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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 m^2 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 AVERROES patients (Table 1). Older patients compared with younger patients were more often female (48 versus 38%, respectively, *P*-value <0.0001), with higher mean $CHADS_2$ (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 <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 AVERROES 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

	Age <75 years (*N* = 3,700)	Age ≥75 years (*N* = 1,898)	*P*-value*	Age <85 years (*N* = 5,223)	Age ≥85 years (*N* = 366)	*P*-value*
Female sex	1,402 (37.9)	919 (48.4)	<0.0001	2,118 (40.5)	203 (55.5)	<0.001
Systolic blood pressure, mm Hg	131.4 ± 16.1	132.0 ± 17.1	0.30	1,31.6 ± 16.3	131.2 ± 18.3	0.57
Weight, kg	82.5 ± 19.8	72.6 ± 15.4	<0.0001	79.8 ± 19.2	68.8 ± 13.1	<0.001
Body-mass index, kg/m^2	29.0 ± 5.9	26.9 ± 4.8	<0.0001	28.5 ± 5.7	26.2 ± 4.5	<0.001
Prior stroke or TIA	441 (11.9)	323 (17.0)	<0.0001	692 (13.2)	72 (19.7)	<0.001
Hypertension, receiving treatment	3,314 (89.6)	1,523 (80.3)	<0.0001	4,535 (86.7)	302 (82.7)	0.04
Heart failure	1,471 (39.8)	699 (36.9)	0.04	2,034 (38.9)	136 (37.3)	0.54
Diabetes, receiving treatment	727 (19.7)	368 (19.4)	0.83	1,039 (19.9)	56 (15.3)	0.03
Classification of AF			<0.0001			<0.001
Paroxysmal	1,061 (28.7)	451 (23.8)		1,433 (27.4)	79 (21.6)	
Persistent	826 (22.3)	351 (18.5)		1,118 (21.4)	59 (16.1)	
Permanent	1,812 (49.0)	1,095 (57.7)		2,679 (51.2)	228 (62.3)	
Study dose of 2.5 mg twice daily of apixaban or apixaban-placebo	25 (0.7)	336 (17.7)	<0.0001	220 (4.2)	141 (38.5)	<0.001
Previous VKA use	1,406 (38.0)	809 (42.6)	0.001	2,067 (39.5)	148 (40.4)	0.73
eGFR[a]	73.2 ± 16.9	60.1 ± 16.1	<0.0001	69.8 ± 17.4	53.9 ± 15.6	<0.001
<60 ml/min	812 (22.0)	956 (50.4)		1,518 (29.0)	250 (68.3)	
≥60 ml/min	2,886 (78.0)	942 (49.6)		3,712 (71.0)	116 (31.7)	
$CHADS_2$						
Mean score	1.7 ± 0.9	2.7 ± 1.1	<0.0001	2.0 ± 1.0	2.7 ± 1.1	<0.001
0–1	1,808 (48.9)	218 (11.5)		1,999 (38.2)	27 (7.4)	
2	1,291 (34.9)	707 (37.3)		1,846 (35.3)	152 (41.6)	
3–6	599 (16.2)	971 (51.2)		1,384 (26.5)	186 (51.0)	

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.

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

**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*

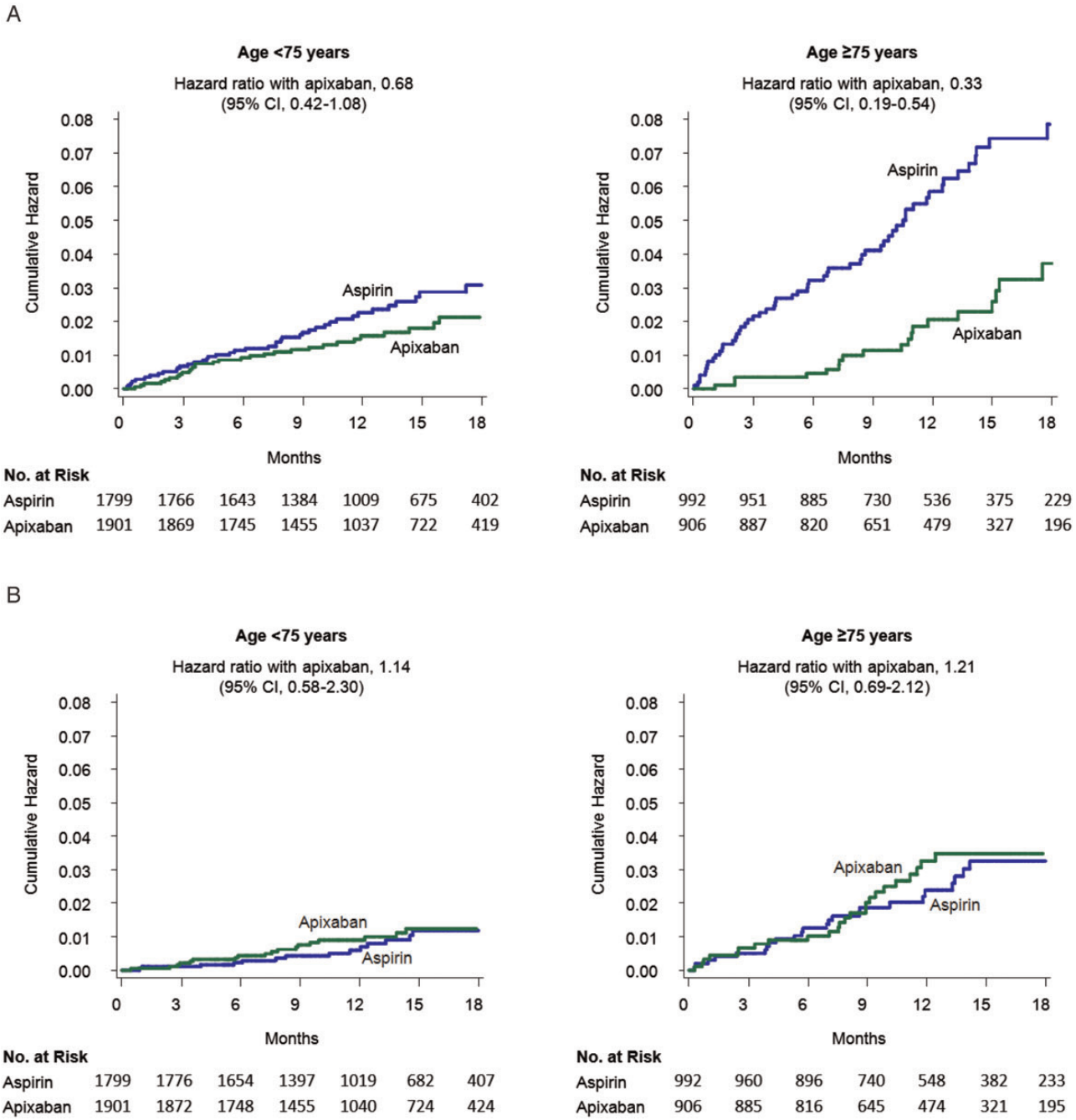

Figure 1. Cumulative hazard rates of stroke (A) and major bleeding (B) in aspirin and apixaban treatment groups, in patients <75 years or ≥75 years old.

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 antiplatelets 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

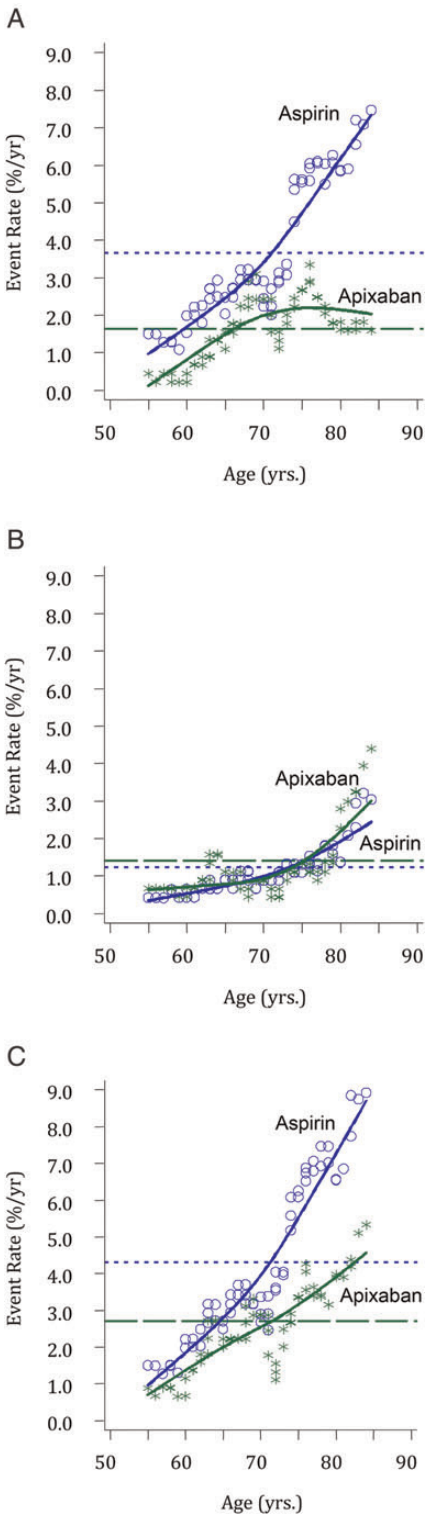

Figure 2. Moving average annual event rates for the outcomes of stroke or systemic embolism (A), major bleeding (B), and stroke or major bleeding (C). The 2,791 patients in the aspirin group and 2,807 patients in the apixaban group with age non-missing were sorted according to their age from youngest to oldest. The first data point on the left represents the first 400 youngest patients plotted at these 400 patients' median age. For the second point, the first 40 patients are removed and replaced with 401st to 440st youngest patients, and so forth.

previously failed VKA therapy and of that group, 9.5% had serious bleeding due to VKA therapy.

In general, apixaban has a similar major bleeding rate to aspirin in patients who were previously not deemed suitable for anticoagulation with VKA. The risk of bleeding increased on both treatments with age (Figure 2B). However even in the very elderly, apixaban was as safe as aspirin in regards to bleeding. For intracranial haemorrhage, there is some evidence that apixaban is safer than aspirin in patients ≥85 years though absolute event rates were low.

Underutilisation of oral anticoagulation in older patients

Anticoagulation is highly effective at preventing stroke in AF [10, 15–18]. Recent trial data continue to show a very high risk of stroke without anticoagulation; in patients ≥75 this rate was 4.4% per year in ACTIVE A and 5.8% per year in AVERROES [10, 19]. In AVERROES, patients ≥85 years had an even higher rate of stroke at 7.5% per year. Current published guidance recommends anticoagulation of older patients with AF because of their high stroke risk [20–22]. Despite the compelling recommendations for stroke prevention, oral anticoagulation continues to be underused in older patients in contemporary registries [7]. In this analysis of the AVERROES trial, the overall benefit of apixaban over aspirin is highly favourable in the elderly and is not off-set by an increasing risk of haemorrhage with ageing.

AVERROES results can be extrapolated to all older patients with AF

Participation in AVERROES was restricted to AF patients deemed unsuitable to receive VKAs. However, the patient features in AVERROES were very similar to those of other recent randomised trials testing antithrombotic therapy in AF patients [16, 17, 23, 24] and to clinical cohorts [25]. Consequently, we believe that the results are applicable to most elderly AF patients. An important advantage of the AVERROES trial design is the comparison with aspirin rather than to warfarin, allowing the effect on clinical events of apixaban to be more fully delineated against mono antiplatelet therapy.

Whilst the number of patients ≥85 years in this subgroup analysis was limited, the findings were consistent with the larger analysis comparing patients ≥75 years with their younger counterparts. The results in both analyses provide support for the efficacy and safety of apixaban in an underrepresented group of patients.

Conclusions

This analysis of the AVERROES trial demonstrates that older patients with AF, even the very elderly, derive benefit from apixaban. Increased age does not increase the risk of bleeding of apixaban when compared to aspirin; and in the very elderly there may even be a benefit of apixaban over aspirin for intracranial haemorrhage. Based on the present analysis, it difficult to justify the use of aspirin in elderly 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 Merck, grant support on behalf of his institution, McMaster University, 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.

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