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REVIEW

Safety and Efficacy of Apixaban in the Treatment of Atrial Fibrillation

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Abstract: Atrial fibrillation is a common arrhythmia that increases the risk of stroke and systemic embolism. Warfarin is a highly effective treatment in reducing this risk, but a narrow therapeutic range, drug and food interactions, required monitoring, and bleeding limit its use. We review Apixaban, an oral inhibitor of Factor Xa, which has been shown in large randomized trials to have superior efficacy in stroke reduction without an excess in bleeding events when compared with aspirin in those deemed unsuitable to receive warfarin, and demonstrates superior efficacy in reducing stroke and systemic embolism in addition to a reduction in bleeding events when compared to warfarin.

Keywords: apixaban, atrial fibrillation, stroke, systemic embolism

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Introduction

Atrial fibrillation (AF) is a heart rhythm disorder characterised by fast irregular atrial depolarisation. It is associated with an excess risk of stroke and systemic embolisation which is at least in part attributable to thrombus formation within the left atrium. Warfarin is highly efficacous in reducing the incidence in systemic thrombo-embolism, but its use is limited by the narrow therapeutic range, the need for monitoring, and food and drug interactions. Studies evaluating the efficacy of warfarin compared with placebo demonstrate a 62% (95% confidence interval [CI] 48%–72%) relative risk reduction of stroke and systemic embolisation.[1] In comparison aspirin is less efective, with a relative risk reduction of stroke and systemic embolisation compared to placebo of 22% (95% CI 2%–38%).[1] The combination of aspirin and clopidogrel results in an excess of stroke and systemic embolisation when compared with warfarin (5.6% vs. 3.9% per year, $P = 0.0003$).[2] Apixaban is a new oral anticoagulant (OAC) which can be used to reduce the risk of embolic events in pateints with AF. This article reviews the clinical pharmacology, clinical trial data, efficacy, and adverse effects of apixaban.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile

Apixaban is an orally active small molecule reversible inhibitor of Factor Xa[3,4] (FXa), thus inhibiting thrombin and trypsin. It inhibits both free FXa and FXa bound within the prothrombinase complex or associated with a clot.[5]

Apixaban produces concentration dependent increases in the activated partial thromboplastin time (aPTT), and prothrombin time (PT).[6] In healthy volunteers, dose-proportional increases in clotting times are observed. After administration of a total daily dose of 50 mg for 7 days the aPTT, PT, and international normalised ratio (INR) increased by 1.2, 3, and 1.5 fold respectively.[7] The dose response effect results in a predictable degree of anticoagulation. Effects on the clotting cascade can be evaluated using either an FXa inhibition assay or the PT,[4] but monitoring is not usually required.

Apixaban is rapidly absorbed, reaching peak plasma concentration 1–3 hours following administration with an absolute bioavailability of 66%.[8] After multiple doses of apixaban there is only mild accumulation once steady state concentrations are reached on day 3.[9,10] Discontinuation of apixaban results in an initial rapid decline in plasma concentration followed by a more gradual terminal phase, with a mean elimination half-life of 8–15 hours in healthy subjects.[10,11] Apixaban is typically administered twice daily.

Apixaban undergoes oxidative metabolism, predominantly via the cytochrome P_{450} (CYP) 3A4 enzyme.[12] The most prominent metabolite is O-demethyl apixaban sulphate.[10] There is minimal potential for apixaban to inhibit or induce CYP, or to form reactive metabolites. Apixaban does not inhibit CYP1A2, 2C8, 2C9, 2C19, 2D6, or 3A4, nor does it induce CYP1A2, 2B6, or 3A4,[4] and the potential for drug-drug interactions is low. Apixaban and its metabolites are excreted by multiple elimination pathways.[10] Approximately 25% of the drug and its metabolites are excreted by the kidneys, with the remainder via the faecal route.[10]

There is currently no antidote available to reverse the effects of apixaban in the event of overdose or major bleeding. Prothrombin complex concentrate has demonstrated efficacy for reversing FXa inhibition in rats[13] and in healthy human subjects.[14] Whilst further clinical evaluation is required, this agent may represent a therapeutic option for reversal of FXa inhibition. Until such an agent is clinically proven, and given apixaban's short elimination half life, a supportive approach is recommended in the setting of overdose or major bleeding.

Clinical Trials, Safety, and Efficacy

Two large event driven trials have evaluated apixaban in patients with AF. The AVERROES[15] (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study evaluated the use of apixaban in patients with AF who were either not suitable for warfarin or not willing to take it. The ARISTOTLE[16] (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) study evaluated the use of apixaban compared to warfarin in patients with AF at high risk of stroke and systemic embolism.

AVERROES[15]

AVERROES was a double blind placebo controlled randomised trial of 5599 patients with AF in whom

warfarin therapy was deemed to be unsuitable. Participants were randomised in a 1:1 fashion to receive either apixaban or aspirin (at a dose of 84–324 mg at the discretion of the treating clinician). The standard apixaban dose was 5 mg twice daily. A reduced dose of apixaban of 2.5 mg twice daily was used if the participatant was aged >80 years, weighed <60 kg, or if the serum creatinine was >133 umol/L.

Participtants were included if aged >50 years and had an electrocardiogram (ECG) within 6 months prior to enrolment documenting AF, and at least one of: prior stroke or transient ischaemic attack (TIA), hypertension, age >75, diabetes, NYHA > 2, left ventricular ejection fraction (LVEF) < 35%, or peripheral vascular disease (PVD). In addition, patients could not be eligible to receive warfarin either because it had already been demonstrated to be unsuitable or was expected to be unsuitable. The most common reason for warfarin unsuitability was an assessment that the INR could not or was not likely to be measured at requested intervals (46% of participants), though approximately half of participants had multiple reasons for unsuitability. Subjects were excluded from the study for conditions other than AF for which long-term warfarin therapy was indicated, valvular disease requiring surgery, a serious bleeding event in the previous 6 months or a high risk of bleeding.

Prospective statistical analysis estimated that 5600 participants and 226 primary events would have 90% power to detect a relative risk reduction of 35%. The primary efficacy outcome was stroke or systemic embolism. Due to an excess of primary efficacy end points being met in the aspirin group the study was terminated early with mean follow-up of 1.1 years.

The primary safety outcome was major bleeding according to the International Society of Thrombosis and Haemostasis (ISTH) definition, defined as a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding.[17]

The rate of stroke or systemic embolism was significantly lower at 1.6% per year among those assigned to apixaban compared with 3.7% per year among those assigned to aspirin (95% CI 0.32–0.62, $P < 0.001$). The corresponding rates of ischemic stroke were 1.1% per year and 3.0% per year (95% CI 0.25–0.55, $P < 0.001$). The rate of major bleeding was 1.4% per year among those taking apixaban and 1.2% per year among those taking aspirin (95% CI 0.74–1.75, $P = 0.57$). There were a total of 6 cases of intracranial haemorrhage among patients receiving apixaban and 9 among those receiving aspirin. A key secondary endpoint was the rate of death, which was 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (95% CI 0.62–2.02, $P = 0.07$).

ARISTOTLE[16]

ARISTOTLE was a double blind placebo controlled randomised trial of 18201 warfarin eligible patients with AF. Participants were randomised 1:1 to either apixaban or warfarin (in a dose adjusted fashion to achieve an INR of 2.0–3.0). The apixaban dose was 5 mg twice daily, unless the participatant was aged >80 years, weighed < 60 kg, or if the serum creatinine was > 133 umol/L, in which case dosing of apixaban was 2.5 mg twice daily.

Participants were included if they had AF or atrial flutter documented by ECG at enrollment or if this had been documented twice over the prior 12 months. In addition subjects had to have at least one of the following thromboembolic risk factors: prior stroke, transient ischaemic attack (TIA), systemic embolism, hypertension requiring pharmacological therapy, age >75, diabetes, symptomatic heart failure within the previous 3 months, or left ventricular ejection fraction (LVEF) < 40%. Key exclusion criteria were AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF that required warfarin therapy, stroke within the previous 7 days, a need for aspirin at a dose of >165 mg a day or need for both aspirin and clopidogrel, and serum creatinine > 221 umol/L.

Prospective statistical analysis calculated that in order to prove non-inferiority 18000 participants would be required and 448 primary events observed over a 2 year period to provide a power of 90% to ensure that the upper limit of the 95% confidence interval for relative risk would be less than 1.38. The primary efficacy outcome was stroke or systemic embolism, and the primary safety outcome was major bleeding using the ISTH definition described above.[17]

For subjects randomized to warfarin the INR was between 2.0–3.0 for 66% of the study duration.

The primary efficacy outcome was significantly lower at 1.27% per year among those assigned to apixaban compared with 1.60% per year among those assigned to warfarin (95% CI 0.66–0.95, $P < 0.001$ for non-inferiority and $P = 0.01$ for superiority). The corresponding rates of ischemic stroke were 0.97% per year and 1.05% per year (95% CI 0.74–1.13, $P = 0.42$). The rate of major bleeding was lower in those treated with apixaban, at 2.03% per year compared to 3.09% per year among those taking warfarin (95% CI 0.60–0.80, $P < 0.001$). The rate of intracranial haemorrhage was lower in the apixaban group at 0.24% per year compared to 0.47% per year among those taking warfarin (95% CI 0.35–0.75, $P < 0.001$). A key pre-specified secondary endpoint was death from any cause. This was lower in the apixaban group at 3.52% per year compared to 3.94% per year in the warfarin group (95% CI 0.80–0.99, $P = 0.047$).

Patient Preference

While warfarin is an effective treatment in reducing the incidence of stroke and systemic embolism, a narrow therapeutic range, food and drug interactions, monitoring with blood tests, and risk of bleeding limit its use. These limitations result in patients spending approximately half the time with a therapeutic INR, and under-utilisation of warfarin.[18–20] While the requirement for INR testing can be a barrier to warfarin therapy, this interaction with health care services may enhance medication adherance. Due to the study design of AVERROES[15] and ARISTOTLE[16] these issues were unable to be formally evaluated in these trials. Adherance to apixaban may also be adversely effected by its twice daily dose regime, which is the same as dabigatran, and compares to once daily dosing of rivaroxaban and warfarin.

In the AVERROES[15] trial, at 2 years, the rates of permanent discontinuation of the study medication were 17.9% per year in the apixaban group and 20.5% per year in the aspirin group (95% CI 0.78–0.99; $P = 0.03$). In the ARISTOTLE[16] trial fewer patients in the apixaban group discontinued the study medication before the end of the study than in the warfarin group, 25.3% of the patients in the apixaban group versus 27.5% of patients in the warfarin group ($P = 0.001$).

There does not appear to be any significant non-bleeding adverse drug effects with apixaban therapy. Non-bleeding adverse drug effects occurred at a similar rate in those receiving apixaban compared with warfarin in the ARISTOTLE[16] study (81.5% versus 83.1%), and compared with aspirin in the AVERROES[15] study. This finding is similar to the FXa inhibitor rivaroxaban in the ROCKET AF[21] study. In contrast, in the RE-LY[22] study, there was a statistically higher incidence of dyspepsia and a numerically greater number of myocardial infarctions (though this difference was not statistically significant) on dabigatran compared to warfarin (Table 1). Rates of abnormal liver function tests were similar between the groups in both the AVERROES[15] and the ARISTOTLE[16] study.

The limitations associated with warfarin therapy, together with the safety and efficacy compared with aspirin and with warfarin, and lower rates of apixaban discontinuation in these studies make this an attractive alternative to both aspirin and warfarin. These benefits need to be further examined in the context of healthcare economics.

Clinical Role of Apixaban

The choice of oral anticoagulant in patients with AF has increased significantly with evidence for apixaban (AVERROES[15] and ARISTOTLE[16]), following on from evidence for dabigatran (RE-LY[22]) and rivaroxaban (ROCKET AF[21]) (Table 1). Because of differences in study design, patient population, and statistical power, the benefits and risks of these agents can not be relibly compared across trials. With this limitation in mind, it is reasonable to draw several conclusions. All three of these agents when compared with warfarin, significantly reduce the risk of hemorrhagic stroke. In all of these studies the reduction in the primary efficacy end point (which included hemorrhagic as well as ischemic stroke) was influenced by this reduction in the risk of hemorrhagic stroke (Fig. 1). Of the three drugs, only dabigatran (at a dose of 150 mg twice daily) significantly reduced the risk of ischemic stroke compared with warfarin, whilst apixaban and rivaroxaban were non-inferior. The rate of ISTH defined major bleeding[17] was reduced with each of the three drugs, as compared with warfarin (Fig. 2), but bleeding remains the major adverse effect of all treatments.

Apixaban is the first of the newer anticoagulants to show a statistically significant reduction in the risk of all cause mortality compared with warfarin.

Table 1. Factor Xa and direct thrombin inhibitors used in clinical trials for prevention of stroke or systemic embolisation in patients with atral fibrillation and clinical risk factors for stroke.

	Apixaban		**Dabigatran**		**Rivaroxaban**
Action	Factor Xa inhibitor		Direct thrombin inhibitor		Factor Xa inhibitor
Excretion	Hepatic, biliary, and renal (~25%)		Predominantly renal (~80%)		Hepatic and renal (~50%)
Plasma half life	8–15 hours		12–17 hours		5–9 hours
Trial	AVERROES[15]	ARISTOTLE[16]	RE-LY[22]		ROCKET AF[21]
Number of participants	5,559	18,201	18,113		14,264
Dose assessed	5 mg bd 2.5 mg bd[a]	5 mg bd 2.5 mg bd[a]	150 mg bd	110 mg bd	20 mg daily 15 mg daily*
Comparator	Aspirin	Warfarin (INR 2.0–3.0)	Warfarin (INR 2.0–3.0)		Warfarin (INR 2.0–3.0)
Trial design	Double blind	Double blind	Open label		Double blind
Participant age	70 ± 9	70 ± 6	71.4 ± 8.6	71.5 ± 8.8	73 (IQR 65–78)
$CHADS_2$ score	2.0 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	2.2 ± 1.2	3.48 ± 0.94
Discontinuation rate	18% at 2 years	25% at ~2 years	21% at 2 years	21% at 2 years	24% at 590 days
Time with therapeutic INR	N/A	Mean 62%	Mean 64%	Mean 64%	Mean 55%
Non-bleeding adverse drug effects	Nil		Dyspepsia (11.3% vs. warfarin 5.8%, $P < 0.001^+$) MI (0.74% per year vs. warfarin 0.53% per year, $P = 0.048^+$)		Nil

Notes: [a]A reduced dose of apixaban was 2.5 mg twice daily was used if the participatant was aged >80 years, weighed <60 kg, or if the serum creatinine was >133 umol/L; *Reduced dose of rivaroxaban was 15 mg daily in patients with a creatinine clearance of 30 to 49 mL per minute; [+]Data derived from the comparison of dabigatran 150 mg twice daily to warfarin.
Abbreviations: AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; RE-LY, Dabigatran versus Warfarin in Patients with Atrial Fibrillation; ROCKET AF, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation; bd, twice daily; IQR, interquartile range; MI, myocardial infarction.

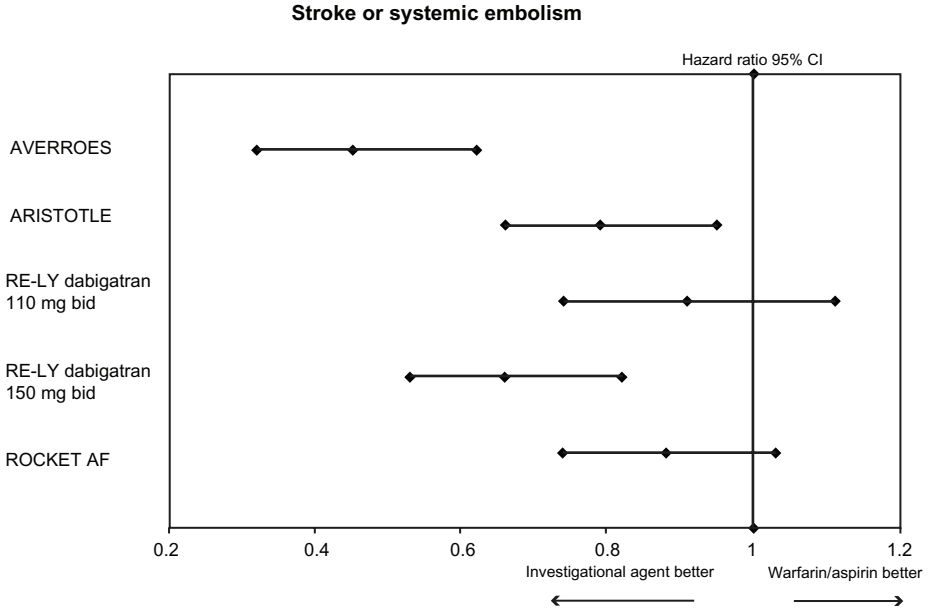

Figure 1. Efficacy endpoint of stroke and systemic embolism in clinical trials involving direct thrombin and oral factor Xa inhibitors compared with aspirin or dose adjusted warfarin in patients with atrial fibrillation and clinical risk factors for stroke.
Note: Data presented are based on the intention-to-treat analyses from each of the trials.
Abbreviations: AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; RE-LY, Dabigatran versus Warfarin in Patients with Atrial Fibrillation; ROCKET AF, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation; bd, twice daily.

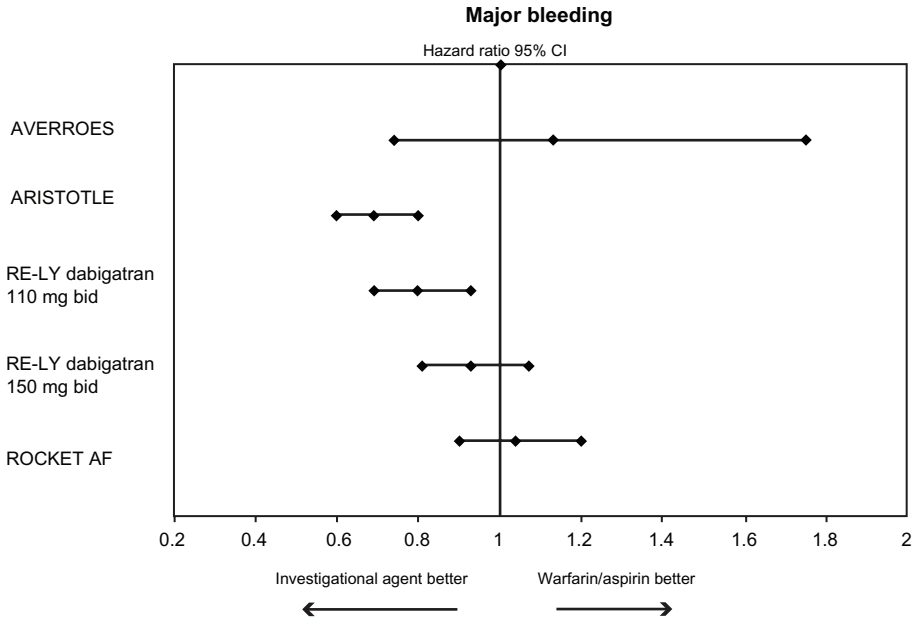

Figure 2. Safety endpoint of major bleeding according to the International Society of Thrombosis and Haemostasis (ISTH) definition in clinical trials involving direct thrombin and oral factor Xa compared with aspirin or dose adjusted warfarin in patients with atrial fibrillation and clinical risk factors for stroke.
Abbreviations: AVERROES, Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; RE-LY, Dabigatran versus Warfarin in Patients with Atrial Fibrillation; ROCKET AF, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation; bd, twice daily.

Although this finding is notable, both dabigatran and rivaroxaban, compared with warfarin, showed similar trends. In addition apixaban is the first of these agents to be demonstrated superior to aspirin in patients unsuitable for warfarin therapy, a patient group that has not been evaluated with dabigatran or rivaroxaban.

The use of apixaban in patients with AF is currently under review by the US Food and Drug Administration (FDA) and the European Medicines Agency. Given the outcomes of the review process for the direct thombin inhibitor dabigatran and FXa inhibitor rivaroxaban it seems likely these agencies will approve the use of apixaban in patients with AF.

Conclusions

The oral FXa inhibitor apixaban is one of several novel anticoagulants that can be used as an alternative to warfarin in patients with AF. The AVERROES trial demonstrates superior efficacy in stroke reduction without statistical excess in bleeding events when compared with aspirin in those deemed unsuitable to receive warfarin. The ARISTOTLE trial compared apixaban with warfarin in patients with AF, and demonstrates superior efficacy in reducing stroke and systemic embolism as well as fewer bleeding events. Overall the safety and efficacy of dabigatran, rivaroxaban and apixaban appear to be similar. Given these data, if licensing is approved, apixaban is likely to be a clinically important and useful agent in the management of AF.

Author Contributions

Conceived and designed the experiments: Not applicable. Analysed the data: AM, RS. Wrote the first draft of the manuscript: AM. Contributed to the writing of the manuscript: AM, RS. Agree with manuscript results and conclusions: AM, RS. Jointly developed the structure and arguments for the paper: AM, RS. Made critical revisions and approved final version: AM, RS. All authors reviewed and approved of the final manuscript.

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Competing Interests

Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics

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contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest. Provenance: the authors were invited to submit this paper.

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