Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial

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Abstract

Background: increasing age is associated with a higher prevalence of atrial fibrillation (AF), and higher risks of stroke and bleeding. We report the effects of apixaban versus acetylsalicylic acid (ASA) in older patients (≥75 years and ≥85 years) compared with younger patients with AF unsuitable for vitamin K antagonists.

Methods: AVERROES (Apixaban Versus ASA to Prevent Stroke In AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial (n = 5,599) included 1,898 patients ≥75 years and 366 patients ≥85 years. We compared the baseline characteristics and effects of apixaban compared with aspirin on clinical outcomes by age.

Results: compared with aspirin, apixaban was more efficacious for preventing strokes and systemic embolism in patients ≥85 years (absolute rate [AR] 1%/year on apixaban versus 7.5%/year on aspirin; hazard ratio [HR] 0.14, 95% confidence interval [CI] 0.02–0.48) compared with younger patients (AR 1.7%/year on apixaban versus 3.4%/year on aspirin; HR 0.50, 95% CI 0.35–0.69) (P-value for interaction = 0.05). Major haemorrhage was higher in patients ≥85 years compared with younger patients but similar with apixaban versus aspirin in both young and older individuals (4.9%/year versus 1.0%/year on aspirin and 4.7%/year versus 1.2%/year on apixaban) with no significant treatment-by-age interaction (P-value = 0.65).

Conclusions: older patients with AF are at particularly high risk of stroke if given aspirin and have substantially greater relative and absolute benefits from apixaban compared with younger patients with no greater risk of haemorrhage.

Clinical Trial Registration: ClinicalTrials.gov number: NCT00496769. URL: https://clinicaltrials.gov/ct2/show/NCT00496769.

Keywords: atrial fibrillation, age, elderly, stroke, apixaban, anticoagulation

Introduction

The direct acting non-Vitamin K antagonist oral anticoagulants (e.g. dabigatran, apixaban, rivaroxaban, edoxaban) are increasingly being used over oral vitamin K antagonists (VKA) as standard anticoagulant therapy for prevention of stroke in patients with atrial fibrillation (AF) [1, 2]. Most people with AF are ≥75 years old [3, 4], and have both a
higher risk of stroke [5] and higher risk of bleeding during warfarin anticoagulation compared with younger AF patients [6]. Warfarin is superior to aspirin for stroke prevention irrespective of age. Patients with AF are often deemed unsuitable for oral anticoagulation due to perceived concerns around significant bleeding risks, co-morbidities or compliance and are prescribed anti-platelets instead [7, 8].

Apixaban is a direct and competitive oral factor Xa inhibitor [1]. Compared with warfarin, apixaban reduced the rate of stroke, death and bleeding in patients with AF regardless of age [9]. Relatively little is known about the balance of benefits and risks of apixaban in older patients especially at the extremes of age with AF, in particular those deemed unsuitable for VKA.

The AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) randomised trial demonstrated that apixaban substantially decreased the risk of stroke or systemic embolism without increasing major bleeding compared with aspirin in patients with AF deemed unsuitable for VKA [10].

We present detailed analyses of the effects of apixaban according to age with additional analyses in the very old. We hypothesised that both the relative and absolute reductions in the risk of stroke or systemic embolism would be significantly larger among older versus younger patients.

Methods

**Trial design and patients**

The design and main results of the AVERROES trial have been published [10, 11]. In brief, AVERROES was a prospective, multi-centre, randomised trial of 5,599 patients with AF conducted at 522 centres in 36 countries comparing apixaban with aspirin. Patients with permanent or paroxysmal AF were eligible if they had at least one of the following additional risk factors for stroke: prior stroke or transient ischaemic attack (TIA); age ≥75 years; arterial hypertension on treatment; diabetes mellitus; heart failure, left ventricular ejection fraction ≤35%; or documented peripheral arterial disease. In addition patients were required not to be candidates for oral anticoagulation with a vitamin K antagonist (e.g. warfarin), either because anticoagulant therapy had been demonstrated or was expected to be unsuitable [10]. Serum creatinine >2.5 mg/dl [221 μmol/l] or an estimated creatinine clearance <25 ml/min/per 1.73 m² by the Cockcroft-Gault equation [12] was an exclusion criteria. Patients were randomised to receive apixaban (5 mg twice daily) or aspirin (81–324 mg daily), administered double-blind. A reduced dose of apixaban (2.5 mg bid) was assigned to patients who met at least two of the following criteria: (i) age ≥80 years, (ii) body weight ≤60 kg, or (iii) serum creatinine ≥1.5 mg/dl or 133 μmol/l. In total, 1898 patients aged ≥75 years and 366 patients aged ≥85 years were randomised to either aspirin or apixaban in AVERROES.

The subgroup analysis for patients aged ≥75 years compared with younger patients was conducted to be consistent with current published randomised trials with direct acting oral anticoagulants. The analysis was repeated for patients aged ≥85 years with younger patients to explore treatment outcomes at the extremes of age.

**Outcomes**

All primary and secondary outcome events were adjudicated by two individuals without knowledge of the treatment assignment, using standardised definitions.

The primary efficacy outcome in AVERROES was stroke (ischaemic, haemorrhagic or unspecified) or systemic embolism. The diagnosis of stroke was clinically suspected by an acute onset of focal neurological symptoms lasting >24 h and verified by computed tomography or magnetic resonance imaging of the brain. Other outcomes included death from vascular causes and death from any cause, as well as hospitalisation and hospitalisation from cardiovascular cause.

The primary safety outcome was major bleeding, defined as clinically overt bleeding accompanied by one or more of the following: decrease in haemoglobin of ≥2 g/dl over a 24-h period, transfusion of ≥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 was fatal. Clinically relevant non-major bleeding was defined as clinically overt bleeding that did not satisfy the major criteria above but resulted in either hospital admission for bleeding, physician guided medical or surgical treatment or a change in antithrombotic therapy.

The trial was terminated at an interim analysis after 1.1 years mean follow-up due to clear evidence of the efficacy of apixaban over aspirin [10].

**Statistical analyses**

Analyses were conducted according to the intention-to-treat principle. Patients were kept in the treatment groups to which they were randomised and all randomised patients were included in the analysis except for one patient that had age at baseline missing and was excluded from the analysis. Patients were followed up from randomisation until either study closure or death, and the outcome events were recorded irrespective of whether the patient was receiving study medication.

Baseline characteristics were summarised as means and standard deviations for continuous variables and percentages for categorical variables. Older (≥75 years) and very old patients (≥85 years) were compared with their younger counterparts (<75 years and <85 years, respectively). Significance of the differences between baseline characteristics of the older and younger patients were tested using Wilcoxon two-sample tests and Pearson chi-square tests. All tests of significance were two-sided. P-value for interaction is from the likelihood ratio test of interaction between the effect of apixaban versus aspirin and the effect of age between patients ≥75 years and
<75 years or ≥85 years and <85 years. Significance was established at the 5% level.

We used univariate Cox proportional hazards regression models to estimate hazard ratios with apixaban versus aspirin separately in each age subgroup (<75 years and ≥75 years; <85 years and ≥85 years). Further, significance of the treatment by age interaction was tested in all patients by fitting Cox models that included main effects and the treatment by age interaction.

Annual event rates of the study efficacy and safety outcomes were calculated as number of first events per total number of years of follow-up. To provide a graphical demonstration of the continuous effect of increasing age on the rates of stroke and bleeding events, patients were divided into groups according to their age from youngest to oldest and event rates for the reference group were calculated using 400 youngest patients. Next, the first 40 patients were removed and replaced with 401st to 440st youngest patients, and so forth. Moving average annual event rates over time between aspirin and apixaban are given as a function of age, together with smoothing splines to illustrate unprejudiced relationships. This created an estimate for the rate of events from lower to higher age groups for each treatment arm. We then plotted event rates according to each age grouping to create a graphical representation of the effect of increasing age on event rates.

Analyses were performed using SAS software, version 9.2 of the SAS System for Sun OS (SAS Institute Inc., Cary, NC, USA).

### Results

#### Patient baseline characteristics

Patients ≥75 years at study entry comprised 34% of the AFVERREES patients (Table 1). Older patients compared with younger patients were more often female (48 versus 38%, respectively, $P$-value <0.0001), with higher mean CHADS2 (score 2.7 versus 1.7, respectively, $P$-value <0.0001). While part of this was accounted for by differences in patient age ($P$-value <0.0001) (one point is given for age ≥75 years), there was also a difference in previous stroke or TIA rates ($P$-value <0.0001) [14]. The mean estimated glomerular filtration rate (eGFR) was lower among older patients compared with younger patients (mean 60.1 ml/min compared with 73.2 ml/min, respectively, $P$-value <0.0001). A reduced dosage of apixaban (2.5 mg twice daily) was given to 17.7% of patients ≥75 years compared with 0.7% of younger patients. Patient baseline characteristics were balanced between treatment groups among those ≥75 years (Supplementary data, Table S1, available in Age and Ageing online).

Patients ≥85 years comprised 6% of AFVERREES randomised patients (Table 1). These very old patients were more often female (50.5 versus 40.5%, respectively, $P$-value <0.001), had higher CHADS2 scores (2.7 versus 2.0, respectively, $P$-value <0.001) and lower eGFR (mean 53.8 versus 69.8 ml/min respectively, $P$-value <0.001).

#### Table 1. Patient baseline characteristics according to age

<table>
<thead>
<tr>
<th>Classification of AF</th>
<th>Age &lt;75 years (N = 3,700)</th>
<th>Age ≥75 years (N = 1,898)</th>
<th>$P$-value*</th>
<th>Age &lt;85 years (N = 5,223)</th>
<th>Age ≥85 years (N = 366)</th>
<th>$P$-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>1,402 (37.9)</td>
<td>919 (48.4)</td>
<td>&lt;0.0001</td>
<td>2,118 (40.5)</td>
<td>203 (55.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131.4 ± 16.1</td>
<td>132.0 ± 17.1</td>
<td>0.30</td>
<td>131.6 ± 16.3</td>
<td>131.2 ± 18.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82.5 ± 19.8</td>
<td>72.6 ± 15.4</td>
<td>&lt;0.0001</td>
<td>79.8 ± 19.2</td>
<td>68.8 ± 13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body-mass index, kg/m²</td>
<td>29.0 ± 5.9</td>
<td>26.9 ± 4.8</td>
<td>&lt;0.0001</td>
<td>28.5 ± 5.7</td>
<td>26.2 ± 4.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior stroke or TIA</td>
<td>441 (11.9)</td>
<td>323 (17.0)</td>
<td>&lt;0.0001</td>
<td>692 (13.2)</td>
<td>72 (19.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension, receiving treatment</td>
<td>3,314 (89.6)</td>
<td>1,523 (80.3)</td>
<td>&lt;0.0001</td>
<td>4,535 (86.7)</td>
<td>302 (82.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1,471 (39.8)</td>
<td>699 (36.9)</td>
<td>0.04</td>
<td>2,034 (38.9)</td>
<td>136 (37.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Diabetes, receiving treatment</td>
<td>727 (19.7)</td>
<td>368 (19.4)</td>
<td>0.83</td>
<td>1,039 (19.9)</td>
<td>56 (15.3)</td>
<td>0.03</td>
</tr>
<tr>
<td>eGFRa</td>
<td>73.2 ± 16.9</td>
<td>60.1 ± 16.1</td>
<td>&lt;0.0001</td>
<td>69.8 ± 17.4</td>
<td>53.9 ± 15.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous VKA use</td>
<td>1,406 (38.0)</td>
<td>809 (42.6)</td>
<td>0.001</td>
<td>2,067 (39.5)</td>
<td>148 (40.4)</td>
<td>0.73</td>
</tr>
<tr>
<td>CHADS2</td>
<td>1.7 ± 0.9</td>
<td>2.7 ± 1.1</td>
<td>&lt;0.0001</td>
<td>2.0 ± 1.0</td>
<td>2.7 ± 1.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean score</td>
<td>1.7 ± 0.9</td>
<td>707 (37.3)</td>
<td></td>
<td>1,846 (35.3)</td>
<td>152 (41.6)</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>1,808 (48.9)</td>
<td>218 (11.5)</td>
<td></td>
<td>1,999 (38.2)</td>
<td>27 (7.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1,291 (34.9)</td>
<td>707 (37.3)</td>
<td></td>
<td>1,846 (35.3)</td>
<td>152 (41.6)</td>
<td></td>
</tr>
<tr>
<td>3–6</td>
<td>599 (16.2)</td>
<td>971 (51.2)</td>
<td></td>
<td>1,384 (26.5)</td>
<td>186 (51.0)</td>
<td></td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean ± SD, categorical variables are expressed as n (%).

TIA, transient ischaemic attack; VKA, vitamin K antagonist; GFR, glomerular filtration rate; AF, atrial fibrillation.

*Calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [13].

$^a$P-value is from Wilcoxon two-sample test for continuous variables and from Pearson chi-square test for categorical variables.
Effect of treatment assignment on study outcomes in patients ≥75 years

The annual absolute rates of stroke and systemic embolism increased with age in patients assigned to apixaban (absolute rate (AR) 1.5%/year and 2.0%/year with age <75 and ≥75 years respectively), but were significantly lower at each age cut-off than on aspirin (AR 2.3%/year and 6.1%/year with age <75 and ≥75 years respectively). The relative reduction in stroke or systemic embolism with apixaban compared to aspirin was larger in patients ≥75 years (hazard ratio (HR) 0.33, 95% CI 0.20–0.54) compared with patients <75 years (HR 0.63, 95% CI 0.39–0.98; P-value interaction 0.06). The absolute reduction of stroke and systemic embolism was also much larger for patients ≥75 years than for those <75 years; 4.1% per year versus 0.8% per year (Supplementary data, Table S2, available in Age and Ageing online).

The risk of major bleeding increased with age on aspirin; with absolute rates of 2.2%/year with age ≥75 years versus 0.7%/year in patients <75 years. Rates of major bleeding on apixaban were similar to those of aspirin both in older and younger patients (P-value for age interaction 0.90) (Supplementary data, Table S2, available in Age and Ageing online).

Figure 1. Cumulative hazard rates of stroke (A) and major bleeding (B) in aspirin and apixaban treatment groups, in patients <75 years or ≥75 years old.
online). In patients ≥75 years, there were six cases (0.6%/year) of intracranial bleeding on apixaban and eight cases (0.7%/year) among those receiving aspirin.

**Effect of treatment assignment on study outcomes in very old patients ≥85 years**

The absolute rate of stroke or systemic embolism in patients ≥85 was 1.0%/year on apixaban and 7.5%/year on aspirin (HR 0.14; 95% CI 0.02–0.48) (Supplementary data, Table S3, available in *Age and Ageing* online). The absolute rate of stroke or systemic embolism in patients <85 years was 1.7%/year on apixaban versus 3.4%/year on aspirin (HR 0.50; 95% CI 0.35–0.69; P-value <0.001) (P-value for age interaction = 0.05). The absolute reduction in stroke or systemic embolism with apixaban was much larger in patients ≥85 years than in patients <85 years (6.5% versus 1.7%/year). The risk of major bleeding in patients ≥85 years was similar on apixaban and aspirin (4.7%/year and 4.9%/year). Rates of intracranial bleeding in patients ≥85 years were lower on apixaban compared to aspirin (AR 0.5%/year versus 2.9%/year; HR 0.17; 95% CI 0.01–1.02, P-value for treatment effect = 0.05, P-value for age interaction = 0.04).

**Discussion**

**Increased efficacy of apixaban in the elderly**

In this paper we have reported evidence that for stroke prevention, the efficacy of apixaban in comparison to aspirin increases with age. In patients ≥75 years, there was a greater relative risk reduction with apixaban (HR 0.33, 95% CI 0.18–0.56) compared with younger patients (HR 0.68, 95% CI 0.42–1.08; P-value for interaction = 0.04) (Figure 1). The number needed to treat (NNT, calculated as 1/absolute risk reduction) per year to prevent a stroke was 26 in patients ≥75 compared with a NNT of 143 in younger patients. In contrast, the relative efficacy of aspirin to prevent ischaemic stroke decreases as patients with AF age and appears ineffectual as patients enter their eighth decade [8]. The benefit of apixaban with advancing age appears to be due to a rapidly increasing stroke risk on aspirin, whereas the stroke risk on apixaban is relatively consistent across age groups (Figure 2A).

In the absence of a comparator group with no antithrombotic or anticoagulants, it is not possible to determine conclusively from our data if this is due to a loss of efficacy of aspirin with age or an increase in efficacy with apixaban. However, as most elderly patients not anticoagulated will be prescribed aspirin, the findings of this analysis are clinically relevant.

**Risk of bleeding with initiation of apixaban**

Patients enrolled onto AVERROES were not anticoagulated with vitamin K antagonist therapy either because it was unsuitable or expected to be unsuitable. Multiple physician and patient factors were listed for patients not being suitable for VKA but most patients were unsuitable for multiple reasons (Supplementary data, Table S4, available in *Age and Ageing* online). A large proportion of older patients (42.6%) had
presented group of patients. Support for the efficacy and safety of apixaban in an underrepresented group of patients with AF, if apixaban is available.

Key points

- Anticoagulation for stroke prevention
- Direct oral anticoagulation versus aspirin
- Randomised controlled trial
- Subgroup analysis of the elderly

Conflicts of interest

K.H.N.: receiving payment for consulting fees from Boehringer Ingelheim; S.J.C.: receiving payment for serving on the boards of Boehringer Ingelheim, Sanofi-Aventis, Portola and Merck, consulting fees from Boehringer Ingelheim, Sanofi-Aventis, Portola and Bristol-Myers Squibb and lecture fees from Boehringer Ingelheim, Sanofi-Aventis and Portola; J.W.E.: receiving consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, AstraZeneca and Novartis and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly and AstraZeneca; A. A.: receiving payment from Boehringer Ingelheim for giving lectures in the Satellite Symposium; and S.Y.: receiving consulting fees from Boehringer Ingelheim, Sanofi-Aventis, Novartis, AstraZeneca, Bristol-Myers Squibb and GlaxoSmithKline, and grant support from Boehringer Ingelheim, Sanofi-Aventis, Novartis, Astra-Zeneca, GlaxoSmithKline and Bristol-Myers Squibb. R.G.H.: receiving consulting fees and grant support from Bayer Healthcare.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References


