REVIEW

An evidence-based review of apixaban and its potential in the prevention of stroke in patients with atrial fibrillation

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Abstract: Atrial fibrillation (AF) is a common cardiac arrhythmia, especially in the elderly population. It is associated with cardioembolic complications, particularly strokes, resulting in severe functional deficit or death. AF patients are first stratified into low, intermediate, and high risk for thromboembolic events using the $CHADS_2$ and CHA_2DS_2-VASc score systems. Depending on their risks, patients are treated with either therapeutic anticoagulation with warfarin or acetylsalicylic acid for stroke prevention. Although warfarin is the recommended therapy, it is underutilized clinically due to concern for narrow therapeutic window, drug-to-drug and drug-to-food interactions, and hemorrhagic complications. Newer anticoagulant agents such as dabigatran (a direct thrombin inhibitor) and rivaroxaban (a direct factor Xa inhibitor) have already been approved by US Food and Drug Administration for stroke prevention in patients with nonvalvular atrial fibrillation. Apixaban is the newest oral direct factor Xa inhibitor and it has been extensively studied in the AVERROES and ARISTOTLE trials. Apixaban demonstrated reduced incidence of primary outcome of stroke and bleeding events when compared with warfarin. Apixaban is currently being reviewed by the Food and Drug Administration as a stroke prophylactic agent. In addition, there are several other indirect factor Xa inhibitors and vitamin K antagonists under study presently. Results from these studies will provide us with information about possible alternatives to warfarin.

Keywords: atrial fibrillation, stroke prevention, apixaban

Core evidence: clinical impact summary for apixaban and the reduction of major adverse cardioembolic events in patients with nonvalvular atrial fibrillation

Outcome measure	Evidence	Implications
Disease-oriented evidence		
Clinical		
	AVERROES trial	
Composite of stroke and systemic embolism	1.6% per year in patients receiving apixaban compared with 3.7% per year in patients receiving ASA (HR 0.45; 95% CI: 0.32–0.62; $P < 0.001$)	In patients with AF, treatment with apixaban compared with ASA was significantly better in reducing the rate of stroke and systemic embolism
	ARISTOTLE trial	
Composite of stroke and systemic embolism	1.27% per year in patients receiving apixaban compared with 1.60% per year in patients receiving warfarin (HR 0.79; 95% CI: 0.66–0.95; $P = 0.01$)	Compared with warfarin, treatment with apixaban was noninferior in reducing the rate of stroke and systemic embolism in patients with nonvalvular AF
		(Continued)

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(*Continued*)		
Outcome measure	**Evidence**	**Implications**
Hemorrhagic stroke	0.24% per year in patients receiving apixaban compared with 0.47% per year in patients receiving warfarin (HR 0.51; 95% CI: 0.35–0.75; *P* < 0.001)	Compared with warfarin, treatment with apixaban was associated with a significantly lower risk of hemorrhagic stroke
Death from any cause	3.52% per year in patients receiving apixaban compared with 3.94% per year in patients receiving warfarin (HR 0.89; 95% CI: 0.80–0.998; *P* = 0.047)	Compared with warfarin, treatment with apixaban was associated with a marginally lower risk of death from any cause
Patient-oriented evidence		
	ARISTOTLE trial	
Bleeding complication		
ISTH major bleeding	2.13% per year in patients receiving apixaban compared with 3.09% per year in patients receiving warfarin (HR 0.69; 95% CI: 0.60–0.80; *P* < 0.001)	Compared with warfarin, treatment with apixaban was associated with a lower risk of ISTH major bleeding
Intracranial bleeding	0.33% per year in patients receiving apixaban compared with 0.80% per year in patients receiving warfarin (HR 0.42; 95% CI: 0.30–0.58; *P* < 0.001)	Compared with warfarin, treatment with apixaban was associated with a significantly lower risk of intracranial bleeding
Gastrointestinal bleeding	0.76% per year in patients receiving apixaban compared with 0.86% per year in patients receiving warfarin (HR 0.89; 95% CI: 0.70–1.15; *P* = 0.37)	Compared with warfarin, treatment with apixaban was associated with a nonstatistically significant lower risk of gastrointestinal bleeding
Major or clinically relevant nonmajor bleeding	4.07% per year in patients receiving apixaban compared with 6.01% per year in patients receiving warfarin (HR 0.68; 95% CI: 0.61–0.75; *P* < 0.001)	Compared with warfarin, treatment with apixaban was associated with a lower risk of major or clinically relevant nonmajor bleeding
Net clinical outcomes		
Stroke, systemic embolism, or major bleeding	3.17% per year in patients receiving apixaban compared with 4.11% per year in patients receiving warfarin (HR 0.77; 95% CI: 0.69–0.86; *P* < 0.001)	Compared with warfarin, treatment with apixaban was associated with improved net clinical outcomes of stroke, systemic embolism, or major bleeding
Stroke, systemic embolism, major bleeding, or death from any cause	6.13% per year in patients receiving apixaban compared with 7.20% per year in patients receiving warfarin (HR 0.85; 95% CI: 0.78–0.92; *P* < 0.001)	Compared with warfarin, treatment with apixaban was associated with improved net clinical outcomes of stroke, systemic embolism, major bleeding, or death from any cause
Quality of life measures	Not available	
Economic evidence	Not available	

Abbreviations: ASA, acetylacylic acid; AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; ISTH, International Society on Thrombosis and Haemostasis.

Introduction

Apixaban belongs to a new class of direct Factor Xa (FXa) inhibitors. It had been studied extensively in two phase III trials [The Apixaban Versus Acetylsalicylic Acid to Prevent Stroke (AVERROES) and Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE)] as potential alternatives to warfarin for stroke prevention in atrial fibrillation (AF) patients.[1–4] These studies are particularly important because AF is the most common cardiac arrhythmia and is especially prevalent in the older population. It is also associated with many comorbid conditions including cardioembolic strokes.[5] Therapeutic anticoagulation is the treatment of choice in moderate- to high-risk AF patients because it is the only treatment that

has been shown to reduce the risk of embolic phenomena and mortality.[6] However, its usage has been limited due to several issues, such as the need for frequent monitoring, multiple drug-to-drug and drug-to-food interactions, and the risk of hemorrhagic complications.[7,8] As a result, newer antithrombotic agents have been developed and studied. In this review, we examine the need for new anticoagulants and provide a review of apixaban and its effect in stroke prevention.

Stroke prevention in atrial fibrillation and the need for newer anticoagulants

AF patients (both valvular and nonvalvular) are at increased risk of developing cardioembolic strokes, and these AF-related complications often result in severe functional deficits or death.[9] Because these embolic events can be devastating, multiple schemes such as the CHADS$_2$ risk score index (Table 1) and the CHA$_2$DS$_2$-VASc score (Table 2) have been utilized to classify AF patients into different risk groups.[6,10–12] The CHADS$_2$ system identified five major risk factors – congestive heart failure, hypertension, age > 75 years, diabetes mellitus, and previous stroke or transient ischemic attack (TIA). In this scoring system, a previous stroke or TIA is assigned two points while the other factors are assigned one point. Although it is a useful system, the CHADS$_2$ scoring system omitted some important risk factors such as thyrotoxicosis, female sex, and coronary artery disease or peripheral artery disease, which may underestimate

Table 1 CHADS$_2$ index to calculate stroke risk in patients with nonvalvular atrial fibrillation not treated with anticoagulation

CHADS$_2$ risk criteria	Score
Congestive heart failure	1
Hypertension	1
Age > 75	1
Diabetes mellitus	1
Prior stroke or transient ischemic attack	2
CHADS$_2$ score	**Adjusted stroke rate (% per year)**
Stroke risk based on CHADS$_2$ score	
0	1.9%
1	2.8%
2	4.0%
3	5.9%
4	8.5%
5	12.5%
6	18.2%

Table 2 CHAD$_2$DS$_2$-VASc risk score for predicting stroke and thromboembolism in patients with atrial fibrillation using novel risk factor-based approach

CHAD$_2$DS$_2$-VASc risk criteria	Score
Congestive heart failure/LV dysfunction (LVEF ≤ 40%)	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74	1
Sex category (female sex)	1
Maximum score	9

the cardioembolic risks and end up placing more patients in the intermediate-risk groups. Subsequently, researchers evaluated for other risk stratification systems to better stratify AF patients.

The newer CHA$_2$DS$_2$-VASc score added three new risk factors (history of vascular disease, age 65–74 years, and female sex) in addition to the five risk factors listed in the CHADS$_2$ system. In the CHA$_2$DS$_2$-VASc score scheme, age > 75 years is assigned two points, on a par with previous stroke and TIA.[11,12] Based on this new scoring scheme, women and elderly patients (≥75 years) who were previously identified as "intermediate risk" are now placed into a "high-risk" category with a recommendation for full anticoagulation.

People are placed into different risk groups and prescribed appropriate antithrombotic therapy. In high-risk patients (CHADS$_2$ score ≥ 2), oral anticoagulation with warfarin has been the standard to prevent the cardioembolic complications including stroke until recently.[6] In patients with intermediate-risk (score of 1), acetylsalicylic acid (ASA) may be used although warfarin is still preferred. On the other hand, ASA is recommended in the low-risk patients (score of 0). Antithrombotic therapy maybe deferred in patients with lone AF or in patients who have contraindication to antithrombotic therapy.[6]

Although therapeutic anticoagulation with warfarin has been proven to reduce the risk of embolic phenomenon and mortality in AF patients, it is underutilized in high-risk patients.[6,13] Warfarin use has been limited by several properties such as slow onset of action, narrow

therapeutic window, variable cytochrome P450-dependent metabolism, significant amount of drug-to-food and drug-to-drug interactions, and risk of bleeding complications such as intracranial hemorrhage in the elderly patients (Table 3).[11,13–17] Because of all of these issues, patients need to undergo frequent international normalized ratio monitoring and dosage adjustment in order to achieve and maintain appropriate levels. Unfortunately, therapeutic anticoagulation is obtained in less than one third of the time. Subtherapeutic anticoagulation exposes patients to cardioembolic events, and supratherapeutic anticoagulation subjects patients to bleeding complications.[18] In addition, it is difficult to achieve the desired time in the therapeutic range with warfarin. It is also expensive and impairs quality of life because of frequent doctor and laboratory visits.[19] In addition, elderly patients and patients with severe renal impairment are at high risk of developing cardioembolic complications as well as increased risk of bleeding with warfarin use. Older patients often have cognitive impairment and physical limitations which place them at increased risk for bleeding. Patients with renal impairment can have functional abnormalities within the platelets and other coagulation pathways such as altered von Willebrand factor that can place them at a higher risk of bleeding.[20–22]

Because of these reasons, the use of warfarin for stroke prevention has been challenging and is associated with significant impairment. Therefore, there has been a need to find better therapeutic agents for the prevention of thromboembolic events and strokes in AF patients.

The search for newer agents for stroke prevention in patients with atrial fibrillation

Multiple new drugs have been evaluated as potential alternative anticoagulants for stroke prevention in AF patients. ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) and ACTIVE A (a separate arm of the ACTIVE W) trials evaluated dual antiplatelet therapy of acetylsalicyclic acid and clopidogrel as alternative to warfarin. Results from the ACTIVE trials demonstrated that warfarin is superior to dual antiplatelet therapy and that warfarin is still the antithrombotic agent of choice. In patients who cannot tolerate or safely sustain anticoagulation with warfarin, dual antiplatelet therapy may be considered.[23–25]

Due to the limitations of warfarin and dual antiplatelet therapy, there has an ongoing search for newer and better oral anticoagulants for stroke prophylaxis. Efforts have been directed at finding agents with rapid onset of action, fewer food and drug interaction, and more predictable anticoagulation. As a result, direct thrombin inhibitors, direct and indirect FXa inhibitors, and other vitamin K antagonists have emerged and have been evaluated in various clinical trials. In the following sections, we will discuss briefly some of

Table 3 Warfarin interactions with drugs, natural health products, and food[15–17]

Drugs		Natural health products	Food
Drug class	**Drug examples**		
Antibiotics	Macrolides, fluoroquinolones, metronidazole, clo-trimoxazole, rifampin	Bilberry	Avocado
		Coenzyme Q10	Cranberry juice
Antifungals	Fluconazole, miconazole, itraconazole	Dashen	Garlic
Antidepressants	SSRIs – citalopram, sertraline	Devil's claw	Ginger
Nonsteroidal anti-inflammatory agents	Acetylsalicylic acid, celecoxib	Dong Quai	Licorice
Stomach ulcer/acid-reducing agents	Cimetidine, omeprazole	Feverfew	Hawthorne
Lipid-lowering agents	Fibrates, lovastatin, simvastatin, fluvastatin	Fenugreek together with Boldo	Mango
		Fish oil supplements with EPA and DHA	Peppermint
		Ginkgo biloba	Soy protein products (soy milk, tofu)
		Ginseng	Wildberry
		Green tea	
		Horse chestnut	
		Lycium barbarum	
		Red clover	
		St John's Wort	
		Vitamin C	
		Vitamin E	
		Vitamin K	

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.

these agents and focus our primary attention on the newest of these agents, apixaban.

Direct thrombin inhibitors

Dabigatran is a new oral direct thrombin inhibitor which has been approved by the United States Food and Drug Administration (FDA) for stroke prevention in nonvalvular AF patients. Dabigatran was extensively studied in the Dabigatran with or without concomitant acetylsalicylic acid compared with warfarin alone in patients with nonvalvular atrial fibrillation (PETRO study) and the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY study).[26–29] The RE-LY study compared dabigatran etexilate with dose-adjusted warfarin in 18,113 patients in a multicenter, randomized, open-label study. Results of this study showed that dabigatran 150 mg twice daily was superior to warfarin and dabigatran 110 mg twice daily was noninferior to warfarin in primary outcomes of stroke and systemic embolism. Overall, there was a lower risk of bleeding (major, life-threatening, intracranial, and major or minor bleeding) but a higher incidence of dyspepsia compared to warfarin.[29] Based on the safety and efficacy results from the RE-LY study, the FDA approved dabigatran for stroke prevention in nonvalvular AF patients (150 mg twice daily for patients with normal renal function and 75 mg twice daily for patients with renal impairment) in October 2010. Dabigatran was added as a first-line option for anticoagulation in high-risk AF patients in the 2011 Updated of the ACC/AHA practice guideline for atrial fibrililation.[30]

Dabigatran has been extensively used by clinicians around the world since its approval and there has been concern regarding an increased risk of gastrointestinal bleeding (especially in the elderly). In addition, the manufacturer has reported 260 fatal bleeding events after reviewing the postmarketing database. These findings have prompted several actions to be taken by different countries, including labeling updates in Europe and the United States, safety advisories issued in Japan and Australia, and an FDA investigation to determine whether the reports of bleeding in patients taking dabigatran are occurring more commonly than would be expected.[31] An extension of the RE-LY study, the RELY-ABLE study (RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation Who Completed RE-LY Trial – NCT00808067), is actively ongoing to evaluate the long-term safety of dabigatran.

Direct factor Xa inhibitors

FXa is the first member of the final common pathway in the coagulation cascade. Its primary role is to convert prothombin into thrombin which then participates in the thrombus formation. Direct FXa inhibitors inactivate both prothrombinase-bound FXa and free FXa.[14,32,33] Several new agents have been developed as director FXa inhibitors, and these include rivaroxaban, apixaban, and edoxaban.

Rivaroxaban is the first direct FXa inhibitor that has been evaluated and recently approved for clinical use for stroke prophylaxis in atrial fibrillation. It has a half-life of 5–9 hours in the healthy individual and 9–13 hours in elderly patients. It is renally excreted in 66% of the time. It is metabolized by the CYP3A4 enzyme pathyway.[33] Its use in atrial fibrillation was investigated in the Rivaroxaban Once-daily Oral Direct Factor Xa Inhibition Compared with the Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial as stroke prophylactic agent for AF patients. The result of this study showed that rivaroxaban was noninferior to warfarin in preventing stroke and systemic embolism. The rivaroxaban group had fewer intracranial bleeding but more gastrointestinal bleeding events when compared to the warfarin group. These data demonstrated that rivaroxaban is a good alternative to warfarin in AF patients who are at moderate to high risk of developing embolic strokes.[34] Although concern was raised during the approval process for its use as once-daily administration (due to its short half-life), it has been approved by the FDA for prevention of stroke in patients with nonvalvular AF in November 2011. There has not yet been sufficient substantive clinical exposure with rivaroxaban to evaluate its efficacy and safety in clinical practice.

Apixaban – newest direct factor Xa inhibitor

Apixaban is the newest selective, reversible, oral, direct FXa inhibitor that has been evaluated for the prevention of strokes in patients with AF in multiple trials. It has a rapid onset of action (3 hours) and a mean half-life of 12 hours. It is metabolized by the kidney, liver (primarily by CYP3A4, CYP3A5, and sulfotransferase 1A1), and the intestine. It is excreted 25% renally and 75% through the hepatobiliary system which is different from rivaroxaban (66% renal excretion). Its absorption is not affected by food and it needs to be taken in a twice-daily dosing format. It is essential for clinicians to be cautious about concomitant use with CYP3A4 inhibitors and inducers, as the pharmacokinetics of the drug will be altered in such settings.[32] A recent crossover study evaluated the pharmacokinetics, pharmacodynamics, and safety of coadministration of enoxaparin and apixaban in 20 healthy subjects. Concomitant usage of apixaban and enoxaparin

resulted in a 42% increase in peak anti-Xa activity. Similarly, the peak anti-Xa activity was 15% higher when apixaban was coadministered with enoxaparin compared to apixaban alone. Overall, the study showed that the pharmacokinetics of apixaban were not affected by enoxaparin even though there was a modest increase in anti-Xa activity when enoxaparin was used concurrently with apixaban. Furthermore, the finding also suggested that co-administration of apixaban and enoxaparin was safe and well tolerated in healthy volunteers.[35]

Apixaban has been evaluated in two recent phase III randomized trials for stroke prevention in AF patients. The first study was the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke (AVERROES trial). It was an international (36 countries), multicenter (522 centers), double-blinded, and double-dummy trial which enrolled 5599 AF patients over a 2-year period (September 2007–December 2009). The patients enrolled in this trial were those who were not candidates for vitamin K antagonist therapy because of previous intolerance to or ineligibility for warfarin therapy.[1,2]

Patients participating in the AVERROES trial had to be ≥50 years old and to have had atrial fibrillation documented in the 6 months before enrollment or by 12-lead electrocardiography on the day of screening. Patients also had to have at least one of the risk factors for stroke which included prior stroke or TIA, age ≥ 75 years, arterial hypertension (on treatment), diabetes mellitus (receiving treatment), heart failure (New York Heart Association class ≥2 at the time of enrollment), a left ventricular ejection fraction of ≤35%, or documented peripheral-arterial disease. Patients were excluded if they needed long-term anticoagulation for reasons other than atrial fibrillation, if they had valvular disease requiring surgery, a history of a serious bleeding event in the past 6 months or if they were at high risk for bleeding, current alcohol or drug abuse or psychosocial issues, if they had a life expectancy <1 year, severe renal insufficiency (serum creatinine >2.5 mg/dL or a calculated creatinine clearance of <25 mL per minute), abnormal liver function test (an alanine aminotransferase or aspartate aminotransferase level > twice the upper limit of the normal range or a total bilirubin >1.5 times the upper limit of the normal range), and allergy to acetylsalicylic acid.[1,2]

Patients who met the inclusion and exclusion criteria were then randomly assigned through a 24-hour central, computerized, automated voice-response system to receive either acetylsalicylic acid (81–324 mg per day) or apixaban (5 mg twice daily or 2.5 mg twice daily in those patients who met two of the following criteria: age ≥ 80 years, weight ≤ 60 kg, or serum creatinine concentration ≥1.5 mg/dL).

Primary efficacy outcome of the study was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism. The primary safety outcome was the occurrence of major bleeding defined by clinically overt bleeding with one of more of the following: drop in hemoglobin level of ≥2 g/dL over 24-hour period, transfusion of ≥2 units of packed red cells, bleeding at critical site, or fatal bleeding. Study also included other outcomes such as rates of myocardial infarction, death from vascular causes, death from any cause, and composites of major vascular events.

The AVERROES trial was terminated early by the data and safety monitoring committee when the interim efficacy analysis showed that apixaban was better than acetylsalicylic acid for the primary outcome in February 2010.[36]

As shown in Table 4, both study groups had similar baseline clinical characteristics. Of the patients enrolled in the study, 63%–64% of patients had a CHADS$_2$ score ≥ 2. The result of the study revealed that patients treated with apixaban had a statistically significant reduction in stroke and systemic embolic rates when compared with the acetylsalicylic acid group (1.6% per year vs 3.7% per year, hazard ratio [HR] with apixaban 0.45, $P < 0.001$; Table 5). The apixaban group had a lower rate of ischemic stroke (1.1% per year vs 3.0% per year, HR with apixaban 0.37, $P < 0.001$) and fewer (six vs nine) hemorrhagic strokes. The rate of death was not statistically significant between the two groups (3.5% per year in the apixaban group vs

Table 4 Baseline characteristics of the patients in the AVERROES trial

Variable	Apixaban (n = 2808)	Aspirin (n = 2791)
Age (mean ± standard deviation, years)	70 ± 9	70 ± 10
Risk factors for stroke (number, %)		
Prior stroke or transient ischemic attack	390 (14%)	374 (13%)
Hypertension, receiving treatment	2408 (86%)	2429 (87%)
Heart failure NYHA class 1 or 2	932 (33%)	878 (31%)
Heart failure NYHA class 3 or 4	186 (7%)	175 (6%)
Left ventricular ejection fraction ≤35%	144 (5%)	144 (5%)
Diabetes receiving treatment	537 (19%)	559 (20%)
CHADS$_2$ (number, %)		
Mean score	2.0 ± 1.1	2.1 ± 1.1
0 or 1	1004 (36%)	1022 (37%)
2	1045 (37%)	954 (34%)
≥3	758 (27%)	812 (29%)

Data from Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 3, 2011;364(9):806–817.
Abbreviation: NYHA, New York Heart Association.

4.4% per year in the acetylsalicylic acid group, HR with apixaban 0.79, $P = 0.07$).[1,2]

As for safety outcomes, there was no statistically significant difference between the incidence of major bleeding (1.4% per year vs 1.2% per year, HR with apixaban 1.13, $P = 0.57$) and minor bleeding (HR with apixaban 1.24, $P = 0.05$). The composite endpoint consisting of stroke, systemic embolism, myocardial infarction, death from vascular causes, or major bleeding events was lower in the apixaban group (5.3% per year vs 7.2% per year, HR with apixaban 0.74, $P = 0.003$ based on the intention-to-treat method). The apixaban group also had fewer hospitalizations for cardiovascular causes (12.6% per year vs 15.9% per year, HR with apixaban 0.79, $P < 0.001$; Table 5). In addition, patients in the apixaban group had fewer serious adverse events (22% vs 27%, $P < 0.001$). Based on these results, it was concluded that apixaban was associated with substantial clinical benefit in high-risk AF patients who are not candidates for vitamin K antagonist therapy.[1,2]

However, the important clinical question is whether apixaban is noninferior to warfarin therapy for stroke prevention in nonvalvular AF. This was evaluated in the recent Apixaban for the Prevention of Stroke in Subjects with Atrial Fibrillation (ARISTOTLE) trial where apixaban was compared to warfarin in intermediate- to high-risk AF patients in a double-blind, double-dummy study conducted at 1034 sites in 39 countries.[3,4]

Patients were eligible for the study if they had AF or flutter at enrollment or had two or more episodes of AF or flutter (at least 2 weeks apart in the 12 months before enrollment as documented by electrocardiography). Patients also needed to have at least one of the risk factors for stroke: age $\geq$ 75 years; previous stroke, TIA, or systemic embolism; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction of $\leq$40%; or diabetes mellitus or hypertension requiring pharmacologic treatment. Patients were excluded if they had atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation, stroke within the previous 7 days, a need for acetylsalicylic acid at a dose of >165 mg a day or needed both acetylsalicylic acid and clopidogrel, and severe renal insufficiency (serum creatinine level > 2.5 mg/dL or calculated creatinine clearance of <25 mL/minute).[3,4]

Eligible patients were randomized to receive either warfarin (dose adjusted to achieve an international normalized ratio of 2.0–3.0) or apixaban (5 mg twice daily or 2.5 mg twice daily in those patients who met $\geq$ two criteria: age $\geq$ 80 years, weight $\leq$ 60 kg, or serum creatinine concentration $\geq$1.5 mg/dL). International normalized ratios were monitored with the use of a blinded, encrypted, point-of-care device.[3,4]

The primary efficacy outcome was stroke (ischemic, hemorrhagic, or uncertain type) or systemic embolism. The key secondary efficacy outcome was death from any cause and

Table 5 Efficacy and safety of apixaban in the AVERROES trial

Event rate (% per year)	Apixaban	Aspirin (ASA)	Hazard ratio (95% CI)	*P* value
Efficacy endpoints				
Stroke or systemic embolism	1.6%	3.7%	0.45 (0.32–0.62)	<0.001
Stroke, SEE, MI, or vascular death	4.2%	6.4%	0.66 (0.53–0.83)	<0.001
MI	0.8%	0.9%	0.86 (0.50–1.48)	0.59
Vascular death	2.7%	3.1%	0.87 (0.65–1.17)	0.37
CV hospitalizations	12.6%	15.9%	0.79 (0.69–0.91)	<0.001
Total death	3.5%	4.4%	0.79 (0.62–1.02)	0.07
Safety endpoints				
Major bleeding	1.4%	1.2%	1.13 (0.74–1.75)	0.57
Clinically relevant nonmajor bleeding	3.1%	2.7%	1.15 (0.86–1.54)	0.35
Intracranial bleeding	0.4%	0.4%	0.85 (0.38–1.90)	0.69
Minor bleeding	6.3%	5.0%	1.24 (1.00–1.54)	0.05
Fatal bleeding	0.1%	0.2%	0.67 (0.19–2.37)	0.53

Notes: The primary efficacy outcome is stroke (ischemic or hemorrhagic) or systemic embolism. The primary safety outcome is major bleeding, defined as clinically overt bleeding that is accompanied by one or more of the following: a decrease in hemoglobin of $\geq$2 g/dL over a 24-hour period, a transfusion of $\geq$2 units of packed red blood cells, bleeding that occurs in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal), or bleeding that is fatal. Other outcomes of interest include myocardial infarction, vascular death, and all-cause death and composites of major vascular events and the net clinical benefit. The percentage per year is the rate per 100 patient-years of follow-up.
Data from Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 3, 2011;364(9):806–817.
Abbreviations: ASA, acetylsalicylic acid; SEE, systemic embolic event; MI, myocardial infarction; CV, cardiovascular; CI, confidence interval.

rate of myocardial infarction. The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria: clinically overt bleeding accompanied by a decrease in the hemoglobin level of $\geq$2 g/dL or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death. The secondary safety outcome was a composite of major bleeding and clinically relevant nonmajor bleeding. Other safety outcomes included any bleeding, other adverse events, and liver-function abnormalities.[3,4]

This study enrolled 18,201 patients from December 2006 to April 2010. As shown (Table 6), both study groups had similar baseline clinical characteristics. Of the patients enrolled in the study, 66% of patients had a CHADS$_2$ score $\geq$ 2. The result of this study showed (Table 7) that after the median follow-up of 1.8 years, patients in the apixaban group had a lower incidence of the primary outcome than the warfarin group (1.27% per year vs 1.60% per year, HR in the apixaban group 0.79, $P < 0.001$ for noninferiority and $P = 0.01$ for superiority). The apixaban group also had fewer hemorrhagic strokes (49% less) and fewer ischemic and uncertain types of stroke (8% less). Patients who were treated with apixaban also had a reduced death rate from any cause, (3.52% per year vs 3.94% per year, HR 0.89, $P = 0.047$), from cardiovascular causes (1.80% per year vs 2.02% per year, HR 0.89), and from noncardiovascular cause (1.14% per year vs 1.22% per year, HR 0.93).[3,4] The reduction in mortality observed with apixaban has not been shown in previous trials with other FXa inhibitors.

As for safety outcomes, patients in the apixaban group had a lower incidence of major bleeding (as defined by the ISTH) as compared to warfarin (2.13% per year vs 3.09% per year, HR 0.69, $P < 0.001$). The apixaban group also had a reduced rate of intracranial bleeding (0.33% per year vs 0.80% per year, HR 0.42, $P < 0.001$). There was a 27% reduction in the rate of major bleeding in the apixaban group when analyzed by the intention-to-treat principle. Moreover, there was no difference in the incidence of adverse events or liver-function testing.[3,4]

Based on the results of the AVERROES and ARISTOTLE trials, apixaban clearly seems to offer better overall outcomes when compared with therapeutic anticoagulation with warfarin. It not only had a reduced incidence of primary outcome of stroke and systemic embolism, it also had fewer incidences of bleeding (including major bleeding and gastrointestinal bleeding) in all age groups. Additionally, apixaban group also had a lower incidence of myocardial infarction. These findings demonstrate that apixaban is a suitable alternative to warfarin as a stroke prophylactic agent in patients with nonvalvular AF.

Comparison of apixaban with other new oral anticoagulant agents

Presently, dabigatran (direct thrombin inhibitor) and rivaroxaban (direct FXa inhibitor) are approved by the FDA for stroke prophylaxis for patients with nonvalvular AF and apixaban is currently undergoing review for same indication. Results from phase III trials have demonstrated that all three agents have the benefit of reducing the primary endpoint of stroke and systemic embolism; however, they have different pharmacokinetic properties and metabolic pathways. Both dabigatran and rivaroxaban are primarily renally excreted, and their dosages need to be adjusted in patients with renal impairment (eg, 75 mg twice daily in patients with renal impairment). Some have even suggested avoidance of the use of these agents together in patients with severe renal dysfunction. In contrast, apixaban is mostly excreted in gastrointestinal tract (75%) with only 25% excretion through the kidneys.[32,33] Therefore, apixaban may be safer in patients with renal insufficiency; however, its use in patients with hepatobiliary disease will require close monitoring. Rivaroxaban and apixaban are both metabolized by the cytochrome CYP3A4 system and as such are subjected to drug-to-drug interactions with medications that are inducers or inhibitors of the CYP3A4 system. All of the newer oral anticoagulants are also subjected to interactions with P-glycoprotein inducers and inhibitors.[32,33]

Table 6 Baseline characteristics of the patients in the ARISTOTLE trial

Variable	Apixaban (n = 9120)	Warfarin (n = 9081)
Age (median, years)	70	70
Qualifying risk factors (number, %)		
Age $\geq$ 75	2850 (31.2%)	2828 (31.1%)
Prior stroke, TIA, or systemic embolism	1748 (19.2%)	1790 (19.7%)
Heart failure or reduced left ventricular ejection fraction	3235 (35.5%)	3216 (35.4%)
Diabetes	2284 (25.0%)	2263 (24.9%)
Hypertension requiring treatment	7962 (87.3%)	7954 (87.6%)
CHADS$_2$ (number, %)		
Mean score	2.1 $\pm$ 1.1	2.1 $\pm$ 1.1
1	3100 (34.0%)	3083 (34.0%)
2	3262 (35.8%)	3254 (35.8%)
$\geq$3	2758 (30.2%)	2744 (30.2%)

Data from Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992.
Abbreviation: TIA, transient ischemic attack.

Table 7 Results of the ARISTOTLE trial

Event rate (% per year)	Apixaban event rate	Warfarin event rate	Hazard ratio (95% CI)	P-value noninferiority
Primary and secondary efficacy outcome				
Stroke or systemic embolism	1.27%	1.60%	0.79 (0.66–0.95)	0.01
Stroke	1.19%	1.51%	0.79 (0.65–0.95)	0.01
Hemorrhagic stroke	0.24%	0.47%	0.51 (0.35–0.75)	<0.001
Death from any cause	3.52%	3.94%	0.89 (0.80–0.998)	0.047
Primary safety outcome				
ISTH major bleeding	2.13%	3.09%	0.69 (0.60–0.80)	<0.001
Intracranial	0.33%	0.80%	0.42 (0.30–0.58)	<0.001
Gastrointestinal	0.76%	0.86%	0.89 (0.70–1.15)	0.37
Other location	1.79%	2.27%	0.79 (0.68–0.93)	0.004
Major or clinically relevant nonmajor bleeding	4.07%	6.01%	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	0.52%	1.13%	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	1.29%	2.18%	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	0.96%	1.69%	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	1.55%	2.46%	0.63 (0.54–0.75)	<0.001

Data from Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981–992.
Abbreviations: CI, confidence interval; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; TIMI, Thrombolysis in Myocardial Infarction; ISTH, International Society on Thrombosis and Haemostasis.

Comparison of the risk/benefit profiles of these new oral anticoagulants with warfarin reveals that all three resulted in lower rates of the primary outcome of stroke and systemic embolism as well as lower risks of bleeding (life-threatening bleeding, intracranial bleeding, and major and minor bleeding). Of the three agents, only treatment with apixaban was found to be associated with a lower risk of overall mortality as well as cardiovascular mortality as compared to warfarin in the ARISTOTLE trial. Although head-to-head comparison of the three newer anticoagulants is lacking, the available data do indicate that treatment with apixaban in the ARISTOTLE trial was associated with a lower rate of gastrointestinal bleeding. This is particularly important because, as stated earlier, clinical use of dabigatran has been reported to be associated with a significant risk of life-threatening gastrointestinal bleeding, such as a case report of fatal rectal bleeding.[37] Additionally, a recent pooled analysis of phase 3 trials compared the use of the three new oral anticoagulants (dabigatran, rivaroxaban, and apixaban) with enoxaparin for thromboprophylaxis after total hip or total knee replacement. The result showed that these new oral anticoagulants were more efficacious than enoxaparin in preventing venous thromboembolism after total hip or total knee replacement with similar bleeding risk. In addition, apixaban had the lowest clinically relevant bleeding risk (relative risk 0.81) among the three new oral anticoagulants.[38]

If apixaban use is indeed associated with a lower rate of gastrointestinal bleeding in clinical practice, it is likely to become the preferred agent.

Summary

Atrial fibrillation is the most common arrhythmia encountered in clinical practice and it is associated with significant adverse clinical outcomes, especially cardioembolic strokes. Although therapeutic anticoagulation with warfarin has been the standard therapy for stroke prophylaxis, it has been underutilized because of its narrow therapeutic window, significant drug-to-drug and drug-to-food interactions, need for frequent monitoring, and bleeding complications. There has been an ongoing search for newer and better oral anticoagulants for stroke prophylaxis in AF. The research during the last decades has led to the recent introduction of two new oral anticoagulants (dabigatran and rivaroxaban) in clinical practice. Apixaban is the newest oral direct FXa inhibitor which has been extensively studied for its use in stroke prophylaxis in the recently completed AVERROES and ARISTOTLE trials. The results of these trials have shown that treatment with apixaban is noninferior to warfarin in preventing stroke and systemic embolic events. Additionally, apixaban was associated with significantly fewer bleeding events especially intracranial hemorrhage. Compared with dabigatran and rivaroxaban, apixaban showed a reduced risk of gastrointestinal bleeding. The net clinical benefit observed during treatment with apixaban was also statistically superior to treatment with warfarin. If apixaban is approved by the FDA (currently under review) for clinical use for stroke prophylaxis, it will certainly add to the therapeutic armory clinicians have in fighting against the

cardioembolic strokes secondary to nonvalvular AF in clinical practice.

Disclosure

The authors report no conflicts of interest in this work.

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