower risk of major bleeding than warfarin in ARISTOTLE (2.13% per year in patients taking apixaban and 3.09% per year in patients taking warfarin, HR 0.69,  $p < 0.001$ ) [Hohnloser *et al.* 2013; Granger *et al.* 2011].

Apixaban, along with all of the DOACs reduced the risk of intracranial hemorrhage compared with warfarin. Apixaban was associated with a similar risk of gastrointestinal bleeding compared with warfarin [Granger *et al.* 2011; Hess *et al.* 2013]. Among patients taking apixaban, age, prior hemorrhage, prior stroke or transient ischemic attack (TIA), diabetes, chronic kidney disease, anemia, aspirin use and nonsteroidal anti-inflammatory drug (NSAID) use were independent predictors of major hemorrhage (see Table 2) [Hyleck *et al.* 2014]. After adjustment, women were significantly less likely to bleed than men [Vinereanu *et al.* 2015]. The HAS-BLED score was predictive of major hemorrhage in patients taking apixaban, although not much more predictive of bleeding



**Figure 1.** Comparison of the effects of apixaban *versus* control on major clinical outcomes in the ARISTOTLE and AVERROES trials [Connolly *et al.* 2011; Granger *et al.* 2011].



**Figure 2.** 30-day mortality related to major bleeding events in patients taking apixaban *versus* warfarin [Hylek *et al.* 2014]. HR, hazard ratio; CI, confidence interval.

than was the CHADS<sub>2</sub> score; the greatest relative benefit of apixaban over warfarin was seen in a reduction of intracranial hemorrhages in patients

with a HAS-BLED score of at least 3 [Lopes *et al.* 2012]. Apixaban was associated with less major bleeding than warfarin regardless of prior warfarin

**Table 2.** Baseline characteristics independently associated with major bleeding in ARISTOTLE [Hylek *et al.* 2014].

Parameter	HR	95% CI	<i>p</i>
<b>Hematocrit &lt; 45%</b>	1.38	(1.24–1.52)	<0.001
<b>History of bleeding</b>	1.38	(1.17–1.63)	0.002
<b>Age (per 10 years)</b>	1.36	(1.23–1.51)	<0.001
<b>NSAIDs at randomization</b>	1.33	(1.07–1.65)	0.0096
<b>Aspirin at randomization</b>	1.31	(1.14–1.52)	0.002
<b>Diabetes</b>	1.24	(1.06–1.45)	0.0067
<b>Prior stroke</b>	1.23	(1.04–1.45)	0.016
<b>Creatinine clearance (&lt;81 ml/min/1.73 m<sup>2</sup>)</b>	1.11	(1.06–1.17)	<0.001
<b>Female sex</b>	0.74	(0.63–0.87)	0.002
<b>Liver disease</b>	0.44	(0.22–0.88)	0.02

CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs.

**Table 3.** Summary of subgroup analysis from the ARISTOTLE trial [Hohnloser *et al.* 2012; Halvorsen *et al.* 2014; Vinereanu *et al.* 2015; Easton *et al.* 2012; Alexander *et al.* 2014; Avezum *et al.* 2015].

Subgroup	Stroke and systemic embolism (% per year)			Major bleeding (% per year)			All-cause mortality (% per year)		
	Apixaban	Warfarin	<i>p</i>	Apixaban	Warfarin	<i>p</i>	Apixaban	Warfarin	<i>p</i>
Cr Cl ≥ 80	0.99	1.12	0.71	1.46	1.84	0.03	2.33	2.71	0.63
50 < Cr Cl < 80	1.24	1.69		2.45	3.21		3.41	3.56	
Cr Cl ≤ 50	2.11	2.67		3.21	6.44		7.12	8.30	
Age < 80	1.23	1.55	0.91	1.93	2.78	0.74	3.03	3.42	0.73
Age > 80	1.53	1.90		3.55	5.41		6.86	7.44	
Women	1.35	1.81	0.45	1.91	3.29	0.06	3.11	3.41	0.83
Men	1.22	1.49		2.26	2.98		3.37	3.75	
Prior CVA	2.46	3.24	0.71	2.84	3.91	0.69	4.22	4.77	0.89
No prior CVA	1.01	1.23		1.98	2.91		3.37	3.75	
On ASA	1.12	1.91	0.10	3.10	3.92	0.29	3.02	3.61	0.10
Not on ASA	1.11	1.32		1.82	2.78		4.95	4.88	
Valvular disease	1.20	1.43	0.38	3.78	5.69	0.12	3.02	3.61	0.10
No valvular disease	1.46	2.08		4.90	6.36		4.95	4.88	

Cr Cl, creatinine clearance (calculated by Cockcroft–Gault equation); ASA, aspirin at randomization; CVA, cerebrovascular accident.

use, international normalized ratio or predicted time in the therapeutic range [Garcia *et al.* 2013; Wallentin *et al.* 2013].

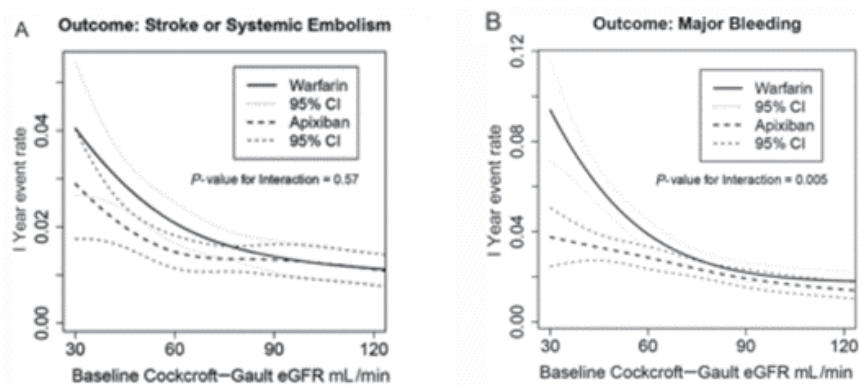
### Anticoagulation of specific patient groups with apixaban

Numerous specific patient groups have been shown to benefit more from apixaban compared with warfarin. Of note, the majority of findings in this section are derived from subgroup analysis, which can be subject to a number of inherent weaknesses, and thus should be interpreted with appropriate caution. (Please see Table 3 for a summary of key subgroup analysis.)

#### *Patients with chronic kidney disease*

Renal impairment is a known independent predictor of stroke, bleeding and all-cause mortality in patients with atrial fibrillation [Lip *et al.* 2013]. Because all currently available DOACs are at least partially excreted by the kidneys, there is a theoretical risk of increased bleeding in patients with impaired renal function. For this reason, patients with serum creatinine greater than 2.5 or glomerular filtration rate of less than 25 ml/min/1.73 m<sup>2</sup> were excluded from ARISTOTLE and AVERROES [Hohnloser *et al.* 2013; Granger *et al.* 2011]. However, compared with dabigatran that is cleared approximately 80% by the kidneys, apixaban and rivaroxaban are excreted approximately





**Figure 3.** (A) Stroke and systemic embolism (% per year) by baseline glomerular filtration rate (GFR). (B) Major bleeding events (% per year) by baseline GFR [Hohnloser *et al.* 2012]. eGFR, estimated glomerular filtration rate.

30% renally and edoxaban about 50% renally [Raghavan *et al.* 2009]. In AVERROES, apixaban reduced primary events by 68% in patients with stage III chronic kidney disease and by 43% in patients with a creatinine clearance greater than 60 ml/min/1.73 m<sup>2</sup> [Eikelboom *et al.* 2012]. In ARISTOTLE, apixaban was associated with fewer strokes or systemic embolisms and with significantly less major bleeding ( $p = 0.03$ ) than warfarin irrespective of creatinine clearance, and more particularly, in those with a creatinine clearance < 60 ml/min/1.73 m<sup>2</sup> ( $p = 0.005$ ) (see Figure 3) [Hohnloser *et al.* 2012].

#### The elderly

Anticoagulation in the elderly is particularly problematic because patients over 80 years are at significantly higher risk of both strokes and bleeding, even when compared with patients aged 65–79 years [Hess *et al.* 2012]. In a recent systematic review, only about 50% of patients with atrial fibrillation over 80 years were adequately anticoagulated, based on their risk of stroke [Garwood and Corbett, 2008]. Of elderly patients started on oral anticoagulants, approximately 26% discontinue their medication within the first year. Of the elderly patients who discontinue anticoagulation, 81% cite safety concerns, such as falls, as the main reason for discontinuation. Of concern, the rates of termination have been observed to be highest among patients with a CHADS<sub>2</sub> score of at least 3 [Hylek *et al.* 2007].

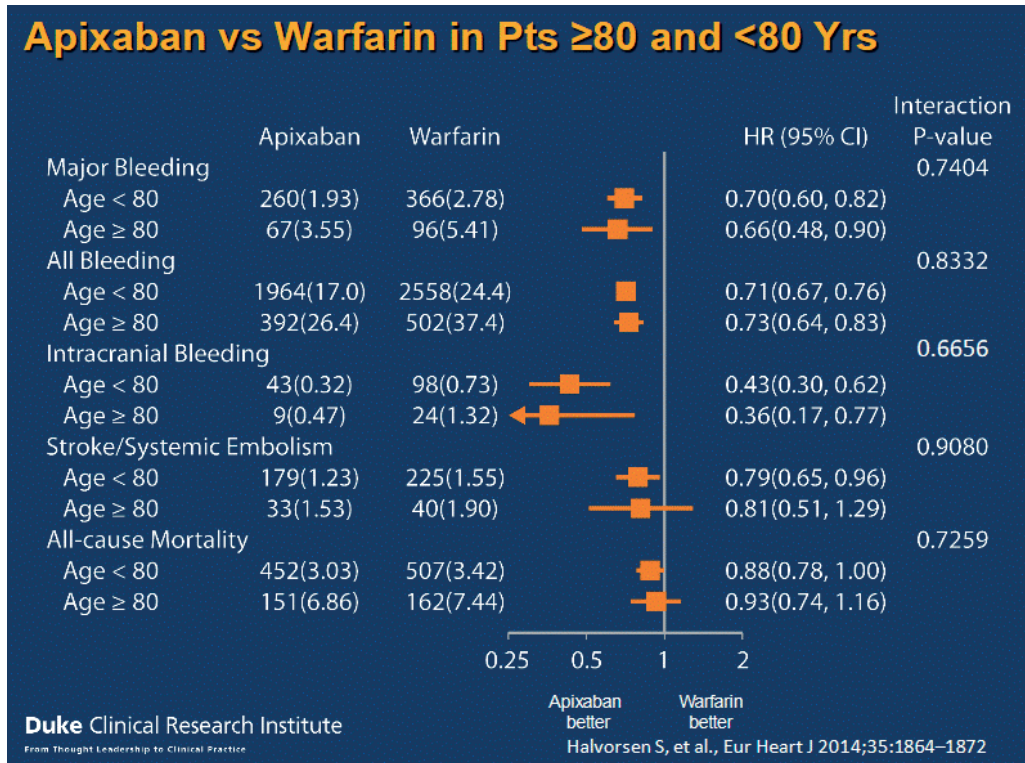
Risk of falling has been very commonly cited as a reason for not anticoagulating the elderly.

However, falling does not appear to be a strong risk factor for major bleeding in patients on systemic anticoagulation regardless of age or baseline stroke risk [Man-Son-Hing *et al.* 1999]. One study suggested that a patient would need to fall over 300 times for the risk of systemic anticoagulation to outweigh the benefit [Sellers and Newby, 2011].

Both ARISTOTLE and AVERROES have shown that apixaban is safe to use in the elderly: compared with aspirin use in 1898 patients aged over 75 years, apixaban was associated with a significant reduction in the risk of stroke (1% versus 7% per year, respectively, or an 87% risk reduction), with no difference in bleeding risk (4.7% versus 4.9% per year, respectively) [Ng *et al.* 2015]. In ARISTOTLE, apixaban resulted in fewer stroke and systemic embolism events, and fewer major bleeding events than warfarin regardless of age ( $p$  for interaction = 0.11); patients over 80-years old had less major bleeding and intracranial bleeding and a trend towards less risk of stroke and systemic embolism, as well as all-cause mortality when taking apixaban compared with warfarin (see Figure 4) [Halvorsen *et al.* 2014].

#### Patients with prior stroke or transischemic attack

The single most significant predictor of stroke risk in patients with atrial fibrillation is prior stroke or TIA [Hess *et al.* 2013]. Despite this known fact, a large systematic review showed that patients with prior stroke and atrial fibrillation were anticoagulated less than 60% of the time



**Figure 4.** Study outcomes from the ARISTOTLE trial by age [Halvorsen *et al.* 2014]. HR, hazard ratio; CI, confidence interval; Pts, patients; Yrs, years.

[Ogilvie *et al.* 2010]. In AVERROES, patients with previous stroke or TIA were three times more likely to experience the primary outcome of stroke and systemic embolism. Patients with prior stroke or TIA benefited even more from apixaban than those without prior stroke or TIA (HR 0.29 *versus* 0.51, respectively) [Diener *et al.* 2012]. Patients in ARISTOTLE with prior stroke had an even greater absolute benefit of taking apixaban with regard to stroke and systemic embolism (absolute risk reduction 0.77/100 person-years) compared with those without prior stroke (0.22/100 person-years;  $p$  for interaction = 0.71) (see Figure 5) [Easton *et al.* 2012].

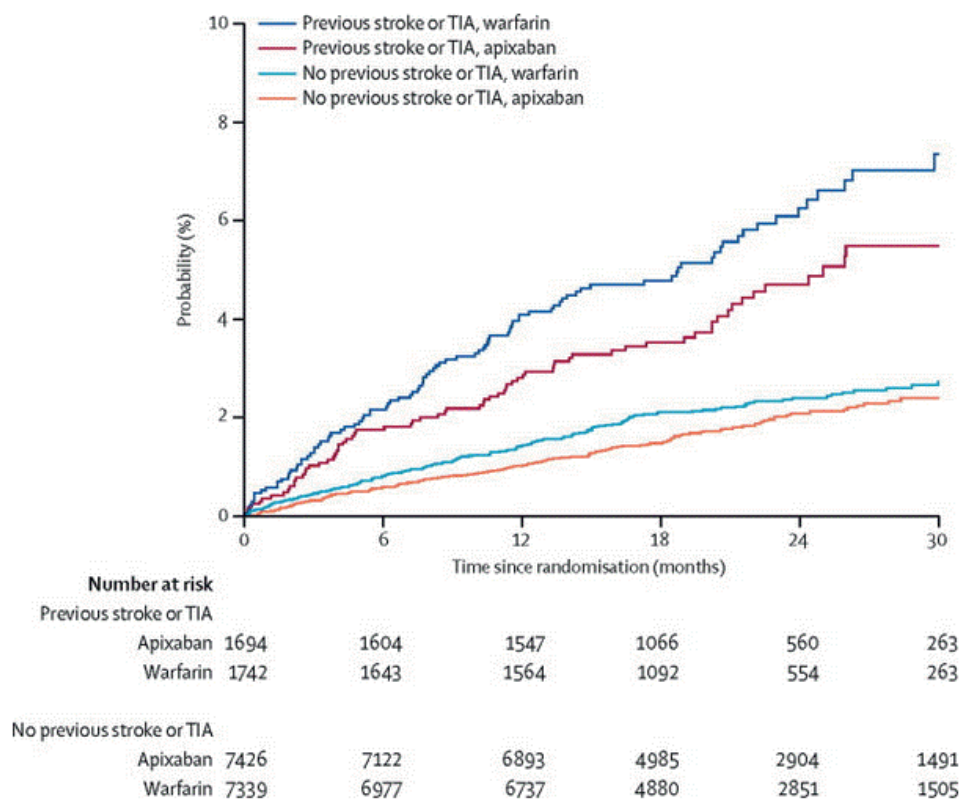
#### Women

Women in ARISTOTLE had a similar overall stroke risk as men and the benefits of apixaban over warfarin were consistent regardless of sex ( $p$  for interaction = 0.45) [Vinereanu *et al.* 2015]. This is thought to be more accurate than the finding in AVERROES that women suffered nearly twice as many strokes as men. The latter observation may have resulted from the fact that women, on average, were older than men with a

significantly larger proportion of women than men who were older than 75 years. Despite this difference, patients treated with apixaban had about 60% risk reduction in the primary outcome of stroke and systemic embolism, regardless of sex [Lip *et al.* 2014].

#### Patients on aspirin

Approximately 35% of all patients taking oral anticoagulants are also on aspirin, and of those patients, 39% do not have atherosclerotic disease [Steinberg *et al.* 2013]. In ARISTOTLE, there was nearly a 50% higher rate of bleeding in patients taking aspirin (compared with patients not taking aspirin) with the oral anticoagulant [Granger *et al.* 2011]. These data suggest that avoiding unnecessary aspirin with apixaban may be an important strategy to reducing bleeding risk. However, regardless of concomitant aspirin use, apixaban was associated with less major bleeding than warfarin (3.1% per year on apixaban with aspirin and 3.92% per year on warfarin with aspirin), as well as improvement in the primary outcome of stroke and systemic embolism ( $p$  for interaction = 0.10) [Alexander *et al.* 2014].



**Figure 5.** Stroke and systemic embolism in patients with and without previous stroke and treated with warfarin *versus* apixaban. With prior CVA: 2.46% per year on apixaban *versus* 3.24% per year on warfarin [hazard ratio (HR) for apixaban 0.76]; without prior CVA: 1.01% per year on apixaban *versus* 1.32 per year on warfarin (HR for apixaban 0.82);  $p$  for interaction = 0.71 [Easton *et al.* 2012]. TIA, transient ischemic attack.

#### *Patients with persistent or permanent atrial fibrillation*

Patients in ARISTOTLE with persistent or permanent atrial fibrillation had a higher stroke risk than patients with paroxysmal atrial fibrillation [Vanassche *et al.* 2015]. The relative benefit of apixaban over warfarin was true regardless of atrial fibrillation type, but it was more pronounced in patients with persistent and permanent atrial fibrillation ( $p$  for all interactions > 0.13) [Al-Khatib *et al.* 2013].

#### *Patients with valvular abnormalities*

Apixaban is currently approved by the Food and Drug Administration for use in the US in patients with atrial fibrillation who do not have valvular heart disease, or what has been termed ‘nonvalvular’ atrial fibrillation. In ARISTOTLE, 4808 (26.4%) of the enrolled patients had

significant (moderate or severe) valvular disease [Granger *et al.* 2011]. When comparing patients with and without valvular disease on apixaban in the ARISTOTLE trial, there was no significant difference regarding the benefits of apixaban *versus* warfarin on stroke or systemic embolism ( $p = 0.38$ ), all-cause mortality ( $p = 0.10$ ) or on major bleeding ( $p = 0.23$ ) [Avezum *et al.* 2015]. Thus, apixaban (and the other DOACs) have consistent benefits and are appropriate to use for patients with most valvular abnormalities, with the exceptions of moderate or severe mitral stenosis (excluded from the trials) or mechanical prosthetic heart valves [who had more strokes, bleeding, and valve thrombosis with dabigatran than with warfarin in a randomized, phase II study to evaluate the safety and pharmacodynamics of oral dabigatran etexilate in patients after heart valve replacement (RE-ALIGN) study] [Eikelboom *et al.* 2013].



### *Patients who are systematically underdosed with apixaban*

As mentioned previously, in ARISTOTLE, patients were systematically dose reduced to apixaban 2.5 mg twice daily (*versus* 5 mg twice daily) if they met two of the following three criteria: age  $\geq$  80 years, serum creatinine  $\geq$ 1.5 or weight  $\leq$ 60 kg. This accounted for approximately 5% of the total patient population. Such patients were also less likely to experience the primary outcome of stroke and systemic embolism (1.7% *versus* 3.3% per year, respectively;  $p = 0.22$ ) and to have major bleeding events (3.3% *versus* 6.7% per year, respectively;  $p = 0.21$ ) if they were on apixaban compared with warfarin. Patients taking apixaban had fewer major bleeding events than patients taking warfarin, regardless of the number of dose-reduction criteria present [Granger *et al.* 2011].

### *Patients with varying risk of stroke*

Risk stratification in the AVERROES trial showed that patients with a CHADS<sub>2</sub> score of 1 had a 0.9% annual stroke risk, compared with 2.1% in patients with a CHADS<sub>2</sub> score of at least 2 [Coppens *et al.* 2013]. Yet, there was significant benefit from apixaban over aspirin regardless of the CHADS<sub>2</sub> score [Flaker *et al.* 2012]. Also, there was similar benefit from apixaban over aspirin in patients with a low CHADS<sub>2</sub> score compared with those with previous intolerance of a vitamin K antagonist [Coppens *et al.* 2014]. Multivariable analysis later revealed that age over 75 years, previous stroke, chronic kidney disease and nonparoxysmal atrial fibrillation were the strongest predictors of stroke [Lip *et al.* 2013].

As was the case in the AVERROES trial, in ARISOTLE, the net benefit of apixaban over warfarin was present regardless of the CHADS<sub>2</sub> or the CHA<sub>2</sub>DS<sub>2</sub>-VASc score ( $p = 0.12$  for stroke and systemic embolism, and  $p = 0.94$  for major bleeding) [Lopes *et al.* 2012]. Because of this difficulty in risk stratification among patients taking apixaban using existing scoring systems, other means of stratification have been evaluated within the ARISTOTLE trial. For example, in ARISTOTLE patients, elevated high-sensitivity troponin levels was found to be independently associated with a higher risk of stroke, cardiovascular death and major bleeding [Hijazi *et al.* 2014a]. The benefit of apixaban over warfarin was consistent regardless of the high-sensitivity troponin level [Hijazi *et al.* 2014b]. Similarly, n-terminal prohormone of brain natriuretic peptide (NT pro-BNP) was shown to

be strongly associated with increased stroke and mortality risk in ARISTOTLE; the benefit of taking apixaban over warfarin was observed regardless of the NT pro-BNP level [Hijazi *et al.* 2013]. The net benefit of apixaban over warfarin was also observed regardless of whether the patients had previously taken warfarin, whether patients were taking amiodarone or whether they had chronic obstructive pulmonary disease [Garcia *et al.* 2013; Flaker *et al.* 2014; Durheim *et al.* 2015].

### **Future directions**

One of the largest concerns related to apixaban (as with the other DOACs) has been the lack of a reversal agent (although the case fatality rate of a major bleeding event on apixaban is lower than on warfarin, as has been previously pointed out) [Hylek *et al.* 2014]. Currently, andexanet alfa is being investigated for potential use as a reversal agent. It is a recombinant factor-Xa molecule with higher affinity for the natural factor-Xa inhibitor than endogenous factor Xa. Animal studies have shown that andexanet alfa is capable of reversing Xa inhibition in a dose-dependent fashion without being prothrombotic [Ghadimi *et al.* 2015]. More recently, andexanet alfa was administered to healthy older volunteers taking apixaban or rivaroxaban; it caused a 94% reduction in anti-Xa activity in patients taking apixaban [Siegal *et al.* 2015]. Further investigation is underway to test the efficacy of this agent in patients with Xa-related bleeding events. In addition, idarucizumab has been shown to rapidly reverse the antithrombin effects of dabigatran in studies of healthy volunteers and in patients with clinically significant bleeding [Eikelboom *et al.* 2015].

Patients with renal dysfunction and atrial fibrillation have more stroke and major bleeding episodes [Lip *et al.* 2013]. While the differential benefit of apixaban over warfarin in treating atrial fibrillation has been previously demonstrated in patients with mild and moderate chronic kidney disease, trials have excluded patients with a creatinine clearance of less than 25 l/min. Thus, the tolerability and efficacy of apixaban in patients with advanced chronic kidney disease and end-stage renal disease (ESRD) are currently unknown [Patel and Piccini, 2015]. A recent study of the pharmacokinetics and pharmacodynamics of apixaban in eight patients with ESRD on hemodialysis showed no significant difference in drug concentrations or clearance, when compared with

eight healthy subjects [Wang *et al.* 2015]. Given the lack of data on the safety of administering apixaban to patients with ESRD without dose adjustment, a randomized clinical trial comparing the use of apixaban with warfarin in patients with atrial fibrillation and ESRD is needed.

With the increasing number of patients who have continuous heart monitoring *via* cardiac-implantable electronic devices (CIED), it has become evident that a large number of patients with no prior known atrial fibrillation experience episodes of incidental or subclinical atrial fibrillation. Recent studies of patients with a CIED have shown that up to 1/3 of all patients with atrial fibrillation detected by device have not had any previous clinical atrial fibrillation [Patel and Piccini, 2015]. The asymptomatic atrial fibrillation and stroke evaluation in pacemaker patients and the atrial fibrillation reduction atrial pacing trial (ASSERT) showed that there was a significantly increased risk of stroke and systemic embolism, as well as of developing clinical atrial fibrillation in 2500 patients with device-detected brief episodes of atrial fibrillation [Healey *et al.* 2012]. Accordingly, the current European Heart Society guidelines recommend considering anticoagulation of patients with device-detected atrial fibrillation [Camm *et al.* 2012]. However, no study has ever shown that the benefit-to-risk ratio of using an oral anticoagulant in such patients is favorable. In order to clarify the net benefit of anticoagulation in this group, the ‘apixaban for the reduction of thromboembolism in patients with device-detected sub-clinical atrial fibrillation’ (ARTESiA) trial is currently underway. This randomized-controlled trial will compare the use of apixaban with aspirin in patients with device-detected atrial fibrillation. Also, the ‘nonvitamin K antagonist oral anticoagulants in patients with atrial high-rate episodes’ (NOAH AFNET 6) trial is currently underway to test whether patients with high atrial rates may benefit from treatment with edoxaban *versus* aspirin *versus* placebo.

Direct current (DC) cardioversion is a very frequent component of the treatment of atrial fibrillation; however, the efficacy and the safety of apixaban use pre- and postcardioversion have only been inferred from data in the ARISTOTLE trial. In ARISTOTLE, there was no difference between warfarin and apixaban in stroke or systemic embolism or in major bleeding events in patients who underwent cardioversion [Camm *et al.* 2012]. A phase IV trial to assess the

effectiveness of apixaban compared with usual care anticoagulation in subjects with nonvalvular atrial fibrillation undergoing cardioversion (EMANATE) trial is currently recruiting patients to compare the use of apixaban with warfarin in patients with atrial fibrillation who are planned to undergo DC cardioversion.

Another key question related to the use of apixaban is its use in patients with atrial fibrillation and coronary artery disease who require the use of antiplatelet therapy and systemic anticoagulation. In ARISTOTLE, patients with atrial fibrillation and coronary artery disease had fewer myocardial infarctions, strokes, bleeding episodes and death on apixaban compared with warfarin, whether or not they were on antiplatelet therapy [Bahit *et al.* 2013]. The apixaban *versus* vitamin k antagonist and aspirin *versus* placebo in patients with atrial fibrillation and acute coronary syndrome or percutaneous coronary intervention (AUGUSTUS) trial is currently underway to compare the use of warfarin with apixaban in the first 6 months following an acute coronary syndrome with or without percutaneous coronary intervention.

### Conclusion

Apixaban is superior to warfarin in preventing stroke and systemic embolism and causes significantly less major bleeding. This has been shown to be the case in a number of high-risk patient populations such as the elderly, patients with moderate CKD, and patients with prior stroke as reviewed in this paper. Several knowledge gaps in relation to the safety and efficacy of apixaban still exist and are being addressed by ongoing randomized clinical trials.

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### Conflict of interest statement

The authors declare that there is no conflict of interest.

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