KEY PAPER EVALUATION

More light at the end of the tunnel - apixaban in atrial fibrillation

Evaluation of Granger CB, Alexander JH, McMurray JJV et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011, 365:981-92 and Connolly SJ Eikelboom J, Joyner C et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011, 364:806-17.

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Abstract

Subjects with atrial fibrillation are at risk of thromboembolic events. The Vitamin K antagonists (e.g. warfarin) are useful at preventing coagulation in atrial fibrillation, but are difficult to use. One of the FXa inhibitors, oral apixaban, has been tested as an anticoagulant in atrial fibrillation. In ARISTOTLE (Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) apixaban was compared to warfarin in subjects with atrial fibrillation, and shown to cause a lower rate of stroke or systemic embolism and of major bleeding, than warfarin. In the AVERROES (Apixaban versus acetylsalicylic acid [ASA] to prevent stroke in atrial fibrillations patients who have failed or are unsuitable for vitamin K antagonist treatment) trial, stroke or systemic embolism occurred less often with apixaban than aspirin, whereas the occurrence of major bleeding, was similar in the groups. Apixaban is much easier for subjects with atrial fibrillation to use than warfarin, as it does not require regular monitoring by a health professional, with dosage adjustment. In addition to replacing warfarin in subjects with atrial fibrillation who are unable or not prepared to use warfarin, apixaban has the potential to replace warfarin more widely in the prevention of thromboembolism in subjects with atrial fibrillation.

Key Words apixaban, aspirin, atrial fibrillation, major bleeding, thromboembolic events, ischaemic and haemorrhagic stroke, warfarin

1. Introduction

Atrial fibrillation is the most common cardiac arrhythmia, and in the US affects 5% of the population over 69 years of age [1]. The risk of atrial fibrillation increases with age, and is associated with hypertension, coronary artery disease, valvular heart disease, heart failure, thyrotoxic heart disease and diabetes [1]. Atrial fibrillation can be asymptomatic, but can also cause palpitations, dyspnea, fatigue, dizziness, angina and, if sustained with an uncontrolled ventricular rate, decompensated heart failure [1]. Atrial fibrillation can be associated with haemodynamic dysfunction, tachycardia-induced cardiomyopathy, systemic thromboembolism, and a marked reduction in quality of life [1]. Atrial fibrillation increases the risk of death, mainly due to thromboembolic events [1]. Thus, 15-25% of all strokes in the US are due to atrial fibrillation [1].

Anticoagulants have been shown to be useful in preventing these thromboembolic events in atrial fibrillation [2]. The Vitamin K antagonists (e.g. warfarin) are the oral agents commonly used to prevent thromboembolism, and warfarin has been shown to improve survival in subjects with atrial fibrillation [3,4]. However, there are problems with vitamin K antagonists, which often prevent people from using them or lead to discontinuation of use [5]. Thus, the Vitamin K antagonists have a highly variable inter-and intra-individual anticoagulant response, with multiple drug and food interactions, necessitating regular monitoring and adjustment of dose [5]. Thus, the development of oral anticoagulants, which are easier to use than the Vitamin K antagonists, has been a priority with the pharmaceutical industry. One approach has been to develop inhibitors of factor Xa (FXa).

FXa is the penultimate enzyme in the coagulation cascade, and is also at the intersection of the intrinsic and extrinsic pathway. FXa combines with factor Va and calcium to form the prothrombinase complex that converts prothrombin to thrombin. Attention on inhibiting FXa arose from the finding that low-molecular-weight heparins, which inhibit FXa to a greater extent than unfractionated heparin, were superior to the unfractionated heparin in the treatment of venous and arterial thrombosis [6]. By inhibiting a late stage in coagulation, it was postulated that the effects of inhibitors of FXa would have less variability, and require less monitoring than the presently used Vitamin K antagonists [6]. Thus, direct inhibition of FXa seems a rational approach to the treatment of thromboembolism. Apixaban is an example of an orally active FXa inhibitor, which does not need to undergo regular dose adjustment [7].

ARISTOTLE (Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation) has compared apixaban to warfarin in subjects with atrial fibrillation, and has shown that apixaban is superior to warfarin in preventing stroke or systemic embolism [8], and this is summarised in Section

2. Although the Vitamin K antagonists have been shown to be useful in preventing thromboembolic events in atrial fibrillation [2], they are often not used for a number of reasons, and the antiplatelet drugs e.g. aspirin, are used instead. As outlined in the rationale for AVERROES (Apixaban versus acetylsalicylic acid [ASA] to prevent stroke in atrial fibrillations patients who have failed or are unsuitable for vitamin K antagonist treatment) trial, 40-50% of subjects with atrial fibrillation who are at moderate or high risk of stroke do not receive a vitamin K antagonist [9]. The most common reason for this is risk of bleeding, with other reasons being demonstrated or expected poor adherence with dosing or monitoring requirements, poor INR (International normalized ratio) control, need for other drugs that interfere with warfarin therapy, lack of adherence to restrictions on alcohol, diet, or non-prescription medications, and unwillingness to take warfarin [9]. AVERROES shows apixaban has promise for preventing stroke or systemic embolism in subjects with atrial fibrillation who are unable or unwilling to take warfarin [10].

2. ARISTOTLE: Methods and results

The methods and results of ARISTOTLE, in which the results show that apixaban is superior to warfarin in atrial fibrillation [8] are combined in this section. ARISTOTLE was a large double-blind clinical trial involving 1034 sites in 39 countries. To be enrolled subjects had to have atrial fibrillation or flutter on ECG, or two episodes of this in the last 12 months. Subjects also had to have one of the following risk factors for stroke: prior stroke or transient ischaemic attack, an age of 75 or older, hypertension, diabetes, heart failure or left ventricular ejection fraction of ≤ 35%, or peripheral artery disease. Subjects with atrial fibrillation were excluded if they required anticoagulant therapy for another condition, stroke within last 7 days, dose of aspirin > 165 mg or aspirin and clopidogrel, or severe renal insufficiency (creatinine clearance < 25 ml/min).

The enrolled 18201 subjects had a mean age of 70 years, and ~85% had persistent or permanent atrial fibrillation and the others paroxysmal atrial fibrillation. The most common qualifying risk factor was hypertension requiring treatment (~87%), followed by heart failure/reduced left ventricular ejection fraction (~35%), age ≥ 75 years (~31%), diabetes (~25%), and prior stroke, transient ischemic attack, or systemic embolism (~20%).

The CHADS2 score (1-6) is an index of the risk of stroke in subjects with atrial fibrillation, with higher scores representing greater risk. The CHADS2 scores were similar for three different groups: ≤ 1 (34%), 2 (36%), and ≥ 3 (30%); with a mean of 2.1.

Subjects were randomised to apixaban 5 mg bid or warfarin. A lower dose of apixaban, 2.5 mg bid, was used in subjects with two or more of the following: age of ≥ 80 years, body weight ≤ 60 kg, and a

serum creatinine level of ≥ 1.5 mg/100 ml. Warfarin dose was adjusted to achieve an INR of 2-3, using 2 mg tablets. This adjustment used INR measurement with a blinded, encrypted, point-of-care INR device, and an algorithm to provide the adjustment of dose. With this approach, subjects were in the therapeutic range for warfarin for a mean of 62% and a median of 66% of time.

The primary efficacy outcome was stroke or systemic embolism. After follow-up of 1.8 years, this occurred in 212 of the 9120 subjects, enrolled in the trial with atrial fibrillation, and given apixaban (rate 1.27%/year) which was less than the 265 of the 9081 subjects given warfarin (rate 1.60%/year, P = 0.01). There were a reduced number of strokes with apixaban and this represented a reduction in haemorrhagic, but not ischemic stroke or systemic embolism. These results were consistent across 21 subgroups e.g. geographic location, pre-warfarin treatment, sex, level of renal impairment etc.

In the secondary efficacy outcomes, there was a slight but significant reduction in death from any cause with apixaban (3.52%/year) versus warfarin (3.94%/year, P = 0.047). However, there were no significant differences in deaths from cardiovascular causes or non-cardiovascular causes, or in myocardial infarction.

The primary safety outcome was major bleeding, as defined by the International Society on Thrombosis, which is overt bleeding accompanied by a decrease in haemoglobin level of at least 2 g/100 ml, or transfusion of 2 units of packed red cells, occurring at a critical time or death. This safety outcome occurred at a rate of 2.13%/year with apixaban, which was significantly lower than with warfarin, 3.09%/year (P < 0.001). This represented a reduction in intracranial and other local major bleeding. The combination of major or clinically relevant non-major bleeding was also less with apixaban than with warfarin. Thus, the net clinical outcome, of stroke, systemic embolism, major bleeding with or without death from any cause was less with apixaban than with warfarin.

Subgroup analysis of subjects with atrial fibrillation in ARISTOTLE who had had a prior stroke or transient ischaemic attack, showed that apixaban was equally beneficial in stroke and nonstroke participants [11].

3. AVERROES: Methods and results

The methods and results of the AVERROES study, where the results show that apixaban is useful in preventing stroke in subjects with atrial fibrillation, who are not taking Vitamin K antagonists [10] are summarised in this section. AVERROES was a large double-blinded clinical trial involving 522 centres in 36 countries, and enrolling 5599 subjects with atrial fibrillation. To be enrolled, subjects had to be 50 years old or older and have had atrial fibrillation in the last 6 months or by 12-lead

electrocardiography on the day of screening. Subjects also had to have one of risk factors for stroke, as described in ARISTOTLE.

Subjects with atrial fibrillation who were excluded from the study, included those with other conditions requiring ongoing anti-coagulant treatment, and those with a high risk of bleeding including active peptic ulcer, a platelet count of <100,000/mm^3, haemoglobin of <10g/10dl, stroke within previous 10 days, documented haemorrhagic tendencies or blood dyscrasia, and renal insufficiency (creatinine clearance < 25 ml/min). Subjects taking a thienopyridine (e.g. clopidogrel) were excluded.

The enrolled 5599 subjects had a mean age of 70 years, and 68% had atrial fibrillation at baseline, about 25% had sinus rhythm, and about 17% had left ventricular hypertrophy. Most of the subjects had permanent atrial fibrillation (52%), some had paroxysmal (27%), and the others had persistent atrial fibrillation. Most of the subjects were being treated for hypertension (~86%), some had heart failure (40%), and some were being treated for diabetes (19%).

The population in AVERROES was predominantly in the lower range of CHADS2: 0 or 1, ~ 37%; 2, ~36%; and ≥ 3, ~28%; with a mean of ~2.0.

The most common 5 reasons for subjects being unsuitable for vitamin K antagonist therapy were:

- Assessment that INR could not or was unlikely to be measured at requested intervals (43%)
- Subject's refusal to take vitamin K antagonist (~37%)
- Not being considered to be at high enough risk of stroke to take vitamin K antagonist (~21%)
- Assessment that INR could not be maintained in therapeutic range (17%)
- Uncertainty about subject's ability to adhere to instructions about vitamin K antagonist therapy (15%)

Subjects were randomly assigned to apixaban, 5 mg twice daily, or a dose of aspirin selected by the local investigator in the range, 81-324 mg/day; with most subjects being assigned to 81 mg (~64%), followed by 162 mg (~26%). A lower dose of apixaban (2.5 mg mg twice day) was used in those who were ≥80 years, ≤ 60 kg, or had renal impairment (serum creatinine level ≥ 1.5 mg/dl).

The primary efficacy outcome was the occurrence of ischaemic or haemorrhagic stroke or systemic embolism. The data and safety monitoring committee stopped the trial early due to benefit in favour of apixaban in the primary efficacy outcome during a mean follow-up of 1.1 years. At this time, the primary efficacy outcome had occurred in 51 of 2808 subjects treated with apixaban, which a rate of 1.6%/year, and both are lower than the occurrence of stroke or systemic embolism in

113 of 2791 (3.7%/year) in subjects treated with aspirin. Of the individual items, the numbers of ischaemic strokes and systemic embolism, but not hemorrhagic strokes, was less with apixaban than aspirin. Hospitalizations for cardiovascular causes was also less with apixaban, 12.6%/year, than with aspirin, 15.9%/year. Rates of death were lower with apixaban (3.5%/year) than with aspirin (4.4%), but this did not reach statistical significance (P = 0.07).

The primary safety outcome was the occurrence of major bleeding, which was the combination of intracranial and extracranial or unclassified bleeding, and this was similar in the apixaban (1.4%/year) and aspirin group (1.2%/year). There was also no significant difference in the intracranial or extracranial bleeding, when assessed separately, with these drugs. The rates of clinically relevant non-major and minor bleeds were also similar with both drugs.

The rates of permanent discontinuation of treatment, after 2 years, were lower with apixaban, 17.9%, than with aspirin, 20.5%. Analysis showed that these findings of efficacy and safety were consistent throughout subgroups.

Recent subgroup analysis of subjects with atrial fibrillation and previous stroke or transient ischaemic attack In AVERROES have shown that the effect of apixaban is similarly effective in subjects who have had a stroke or transient ischaemic attack or not [12].

4. Expert opinion

4.1 Incidence of stroke and death in atrial fibrillation

Apixaban is as least as good as warfarin or aspirin in reducing ischaemic stroke or death. However, it is not clear, whether apixaban has additional beneficial effects on ischaemic stoke or death in subjects with atrial fibrillation. In ARISTOTLE, apixaban 5 mg twice daily reduced the risk of haemorrhagic, but not ischaemic stroke, compared to warfarin [8]. In AVERROES, apixaban reduced the rate of ischaemic, but not haemorrhagic stroke, compared to aspirin [10]. In AVERROES, apixaban did not significantly reduce the death rate (P = 0.07) [10], but in ARISTOTLE it did [8], possible due to the larger sample size. In ARISTOTLE, the subgroup analysis did not show a clear cut benefit of apixaban over warfarin for subjects under 65 years old [8]. A follow-up to ARISTOTLE or longer/other trials with apixaban are needed to determine whether apixaban has a similar or greater benefit to warfarin in preventing ischaemic stroke, and/or is effective in subjects under 65 years old.

In applying clinical trials to practice, it should always be noted that the clinical trials are only true for the dose and population studied. For instance, the findings of AVERROES are only true for the population who were unsuitable and/or unwilling to take warfarin. Apixaban is not effective in

preventing thromboembolism associated with acute coronary syndromes [13]. Thus, in subjects with atrial fibrillation and acute coronary syndromes, apixaban should not be used.

In ARISTOTLE and AVERROES, the CHADS2 scores of risk for atrial fibrillation were not high. Thus, apixaban needs to be studied in populations of subjects with atrial fibrillation that are more at risk i.e. have more risk factors or higher CHADS2 scores, than in ARISTOTLE and AVERROES, before apixaban can be considered for use in this population.

4.2 Therapeutic range of warfarin

In ARISTOTLE, the subjects taking warfarin were only in the therapeutic range for 62% of the time. As pointed out by Vassiliou, this is low compared to the 76% achieved among subjects using warfarin in Sweden, and this might account for the apparent superiority of apixaban over warfarin in subjects with atrial fibrillation [14]. In ARISTOTLE, the time in therapeutic ranged from 80% in Sweden to about 48% in India [8]. A presentation has shown that when the subjects in ARISTOTLE are divided into quartiles (<58%, 58-65.7%, 65.7-72.2%, and ≥ 72.2%) there was a consistent reduction in rates of stroke and major bleeding regardless of INR control, measured as time in therapeutic range, with warfarin [15]. Thus, it seems that the results from ARISTOTOLE are not biased in favour of apixaban, on the basis of low time in therapeutic range for warfarin. However, this needs confirmation by publication in a peer-reviewed journal.

4.3 Renal impairment

In ARISTOTLE, it was shown that the reduction in stroke and systemic embolism was present in subjects with atrial fibrillation and across the levels of renal impairment (no, mild, moderate or severe) [8]. However, as subjects with renal insufficiency were excluded from ARISTOTLE and AVERROES, it should be remembered that there is no evidence to support the use of apixaban in this population, and warfarin should remain as the preferred option to prevent stroke in subjects with atrial fibrillation and renal insufficiency. In subjects with atrial fibrillation and renal insufficiency, who are unable or unwilling to take warfarin, the effects of a low dose of apixaban, 2.5 mg twice daily, may warrant exploration.

4.4 Reversal of effects

Another criticism of apixaban is that there is presently no way to reverse its effects quickly when there is bleeding [16]. However, Sirmini has pointed out that it can take 24 hours to reverse the effects of warfarin by supplying vitamin K, and that a plasma transfusion containing coagulation factors, is required to quickly reverse the effects of warfarin [17]. There is evidence that the anti-

coagulant effect of another FXa inhibitor, rivaroxaban in healthy subjects can be reversed by infusing prothrombin complex [18]. Consequently, prothrombin complex should be tested as a possible antidote to apixaban.

4.5 Cost

A recent study has compared the cost of using apixaban with warfarin in the ARISTOTLE trial, and shown that (excluding the cost of apixaban/warfarin), there was a substantial lower medical cost with apixaban than warfarin [19]. Presumably, the cost of apixaban will decrease if it becomes more widely used, and thus, the overall cost may be less with apixaban than warfarin.

4.6 Ease of use

Apixaban is not available for clinical use in the US at present, but is undergoing a priority review for the prevention of stroke in atrial prevention, and the results will be release shortly [20]. If it approved, apixaban may be substituted for warfarin, in some circumstances, because of its ease of use.

Warfarin is notoriously difficult and time-consuming to use for both the subjects with atrial fibrillation, and the clinicians monitoring the subjects (see Introduction). Often, subjects with atrial fibrillation, who would benefit from using warfarin, do not take it for a variety of reasons, and some of these subjects were enrolled in AVERROES. AVERROES showed that these subjects, who were resistant to using warfarin, were able to use oral apixaban, and more importantly, apixaban had more benefits than using aspirin, as an alternative to warfarin. In ARISTOTLE, the subjects taking warfarin were only in the therapeutic range for 62% of the time, and this also illustrates the difficulties with using warfarin. Thus, for ease of use, subjects with atrial fibrillation, and their doctors, are likely to prefer apixaban over warfarin. Thus, it seems reasonably, that all subjects with atrial fibrillation, who are unable to take warfarin for any reason, should be candidates for receiving apixaban.

The bigger question is whether subjects with atrial fibrillation who are being controlled well with warfarin should be considered for swapping to apixaban. At present, questions still remain as to whether apixaban is superior to warfarin in all subjects with atrial fibrillation (discussed above). Until these matters are resolved, a reasonably approach would be to continue to use warfarin in subjects with good INR control.

If apixaban does partly or fully replace warfarin in the prevention of stroke, in subjects with atrial fibrillation, this will reduce the burden on the subjects with atrial fibrillation. However, apixaban is

competing with two other oral agents (the other FXa inhibitor rivaroxaban and the direct thrombin inhibitor dabigatran) to provide prevention of stroke in atrial fibrillation, in place of warfarin. In combination these agents are providing more light at the end of tunnel for the users of warfarin. However, comparative trials and long term studies of these agents in practice will be required to determine which of the novel oral anticoagulants emerge from the tunnel.

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