

APIXABAN IN THE PREVENTION OF STROKE AND SYSTEMIC EMBOLISM IN NONVALVULAR ATRIAL FIBRILLATION

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SUMMARY

Conventional anticoagulant therapies can significantly reduce the risk of stroke and related complications in patients with atrial fibrillation (AF). Classic oral anticoagulants based on vitamin K antagonism have shown effectiveness in the prevention of thromboembolic complications in this clinical setting. Unfortunately, vitamin K antagonists that have shown effectiveness in the prevention of thromboembolic complications in patients with

nonvalvular AF hold inherent limitations including delayed onset of action, narrow therapeutic index, variability of their response, need for repeated control and numerous interactions with food and other drugs. Since the frequency of stroke related to AF increases with age, guidelines from different scientific societies advise that the risk of bleeding for a patient should be quantified before exposure to anticoagulation and balanced against the risk of stroke with and without anticoagulation. A consequence of assessing this risk/benefit balance is that not all patients with AF at thromboembolic risk receive adequate anticoagulant treatment. Apixaban is a new oral anticoagulant with a direct, specific and reversible inhibitory action on coagulation factor Xa and with demonstrated safety and

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efficacy in the prophylaxis and treatment of venous thromboembolism in several clinical studies involving thousands of patients subjected to major orthopedic surgery. Results of two large phase III trials have demonstrated the efficacy and safety of apixaban compared with aspirin or warfarin, in the prevention of stroke in patients with AF. Apixaban demonstrated superiority over classic vitamin K antagonists on the previously specified outcomes of stroke, systemic embolism, major bleeding and death. For those patients unsuitable for treatment with vitamin K antagonists because of an excessive bleeding risk, apixaban showed more efficacy than aspirin in stroke prevention with a not statistically significant modest increase of major bleeding.

Key words: Apixaban – Stroke – Atrial fibrillation – Coagulation factor Xa inhibitors – Anticoagulants

BACKGROUND

Atrial fibrillation (AF) is the most prevalent arrhythmia. More than 7 million people in the U.S. and E.U. may be affected by some type of arrhythmia and the prevalence of this pathology continues to augment as the life expectancy continues to increase in developed countries (1). The prevalence of AF increases dramatically with age. Ten percent of the population ≥ 80 years can suffer from AF (2). Stroke is the main thromboembolic complication of AF. Patients with AF have a 2- to 7-fold risk of ischemic stroke, with 2-fold increases in mortality and with a subsequent risk of disabling cognitive impairment (3). Stroke due to AF is more disabling than stroke due to other causes and has a higher recurrence rate. From 15% to 30% of individuals who survive a stroke are permanently disabled (4). It is agreed that the world faces a growing epidemic of AF and related stroke (3, 5).

Thromboembolic complications in AF are the result of a hypercoagulable condition developing in the heart atrium. Dimensions of the atrium, disruption of the normal blood circulation leading to a turbulent flow and alterations in the atrial wall have been involved in the thrombogenesis in AF (6). Congenital and acquired alterations in coagulation mechanisms or deficient regulation by natural anticoagulants may further contribute to the development of a procoagulant environment (7). The coagulation pathway is definitely involved in the formation of venous, arterial or atrial thrombi. In the modern cell-based model of hemostasis, coagulation is initiated through the tissue factor/coagulation factor IIa (TF/FVIIa) complex on the surface of a TF-bearing cell and involves three integrated phases: initiation, amplifi-

cation and propagation (8). Factor Xa (FXa) will play a prevalent role in the initiation and propagation phases during the cell-based activation of the coagulation. Inhibition of the coagulation steps contributed by FXa has proved a very efficient mechanism to modulate excessive thrombin generation (9). Inhibition of FXa during the initiation step reduces the initial generation of thrombin through the activation of the FXa–FVa complex on the cell surface. Moreover, inhibition of FXa during the propagation step prevents thrombin generation produced through the assembly of the prothrombinase complex (FVa–FXa and calcium).

Prevention of stroke is the key goal in AF treatment. Overwhelming clinical experience demonstrates that the risk of stroke due to AF can be reduced by two-thirds with effective anticoagulation (3). Oral anticoagulation based on vitamin K antagonists has proven efficacious in the prevention of stroke due to AF although their major drawbacks include their narrow therapeutic window, the large inter- and intraindividual variability in dose response, a slow onset and offset of action, the need for monitoring and extensive food and drug interactions (10). New strategies with more specific mechanisms of action, wider therapeutic range and with lesser pharmacological interactions are needed to optimize the prevention of the fatal or disabling embolic ischemic stroke caused by AF (11-13).

Inhibition of FXa is an efficient way of preventing thrombin generation at both the initiation and propagation steps of the coagulation mechanisms. Apixaban is a new oral anticoagulant with a direct and specific inhibitory action on FXa and with demonstrated safety and efficacy in the prophylaxis and treatment of venous thromboembolism (VTE) in several clinical trials involving thousands of patients. This review will provide an update on basic information on the pharmacology and pharmacokinetics of apixaban, and will attempt to put into perspective the results of recent clinical trials that have comparatively evaluated the antithrombotic potential of apixaban versus standard antithrombotic treatments in patients with nonvalvular AF.

CHEMISTRY

Apixaban (BMS-562247, PM-460) is a direct selective and reversible inhibitor of FXa (Fig. 1). Apixaban binds to the active site on FXa with an elevated affinity ($K_i = 0.08$ nM) and exerts its anticoagulant and antithrombotic mechanisms independently of antithrombin (14). Apixaban is a direct drug that does not require previous

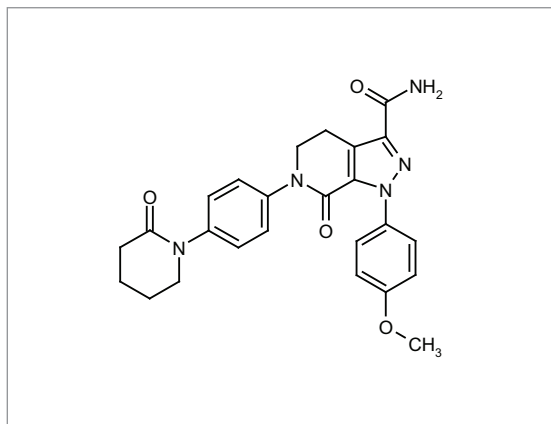


Figure 1. Chemical structure of apixaban.

biotransformation to become active. Synthesis of apixaban has been described in detail (15).

PRECLINICAL PHARMACOLOGY

The *in vitro* anticoagulant action of apixaban has been investigated in plasma from rats, rabbits, dogs and chimpanzees. Apixaban effectively prolongs prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT) and Hep-test (16, 17). The ability of apixaban to inhibit FXa or modify coagulation tests varies among different species. Concentrations required to double PT and APTT in the rat are 7.9 and 20 μM , respectively. Concentrations of apixaban from 3.6 to 7.4 μM added *in vitro* to human plasma are capable of doubling PT and APTT values. Apixaban inhibits thrombin generation in human plasma with a dose–effect relationship from 5 to 400 nM with an IC_{50} ranging from 70 to 100 nM (18).

The antithrombotic action of apixaban has been demonstrated in various experimental models. In rats, apixaban inhibits thrombus formation in arterial and venous vascular territories with an ED_{50} equivalent to 0.72 or 1.55 mg/kg/h, respectively. Apixaban has demonstrated antithrombotic action in a model of arteriovenous shunt in rabbits (16). In an experimental model of venous thrombosis in rabbits, concentrations of apixaban equivalent to 65 nM reduced the size of the original thrombus by up to a 50%, without significant prolongations in bleeding times (19). The antithrombotic activity shown in the previous models followed alterations in routine coagulation tests (APTT, TT and PT).

A favorable therapeutic index was observed for apixaban in comparative studies with thrombin inhibitors in a venous thrombosis model in rabbits (19). Similar antithrombotic efficacy was observed between apixaban, rivaroxaban and dabigatran in the prevention and treatment of venous thrombosis in a rabbit model. Animals treated with apixaban or rivaroxaban exhibited shorter bleeding times compared with dabigatran at equivalent antithrombotic doses. Apixaban has shown a significant potency to inhibit clot-bound FXa activity (20). Apixaban inhibits platelet aggregation induced by tissue factor. Aggregation of platelets by tissue factor is triggered by the thrombin generated during the interaction of tissue factor with FVIIa and FXa on the surface of platelets. The inhibitory action of apixaban in this experimental setting was similar to that of other specific inhibitors of FVIIa or FIIa (21).

Although new oral anticoagulants have been designed to avoid the need for repeated controls required with classic anticoagulant therapy based on vitamin K antagonism, laboratory assessment of new anticoagulants may be occasionally requested (22). Unlike vitamin K antagonists, apixaban does not need repeated adjustments of the doses. If necessary, the anticoagulant effect of apixaban can be occasionally measured even at very low plasma concentrations using a standard laboratory chromogenic anti-Xa assay with either low-molecular-weight heparin (LMWH) or apixaban calibrators (23).

The lack of specific antidotes to reverse the alterations of hemostasis induced by new oral anticoagulants in case of emergencies is a matter of concern. Recent studies using an *in vitro* model of thrombosis with circulating human blood suggest that prothrombin complex concentrates or rFVIIa could effectively reverse the anti-hemostatic action of apixaban (24).

PHARMACOKINETICS AND METABOLISM

After oral administration, 50–66% of apixaban is absorbed through the stomach and small intestine. Apixaban was found the major circulating component in plasma and *O*-demethyl apixaban sulfate was the most significant metabolite. The administered dose is recovered in feces and urine with the parent drug representing approximately half of the recovered dose. Biliary excretion represented a minor elimination pathway. Metabolic pathways identified for apixaban included *O*-demethylation, hydroxylation and sulfation of hydroxylated *O*-demethyl apixaban (25, 26).

Maximal concentration (C_{max}) is reached from 1 to 3 hours after oral administration. After single oral dose of 5 mg, the C_{max} reached is equivalent to 104 ng/mL (27). A total of 87% of the administered apixaban is found bound to proteins. As in previous studies in experimental animals, dose-dependent elevations in plasma levels of apixaban corresponded with prolongations of APTT and PT. After oral administration of multiple doses of apixaban, concentrations increased slightly above the levels observed after single administration, with an accumulation factor of 1.3 to 1.9 (28). The C_{max} for the dose of 5 mg/12 hours is slightly increased compared to the 10-mg dose in a single administration. Apixaban concentration reaches steady state after 3 days, with a half-life of about 9-14 hours.

Apixaban is oxidized through mechanisms dependent on CYP3A4 with minor contributions from a CYP2J2 and CYP1A2 isozymes. The potential of apixaban to inhibit or induce CYP or to generate active metabolites is minimal. Apixaban is a substrate of both CYP3A4 and P-glycoprotein (P-gp). Inhibitors of CYP3A4 and P-gp would increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of thrombosis (29). Therefore, administration of apixaban is not recommended for patients receiving concomitant systemic treatment with potent inhibitors of CYP3A4 or P-gp, such as ketoconazole, itraconazole, voriconazole and posaconazole, or ritonavir (30). These drugs may double the total exposure to apixaban. The exposure to apixaban could be further enhanced in the presence of additional factors that increase circulating levels of apixaban (e.g., renal dysfunction). Coadministration of apixaban with potent inducers of CYP3A4 and P-gp (rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's wort) may cause a reduction of almost 50% in the apixaban levels. Coadministration of apixaban with the latter drugs should be made with reservations (30). Apixaban does not seem to have potential interactions with digoxin, but caution is advised for groups of patients receiving concomitant treatment with nonsteroidal anti-inflammatory drugs, including aspirin. The concomitant use with other inhibitors of platelet aggregation or other antithrombotic agents is not recommended. The efficacy and safety of apixaban versus warfarin was consistent in patients with or without concomitant amiodarone therapy (31).

Elimination of apixaban involves multiple mechanisms including metabolism and biliary and renal excretion of the unmodified drug. Renal clearance accounts for 27% of the total clearance. Food intake did not affect the C_{max}

or AUC of apixaban (27). The intake of foods containing high fat or calorie contents has no effect on the efficacy of apixaban (29). The C_{max} is not affected by mild to moderate renal insufficiency. There is no need for dose adjustment in patients with mild to moderate renal impairment; however, due to the lack of clinical evidence, apixaban is not recommended in patients with creatinine clearance below 15 mL/min or in those with severe hepatic impairment. Apixaban should be used with caution in patients with mild or moderate hepatic impairment (patients with Child-Pugh scores A or B). Table I summarizes the pharmacological and pharmacokinetic features detailed in the previous text.

CLINICAL STUDIES

Venous thromboprophylaxis

Patients subjected to two frequent surgical interventions, such as hip or knee replacement, are at elevated risk of developing thrombotic complications. The protection against thromboembolic complications achieved with LMWHs is perfectly established in these clinical situations. Demonstration of adequate rates of prevention of thrombosis in patients subjected to hip or knee replacement in comparison with the gold standard antithrombotic therapy with LMWH is a proof of concept for any new anticoagulant. Results from preliminary phase II studies on the therapeutic utility index for apixaban indicated that the apixaban dosage regimen with 2.5 mg twice daily (b.i.d.) could provide the highest therapeutic utility index (32).

Three phase III studies evaluated the efficacy and safety of apixaban in the prevention of thrombosis in patients undergoing major orthopedic surgery (Table II). The studies, under the acronym ADVANCE (Apixaban Dose Orally versus Anticoagulation with Enoxaparin), included more than 11,000 patients and the efficacy of oral apixaban at 2.5 mg b.i.d. was compared with that of subcutaneous enoxaparin at 30 mg b.i.d. or 40 mg once a day (33-35). Results of these clinical trials confirmed the efficacy of apixaban versus the standard treatment for the prevention of VTE with enoxaparin (36). In the ADVANCE-1 study, enoxaparin (30 mg b.i.d. as used in the U.S.) or apixaban were initiated 12-24 hours after total knee replacement surgery (33). In this study, apixaban did not reach the criteria for noninferiority for the primary efficacy endpoint compared with enoxaparin, although it showed a lower rate of major and clinically not relevant bleeding complications than enoxaparin. The ADVANCE-2 and ADVANCE-3 studies evaluated the

Table I. Summary of pharmacologic and pharmacokinetic characteristics of apixaban.

Variables	Properties	Ref.
Reference; molecular weight	BMS 562247-01; C ₂₅ H ₂₅ N ₅ O ₄ ; MW 459.49	(15)
Commercial name; licensor	Eliquis®; Bristol-Myers Squibb, Pfizer	(30)
Mechanism of action; specificity	Direct factor Xa inhibition; no prodrug	(18)
Pharmacology	Antithrombotic action in different animal models	(16-18)
Alteration in coagulation tests	TP, TTPA, TTm and Hep-test	(16, 17)
Laboratory measurement	Anti-Xa test with appropriate calibrators	(23)
Thrombin generation inhibition (IC ₅₀)	75-100 µM	(18)
Therapeutic dose	2.5, 5 mg/12 h	(32)
Pharmacokinetics: t _{max} /half-life	1-3 h/9-14 h	(25-27)
Pharmacokinetics: C _{max} at therapeutic doses	100 ng/mL after single therapeutic doses Slightly higher after multiple therapeutic doses	(25-27)
Bioavailability	Half life: 9-14 hours	(25, 26, 32)
Elimination	25% Renal secretion, 50% feces	
Interference with cytochromes and P-gp	CYP3A4 and P-gp	(29)
Strong inducers of CYP3A4 and P-gp will reduced exposure to apixaban (risk of thrombosis)	Rifampin, carbamazepine, phenytoin, phenobarbital, St. John's wort	(29, 30)
Strong inhibitors of CYP3A4 and P-gp will increase the exposure to apixaban (risk of bleeding)	Ketoconazole, itraconazole, ritonavir or clarithromycin	(29, 30)
Reversal of antihemostatic action	PCCs, rFVIIa, aPCCs	(24)

Table II. Summary of clinical trials with apixaban in the prevention of thromboembolic complications.

Aim	Clinical setting and drug comparator	Number of patients	Ref.
Dose selection	Therapeutic utility of apixaban in prevention of venous thromboembolism	Model-based	(32)
Venous thromboprophylaxis after orthopedic surgery	Apixaban vs. enoxaparin knee replacement (ADVANCE 1)	3,195	(33)
	Apixaban vs. enoxaparin: knee replacement, (ADVANCE-2)	3,057	(34, 35)
	Apixaban vs. enoxaparin: hip replacement (ADVANCE-3)	3,866	(34, 35)
Prevention of thromboembolic complications in patients with atrial fibrillation	Apixaban vs. aspirin (ASA): atrial fibrillation (AVERROES)	5,599	(39)
	Apixaban vs. warfarin: atrial fibrillation (ARISTOTLE)	18,201	(40)

efficacy and safety of apixaban in the prevention of VTE in patients undergoing total knee or hip replacement, respectively. In these studies, apixaban showed noninferiority or even superiority for the primary efficacy endpoint (composite of asymptomatic or symptomatic deep

vein thrombosis, nonfatal pulmonary embolism and all-cause mortality), and superiority for the secondary endpoint of prevention of major VTE (34, 35). Bleeding complications observed in the previous studies were similar for both apixaban and enoxaparin.

Stroke related to atrial fibrillation

The major risk factors for stroke in individuals with AF are previous stroke, advanced age, history of hypertension, systolic blood pressure > 160 mmHg and diabetes. The risk of AF-related stroke can be estimated with the CHADS₂ (including Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, prior Stroke or transient ischemic attack [TIA] or thromboembolism) or CHA₂DS₂VASc (CHA₂DS₂ score plus Vascular disease, Age 65-74, Sex category, female) scores that represent on a scale ranging from 1 to 6 or from 1 to 9, respectively, the combined overall impact of the previous factors (3). The implicit bleeding risk from exposure to vitamin K antagonists, the complexity of management and the numerous interactions of classic oral anticoagulants have made it so that not all patients with AF with thromboembolic risk are able to receive anticoagulation treatment (37). Before the introduction of the newer oral anticoagulants, the only alternative to a vitamin K antagonist with a labeled indication for AF was antiplatelet therapy with aspirin, despite the fact that this alternative was less effective than a vitamin K antagonist for prevention of stroke.

The efficacy and safety of oral apixaban for the prevention of stroke in AF was investigated in two large, phase III, double-blind, randomized trials (Table II). The first trial, AVERROES, was designed to address the large unmet need of AF patients at risk of stroke who are unsuitable for or unwilling to take a vitamin K antagonist. Therefore, this trial compared the efficacy of apixaban versus aspirin in patients with AF and at least one risk factor for stroke who have failed or were unsuitable for vitamin K antagonist therapy (37). The second trial, ARISTOTLE wanted to determine whether apixaban was noninferior to warfarin at reducing the combined endpoint of stroke (ischemic or hemorrhagic) and systemic embolism in patients with AF and at least one additional risk factor for stroke (38).

Apixaban versus acetylsalicylic acid in atrial fibrillation: The AVERROES trial

The AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation) trial, was designed to compare the efficacy and safety of apixaban versus aspirin in patients with AF and who, for a variety of reasons, were not candidates for warfarin (39). This double-blind, double-dummy trial enrolled 5,599 patients who were randomized to receive either apixaban 5 mg b.i.d. or aspirin at a dose of 81-324 mg daily.

The primary efficacy endpoint was the occurrence of stroke (ischemic and hemorrhagic) or systemic embolism. Before enrollment, 40% of the patients had used a vitamin K antagonist.

There were 51 primary outcome events in the apixaban patients and 113 among those assigned to aspirin. The rates of death did not differ statistically for both groups (3.5% per year in the apixaban group vs. 4.4% per year in the aspirin group). There were 44 cases of major bleeding in the apixaban group and 39 in the aspirin group; there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin. The risk of a first hospitalization for cardiovascular causes was significantly reduced with apixaban as compared with aspirin (Table III). As will be commented further in the text, treatment effects were consistent among important subgroups. In summary, in patients with AF for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial bleeding. The data and safety monitoring board recommended early termination of the study because of a clear benefit in favor of apixaban.

Apixaban versus warfarin in atrial fibrillation: The ARISTOTLE trial

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, apixaban was compared with warfarin for the prevention of stroke or systemic embolism in patients with AF and at least one additional risk factor for stroke (40). It was a double-blind, double-dummy design, where apixaban 5 mg b.i.d. was compared with warfarin (target international normalized ratio: 2.0 to 3.0) in 18,201 patients. The trial was designed to test the noninferiority of apixaban to warfarin in reducing the rate of ischemic or hemorrhagic stroke or systemic embolism; with key secondary endpoints of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

As summarized in Table IV, a significant reduction was observed for the primary efficacy outcome, a composite of ischemic or hemorrhagic stroke or systemic embolism, compared with warfarin (1.27% per year vs. 1.60% per year; hazard ratio [HR] with apixaban: 0.79; 95% confidence interval [CI]: 0.66 to 0.95; $P < 0.001$ for noninferiority, $P = 0.01$ for superiority). In addition, the rate of major bleeding episodes occurred in 2.13% of patients who received apixaban and 3.09% of patients who

Table III. Efficacy and safety outcomes in the AVERROES trial (39).

Outcome	Apixaban (N = 2,808)		Aspirin (N = 2,791)		HR with apixaban (95% CI)	P value
	No. of patients with first event	Event rate (%/year)	No. of patients with first event	Event rate (%/year)		
Stroke or systemic embolism	51	1.6	113	3.7	0.45 (0.32-0.62)	< 0.001
Stroke	49	1.6	105	3.4	0.46 (0.33-0.65)	< 0.001
Ischemic	35	1.1	93	3	0.37 (0.25-0.55)	< 0.001
Hemorrhagic	6	0.2	9	0.3	0.67 (0.24-1.88)	0.45
Death from any cause	111	3.5	140	4.4	0.79 (0.62-1.02)	0.07
Major bleeding	44	1.4	39	1.2	1.13 (0.74-1.75)	0.57
Intracranial	11	0.4	13	0.4	0.85 (0.38-1.90)	0.69
Gastrointestinal	12	0.4	14	0.4	0.86 (0.40-1.86)	0.71

HR, hazard ratio; CI, confidence interval.

received warfarin (HR: 0.69; 95% CI: 0.60 to 0.80; $P < 0.001$). An important finding of the ARISTOTLE study was the significant reduction in the rates of hemorrhagic stroke complications. These results indicate that treatment with apixaban could result in almost a 50% reduction in the development of one of the most serious side effects observed with the current vitamin K antagonist strategies for the prevention of thromboembolic events in patients with AF. Further analysis of the results revealed that in comparison with warfarin, apixaban was associated with small, but significant reductions in the

likelihood of hospitalization in patients with AF. For every 1,000 patients treated with apixaban instead of warfarin, 13 patients avoided hospitalization an average of 1.5 times during the study (41).

The ARISTOTLE study concluded that apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding and resulted in lower mortality in patients with AF (40). An indirect conclusion of the previously mentioned trial is that treatment with apixaban offers additional benefit for patients with high thromboembolic risk according to the CHADS₂ score.

Table IV. Efficacy and safety outcomes in the ARISTOTLE trial (40).

Outcome	Apixaban (N = 9,120)		Warfarin (N = 9,081)		HR with apixaban (95% CI)	P value
	No. of patients with first event	Event rate (%/year)	No. of patients with first event	Event rate (%/year)		
Stroke or systemic embolism	212	1.27	265	1.6	0.79 (0.66-0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65-0.95)	0.01
Ischemic	162	0.97	175	1.05	0.92 (0.74-1.13)	0.42
Hemorrhagic	40	0.24	78	0.47	0.51 (0.35-0.75)	< 0.001
Death from any cause	603	3.52	669	3.94	0.89 (0.80-0.998)	0.047
Major bleeding	327	2.13	462	3.09	0.69 (0.60-0.80)	< 0.001
Intracranial	52	0.33	122	0.8	0.42 (0.30-0.58)	< 0.001
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70-1.15)	0.37

HR, hazard ratio; CI, confidence interval.

Apixaban was approved by the U.S. Food and Drug Administration (FDA), and the European Medicines Agency (EMA) for nonvalvular AF in 2012 based on the results of the ARISTOTLE trial (42, 43).

Efficacy and safety of apixaban in subgroups of patients with impaired renal function, previous stroke or bleeding risk

Chronic kidney disease (CKD) affects up to 10% of the adult population (44) and carries a high risk for the development of AF (45). In a large population-based study, the HR for the development of AF was doubled for the group of patients with moderate CKD compared with patients with normal renal function independent from other known risk factors for AF (46). Despite this evident increased risk for AF-associated thromboembolism, many patients with renal dysfunction are not receiving oral anticoagulation therapy (47), mostly because of bleeding risk associated with warfarin use (48).

Despite of the absence of significant subgroup interactions, secondary analysis of the AVERROES and ARISTOTLE trials were conducted to evaluate the efficacy and safety across different subgroups of patients according to their impaired renal function, the risk of stroke or their specific risk of bleeding (49, 50). The AVERROES trial included 1,697 (30%) patients with stage III CKD, showing mean glomerular filtration rates (GFRs) of 49 mL/min/1.73 m², which was an independent predictor of primary events (HR: 1.6; *P* = 0.01) and major hemorrhage (HR: 2.2; *P* = 0.02). These patients were older (mean age 75 vs. 68 years) and had more frequent hypertension, diabetes, heart failure and previous stroke (all *P* < 0.01) in comparison with patients with normal renal function (estimated GFRs ≥ 60 mL/min/1.73 m²). The efficacy of apixaban was consistent across these subgroups, with a significant reduction of primary events by 68% (1.8% per year on apixaban vs. 5.6% per year on aspirin; *P* < 0.001) for stage III CKD patients and by 43% (1.6% per year on apixaban vs. 2.8% per year on aspirin; *P* = 0.009) for patients with normal renal function. Treatment with apixaban was associated with a nonsignificant difference in major hemorrhage for patients with stage III CKD (2.5% per year with apixaban vs. 2.2% per year with aspirin). Results were similar in a secondary analysis of the ARISTOTLE trial (50). This study included 7,518 patients (42%) with an estimated GFR of > 80 mL/min, 7,587 (42%) patients with an estimated GFR between > 50 and 80 mL/min, and 3,017 (15%) patients with an estimated GFR of ≤ 50 mL/min. Patients with impaired renal function (≤ 80 mL/min) had a higher rate of car-

diovascular events and bleeding. Compared with warfarin, the incidence of stroke or systemic embolism, major bleeding and mortality was significantly decreased in patients who received apixaban irrespective of renal function. In fact, the risk reduction in major bleeding was greater in patients with an estimated GFR of ≤ 50 mL/min (*P* = 0.005).

It is well established that patients with AF and previous stroke or TIA have a high risk of stroke. To confirm this assumption and to compare the efficacy of apixaban in patients with and without previous stroke or TIA, a pre-specified AVERROES subgroup analysis was performed (51). In patients with previous stroke or TIA, 2.39% events of stroke or systemic embolism per year occurred in the apixaban group compared with 9.16% in the aspirin group (HR: 0.29; 95% CI: 0.15-0.60). Additionally, major bleeding was more frequent in patients with a history of stroke or TIA than in patients without (HR: 2.88; 95% CI: 1.77-4.55) but risk for this event did not differ between treatment groups.

In the ARISTOTLE subgroup analysis of patients with previous stroke or TIA, the incidence of stroke or systemic embolism was 2.46 per 100 patient-years in the apixaban group and 3.24 in the warfarin group (HR: 0.76; 95% CI: 0.56 to 1.03) (52). However, differences did not reach levels of statistical significance in patients without previous stroke or TIA (1.01 per 100 patient-years with apixaban and 1.23 with warfarin; HR: 0.82; 95% CI: 0.65-1.03). Thus, the absolute reduction in the rate of stroke and systemic embolism with apixaban in comparison with warfarin was 0.77 per 100 patient-years (95% CI: -0.08 to 1.63) in patients with previous stroke or TIA and 0.22 (95% CI: -0.03 to 0.47) in those without previous stroke or TIA. The incidence of major bleeding was similar in patients with and without a previous history of stroke or TIA according to received treatment (1.07 per 100 patient-years with apixaban [95% CI: 0.09-2.04] vs. 0.93 with warfarin [95% CI 0.54-1.32]). The investigators concluded that apixaban was particularly effective for patients with previous stroke or TIA.

Treatment with anticoagulants increases the risk of bleeding for the exposed population of patients. The bleeding risk assumed with anticoagulants should be balanced with respect to the underlying risk of stroke in the absence of treatment (53). The risk of stroke can be evaluated through the CHADS₂ scores. A similar score evaluation has been applied to evaluate the risk of bleeding. Thus, the HAS-BLED score (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding

History or Predisposition, Labile INR, Elderly, Drugs or alcohol) has been validated for cohorts of patients subjected to anticoagulant treatments. A HAS-BLED score of more than 3 identifies patients with AF at high bleeding risk (54). In a subanalysis of the AVERROES trial, apixaban was found to reduce stroke with comparable bleeding risks when compared with aspirin (55). Therefore, the rates of both stroke and bleeding increased with higher CHADS₂ scores, but apixaban compared with aspirin was associated with a similar risk of anatomic site of bleeding and a reduced relative risk of stroke. Lip et al. performed a secondary analysis of the AVERROES trial to confirm that there were no significant heterogeneities in the risk of bleeding between treated groups (56). Outcomes were consistent regardless of baseline risk. Apixaban was superior to aspirin for stroke prevention in AF population, with similar rates of major bleeding, in the presence of one or more stroke risk factors, with consistency of the treatment effect by CHADS₂/CHA₂DS₂-VASc scores. A secondary analysis of the ARISTOTLE confirmed that the relative risk reduction in intracranial bleeding tended to be greater in patients with HAS-BLED scores of 3 or higher (HR: 0.22; 95% CI: 0.10-0.48) than in those with HAS-BLED scores of 0-1 (HR: 0.66; 95% CI: 0.39-1.12; *P* for interaction = 0.0604) (57). Therefore, apixaban has benefits compared with warfarin that are consistent across patient risk of stroke and bleeding as assessed by the CHADS₂, CHA₂DS₂-VASc, and HAS-BLED scores.

CONCLUSIONS

AF and related thrombotic complications are important contributors to mortality and morbidity in our societies and represent a major health concern. The steadily rising prevalence and incidence of AF is bound to contribute to a progressive increase in the social and economic burden of stroke and related disabilities. Apixaban is a new oral anticoagulant with a direct, specific and reversible inhibitory action on FXa. Apixaban offers several advantages over classic vitamin K antagonists: effects are reliable at adjusted doses, repeated controls are unnecessary and its reduced half-life predicts a relatively rapid recovery of coagulation mechanisms after the treatment is discontinued. In addition, apixaban shows fewer interactions with food or other drugs and its metabolism seems to be less dependent on cytochrome-related polymorphisms. Apixaban has demonstrated safety and efficacy in the prophylaxis and treatment of VTE, and in the prevention of thromboembolic complications in patients with AF in several clinical studies involving

thousands of patients. Based on the results of the ARISTOTLE studies, the FDA and EMA have recently approved apixaban for the prevention of thromboembolic complications in patients with AF (42, 43). Two phase III clinical trials have investigated the efficacy and safety of apixaban for the acute and extended treatment of VTE (58, 59). Based on the results of these trials, the licensing company may plan to initiate regulatory filings for the approval of new indications on acute and long-term treatment of VTE, as well as for extended prevention of recurrent VTE.

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