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FASTTRACK
CLINICAL TRIAL & REGISTRY UPDATE

Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial

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Aims Atrial fibrillation (AF) is common among patients with impaired renal function. Apixaban, a novel oral anticoagulant with partial renal excretion, was compared with warfarin and reduced the rate stroke, death and bleeding in the ARISTOTLE trial. We evaluated these outcomes in relation to renal function.

Methods and results Baseline glomerular filtration rate (GFR) was estimated using the Cockcroft–Gault and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations as well as cystatin C measurements. According to baseline Cockcroft–Gault, there were 7518 patients (42%) with an estimated GFR (eGFR) of >80 mL/min, 7587 (42%) between >50 and 80 mL/min, and 3017 (15%) with an eGFR of ≤50 mL/min. The rate of cardiovascular events and bleeding was higher at impaired renal function (≤80 mL/min). Apixaban was more effective than warfarin in preventing stroke or systemic embolism and reducing mortality irrespective of renal function. These results were consistent, regardless of methods for GFR estimation. Apixaban was associated with less major bleeding events across all ranges of eGFRs. The relative risk reduction in major bleeding was greater in patients with an eGFR of ≤50 mL/min using Cockcroft–Gault {hazard ratio (HR) 0.50 [95% confidence interval (CI) 0.38–0.66], interaction $P = 0.005$} or CKD-EPI equations [HR 0.48 (95% CI 0.37–0.64), interaction $P = 0.003$].

Conclusion In patients with AF, renal impairment was associated with increased risk of cardiovascular events and bleeding. When compared with warfarin, apixaban treatment reduced the rate of stroke, death, and major bleeding, regardless of renal function. Patients with impaired renal function seemed to have the greatest reduction in major bleeding with apixaban.

Keywords Atrial fibrillation • Anticoagulation • Stroke prevention • Bleeding • Apixaban

Introduction

Chronic kidney disease affects up to 10% of the adult population, particularly the elderly,[1] and carries a high risk for cardiovascular disease, including atrial fibrillation (AF).[2] In a large population-based long-term follow-up study with impaired renal function, the hazard ratio (HR) for the development of AF more than doubled in patients with an estimated glomerular filtration rate (GFR) of 15–29 mL/min compared with patients with normal renal function independent from other known risk factors for AF.[3] Whereas it is well appreciated

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that stroke risk in end-stage renal disease is elevated,[4] the importance of renal dysfunction as an independent risk factor for AF-associated thrombo-embolic events is more controversial. However, some studies indicate that a lower level of eGFR is associated with a graded, increased risk of ischaemic stroke or systemic embolism.[5] Despite this increased risk for AF-associated thromboembolism, many patients with renal dysfunction are not receiving oral anticoagulation therapy,[6] mostly because of fear of bleeding with warfarin.[7]

Apixaban is a novel factor Xa inhibitor with good oral bioavailability and only ~25% renal elimination. In the Apixaban for Reduction In STroke and Other ThromboemboLic Events in atrial fibrillation (ARISTOTLE) trial, apixaban, when compared with warfarin, was associated with a 21% relative risk reduction in stroke or systemic embolism, a 11% reduction in total mortality, and a 31% reduction in major bleeds in patients with AF and at least one additional risk factor for stroke.[8,9] Because of the limited renal elimination, the protocol predefined an assessment of the efficacy and safety of apixaban in patients with various degrees of renal dysfunction. For this pre-specified secondary analysis, we used the Cockcroft–Gault method to estimate renal function but also the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), a new equation for the estimation of GFR which was specifically developed to outperform existing creatinine-based GFR estimates with respect to estimating true GFR.[10] As a third method, we used cystatin C which has been proposed to be a more reliable marker of renal function than serum creatinine.[11]

Methods

Patient population

Ethics committee approval was obtained for all investigational sites, and all patients provided written informed consent. To be eligible in ARISTOTLE, patients had to have AF or flutter at enrolment or at least two episodes of AF or flutter documented by electrocardiography at least 2 weeks apart in the 12 months before enrolment. In addition, at least one of the following risk factors for stroke was required: age ≥75 years; prior stroke, transient ischaemic attack, or systemic embolism; symptomatic heart failure within 3 months or left ventricular ejection fraction of no more than 40%; diabetes mellitus; hypertension requiring pharmacological treatment. Major exclusion criteria included AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF that required anticoagulation such as prosthetic heart valve, stroke within 7 days, need for aspirin >165 mg a day or both aspirin and clopidogrel, and severe renal insufficiency [serum creatinine >2.5 mg/dL (221 μmol/L) or calculated creatinine clearance <25 mL/min].[9]

Trial design and outcome measures

The design of ARISTOTLE has been published.[9] In brief, eligible patients were randomly assigned to receive apixaban or dose-adjusted warfarin using a double-blind, double-dummy design. Apixaban (or matching placebo) was dosed at 5 mg twice daily or 2.5 mg twice daily for a subset of patients with two or more of the following criteria: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dL (133 μmol/L). Warfarin (or matching placebo) was provided as 2 mg tablets adjusted to achieve a target international normalized ratio (INR) of 2.0–3.0. International normalized ratios were monitored using a blinded, encrypted point-of-care INR device and an algorithm was provided to guide warfarin dose adjustment.

The primary efficacy endpoint in ARISTOTLE was stroke (ischaemic or haemorrhagic) or systemic embolism. The primary safety outcome was International Society of Thrombosis and Hemostasis (ISTH) major bleeding. Major bleeding was defined as acute or subacute clinically overt bleeding accompanied by one or more of the following: (i) a decrease in the haemoglobin level of ≥2 g/dL over a 24 h period; (ii) a transfusion of ≥2 U of packed red blood cells; and/or (iii) bleeding that is fatal or occurs in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal.[9] A blinded clinical events committee adjudicated all primary and secondary (all-cause deaths, myocardial infarction) outcomes according to pre-specified criteria.

Laboratory methods

At the time of randomization, before initiation of study treatment, a venous EDTA blood sample was drawn for the determination of creatinine and cystatin C levels. The blood was centrifuged, thereafter immediately frozen at −20°C or colder. Aliquots were stored at −70°C to allow batch analysis. Plasma creatinine measurements were performed in a core laboratory using a Roche Modular analyzer with a kinetic colorimetric compensated Jaffe assay (Roche Modular, Meylan, France). Cystatin C was centrally analysed in Uppsala Clinical Research Center (UCR)—laboratory, Sweden, with the Architect system ci8200 (Abbott Laboratories, Abbott Park, IL, USA) using the particle enhanced turbidimetric immunoassay (PETIA) from Gentian (Gentian, Moss, Norway). The lowest limit of detection is 0.05 mg/L according to the manufacturer. The total analytical imprecision of the method is 1.09% at 0.85 mg/L and 1.03% at 3.06 mg/L.[12] The upper reference level, defined as the 97.5th percentile value in an apparently healthy population, is 1.21 mg/L for those who are >65 years.[13]

Glomerular filtration rate estimation

The Cockcroft–Gault GFR was derived from the following equation: (140 − age) × (weight in kg) × (0.85 if female)/(72 × Cr in mg/dL). CKD-EPI GFR was derived from the following equation[9]: GFR (mL/min/1.73 m^2) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if black), where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1, and Scr is expressed in mg/dL. Glomerular filtration rate in mL/min/1.73 m^2 was also estimated from serum cystatin C results in mg/L by the formula $y = 79.901 \times \text{cystatin C}^{-1.4389}$.

Statistical analyses

For the purpose of this pre-specified secondary analysis of ARISTOTLE, patients' GFR was estimated according to the three different methods. The Cockcroft–Gault and CKD-EPI were calculated with creatinine at randomization, and cystatin C eGFR with cystatin C levels at randomization. Patients were classified according to the main trial pre-specified cut-offs and estimated GFR (eGFR) of >80, >50–80, and ≤50 mL/min. We examined the baseline characteristics of patients by categories of renal function. Continuous variables are presented as means and standard deviation (SD), with between-group comparisons, tested by ANOVA for normally distributed data and non-parametric (Kruskal–Wallis) tests otherwise. Categorical variables are presented as counts and percentages and compared by χ^2 tests or Fisher's exact tests, where appropriate.

Primary and secondary efficacy analyses included all randomized patients (intention-to-treat) and included all events from randomization

until the efficacy cut-off date (predefined as 30 January 2011). Bleeding analyses were 'on treatment' including all randomized patients who received at least one dose of the study drug and included all events from receipt of the study drug until 2 days after the last dose of the study drug. Event rates per 100 patient-years of follow-up are reported. Hazard ratios [95% confidence intervals (CI)] comparing apixaban with warfarin were derived from the Cox proportional hazards models. Treatment effects were compared according to renal function, both as a categorical variable and continuous measures, by adding interactions to the model. We report the treatment HRs at varying levels of renal function, regardless of the significance of interaction. Restricted cubic splines were used to allow for non-linearity in the relationship between continuous renal function and outcomes. Interactions with continuous renal function were illustrated by plotting the estimated probability of 1-year events, according to the continuous level of renal function, with separate curves for each treatment group. All analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

According to the Cockcroft–Gault, a total of 7518 patients (42%) were classified according to their baseline eGFR as having a renal function of >80 mL/min, 7587 (42%) having an eGFR of >50–80 mL/min, and 3017 (15%) having an eGFR of ≤50 mL/min. According to CKD-EPI, 5190 (29%), 10 151 (56%), and 2843 (16%) patients were classified according to the eGFR of >80, >50–80, and ≤50 mL/min, respectively. Cystatin C was available in 14 884 patients as part of a biomarker substudy, and 7545 (51%), 5272 (35%) and 2067 (14%) patients were classified according to the eGFR of >80, >50–80, and ≤50 mL/min, respectively. *Tables 1* and *2* show baseline characteristics of patients over all ranges of renal dysfunction. According to renal function classifications, there was an inverse relationship between co-morbidities, stroke risk factors, or the presence of non-paroxysmal AF and decreasing renal function.

Outcomes according to renal dysfunction

Patients with impaired renal function (≤80 mL/min) were at higher risk for all cardiovascular events during the trial. For instance, the annualized stroke rate was 1.05% in patients with an eGFR of >80 mL/min, 1.46% in patients with an eGFR of >50–80 mL/min, and 2.39% in patients with an eGFR of ≤50 mL/min according to the Cockcroft–Gault equation. The annual ischaemic stroke rate in patients with an eGFR of ≤50 mL/min more than doubled that of patients with normal renal function (0.76 vs. 1.70%). All-cause mortality was three times higher in patients with an eGFR of ≤50 mL/min than in subjects with an eGFR of >80 mL/min (2.52 vs. 7.71%).

Similarly, the incidence of major bleeding increased significantly with increasing renal dysfunction (1.65 vs. 4.80%). The associations between decreased kidney function and increased incidence of cardiovascular events were consistent utilizing all three methods of GFR estimation.

Efficacy of apixaban vs. warfarin in patients with renal dysfunction

The superiority of apixaban relative to warfarin for preventing stroke or systemic embolism was consistent, irrespective of degree of renal impairment (*Figure 1*). There were also consistent effects without any significant interactions between treatment effects and renal dysfunction with respect to ischaemic strokes, all-cause mortality, or composite outcome events. The rates of stroke or systemic embolism were also evaluated with eGFR as a continuous variable. As demonstrated in *Figure 2*, apixaban was generally superior to warfarin in preventing primary outcome events across the range of eGFR with no significant interaction between the treatment effect and the level of renal dysfunction. The results were consistent across the Cockcroft–Gault, CKD-EPI, or cystatin C methods of estimation of GFR. Data on ischaemic vs. haemorrhagic stroke related to renal function are shown in the Supplementary material online, *Table S1*.

Safety of apixaban vs. warfarin in patients with renal dysfunction

The incidence of major bleeding events (primary safety outcome) was inversely related to renal function, as described above. For the full range of eGFR and across all categories of renal dysfunction, apixaban was associated with less major bleeding compared with warfarin for all three methods of GFR estimation (*Figure 1*). Bleeding rates were also evaluated with eGFR as a continuous variable using Cockcroft–Gault, CKD-EPI and cystatin C. With Cockcroft–Gault, the relative reduction in major bleeding with apixaban compared with warfarin was significantly greater in patients with an eGFR of ≤50 mL/min with HR (95% confidence interval) of 0.50 (0.38–0.66) (*P*-value for interaction 0.005; *Figure 3A*). Estimating renal function with CKD-EPI showed similar results with a larger reduction in major bleeding in patients with an eGFR of ≤50 mL/min with HR 0.48 (0.37–0.64) (*P*-value for interaction 0.003; *Figure 3B*). When using cystatin C to estimate GFR, apixaban was associated with less bleeding events across all ranges of eGFR, but without any significant interaction with the treatment effect on major bleeding (*P*-value for interaction 0.54; *Figure 3C*).

To examine whether the reduction in bleeding in patients with impaired renal function was due to the more frequent use of the lower apixaban dose (2.5 mg bid), two sensitivity analyses were conducted. First, adjusting for dose (low/standard) by including it as a covariate, both as a main effect and as an interaction between dose and treatment (*Table 3*: Sensitivity 1). Secondly, by excluding all patients on low-dose apixaban and repeating the analysis, only in the patients on standard dose (*Table 3*: Sensitivity 2). In both sensitivity analyses, the interaction between treatment and renal function remained statistically significant for major bleeding, although less significant. This difference is mainly explained by the loss of power from excluding a large proportion of patients with low renal function.

Table 1 Clinical characteristics and medications at the baseline according to renal function by Cockcroft–Gault

Characteristic	>80 mL/min (*n* = 7518; 41%)	>50–80 mL/min (*n* = 7587; 42%)	≤50 mL/min (*n* = 3017; 17%)	*P*-value
Low apixaban dose	1 (0.0%)	96 (1.3%)	733 (24.3%)	<0.0001
Age (mean, SD)	62.9 (8.6)	71.8 (7.5)	77.6 (7.1)	<0.0001
Age ≥75	597 (7.9%)	2922 (38.5%)	2128 (70.5%)	<0.0001
Female sex	1938 (25.8%)	2837 (37.4%)	1609 (53.3%)	<0.0001
Region				
North America	2007 (26.7%)	1697 (22.4%)	754 (25.0%)	<0.0001
Latin America	1269 (16.9%)	1503 (19.8%)	685 (22.7%)	
Europe	3447 (45.8%)	2985 (39.3%)	870 (28.8%)	
Asian Pacific	795 (10.6%)	1402 (18.5%)	708 (23.5%)	
Systolic blood pressure (mean, SD)	131.8 (15.7)	131.6 (16.8)	129.5 (17.0)	<0.0001
Diastolic blood pressure (mean, SD)	81.0 (10.0)	78.7 (10.5)	75.8 (10.9)	<0.0001
Weight (mean, SD)	97.4 (20.2)	77.8 (14.2)	66.3 (13.7)	<0.0001
Prior myocardial infarction	958 (12.7%)	1106 (14.6%)	514 (17.1%)	<0.0001
Congestive heart failure	2300 (30.6%)	2236 (29.5%)	988 (32.7%)	0.0041
Prior stroke, TIA, or systemic embolism	1124 (15.0%)	1639 (21.6%)	756 (25.1%)	<0.0001
Diabetes	2157 (28.7%)	1738 (22.9%)	638 (21.1%)	<0.0001
Hypertension	6739 (89.6%)	6555 (86.4%)	2560 (84.9%)	<0.0001
Prior clinically relevant or spont. bleeding	1177 (15.7%)	1257 (16.6%)	598 (19.8%)	<0.0001
History of fall within previous year	249 (3.7%)	328 (4.8%)	172 (6.2%)	<0.0001
Type of atrial fibrillation				
Paroxysmal	1235 (16.4%)	1142 (15.1%)	396 (13.1%)	<0.0001
Persistent or permanent	6281 (83.6%)	6444 (84.9%)	2621 (86.9%)	
Vitamin K antagonist naïve	3127 (41.6%)	3253 (42.9%)	1376 (45.6%)	0.0008
$CHADS_2$ (mean, SD)	1.9 (1.0)	2.2 (1.1)	2.6 (1.2)	<0.0001
$CHADS_2$ score				
1	3262 (43.4%)	2391 (31.5%)	503 (16.7%)	<0.0001
2	2662 (35.4%)	2678 (35.3%)	1144 (37.9%)	
≥3	1594 (21.2%)	2518 (33.2%)	1370 (45.4%)	
CHA_2DS_2VASC (mean, SD)	2.8 (1.3)	3.7 (1.4)	4.4 (1.4)	<0.0001
CHA_2DS_2VASC score				
1	1269 (16.9%)	304 (4.0%)	23 (0.8%)	<0.0001
2	2247 (29.9%)	1303 (17.2%)	202 (6.7%)	
≥3	4002 (53.2%)	5980 (78.8%)	2792 (92.5%)	
HASBLED (mean, SD)	1.6 (1.0)	2.0 (1.0)	2.2 (1.0)	<0.0001
HASBLED 0–2	6101 (81.2%)	5324 (70.2%)	1993 (66.1%)	
HASBLED ≥3	1417 (18.8%)	2263 (29.8%)	1024 (33.9%)	
Medications at time of randomization				
ACE inhibitor or ARB	5510 (74.5%)	5258 (70.4%)	2015 (67.7%)	<0.0001
Amiodarone	818 (11.1%)	840 (11.3%)	389 (13.1%)	0.0108
β-Blocker	4986 (67.4%)	4694 (62.9%)	1761 (59.2%)	<0.0001
Aspirin	2266 (30.1%)	2369 (31.2%)	977 (32.4%)	0.0651
Clopidogrel	98 (1.3%)	150 (2.0%)	89 (2.9%)	<0.0001
Digoxin	2372 (32.1%)	2359 (31.6%)	1071 (36.0%)	<0.0001
Calcium blocker	2308 (31.2%)	2315 (31.0%)	921 (30.9%)	0.9498
Lipid-lowering agents	3397 (45.9%)	3416 (45.8%)	1347 (45.3%)	0.8203
Non-steroidal anti-inflammatory agent	640 (8.7%)	596 (8.0%)	278 (9.3%)	0.0640

Table 2 Clinical characteristics and medications at baseline according to renal function by cystatin C estimated GFR

Characteristic	>80 mL/min (*n* = 7545; 51%)	>50–80 mL/min (*n* = 5272; 35%)	≤50 mL/min (*n* = 2067; 14%)	*P*-value
Age (mean, SD)	66.9 (9.6)	70.3 (9.1)	73.3 (8.7)	<0.0001
Age ≥75	2949 (39.1%)	2116 (40.1%)	770 (37.3%)	<0.0001
Female sex	2609 (34.6%)	1905 (36.1%)	786 (38.0%)	<0.0091
Region				
North America	1727 (22.9	1277 (24.2%)	565 (27.3%)	<0.0001
Latin America	1526 (20.2%)	1029 (19.5%)	397 (19.2%)	
Europe	3098 (41.1%)	2144 (40.7%)	741 (35.8%)	
Asian Pacific	1194 (15.8%)	822 (15.6%)	364 (17.6%)	
Systolic blood pressure (mean, SD)	131.5 (16.0)	131.7 (16.5)	129.7 (17.0)	<0.0001
Diastolic blood pressure (mean, SD)	80.0 (10.2)	79.1 (10.5)	76.9 (11.1)	<0.0001
Weight (mean, SD)	84.3 (20.2)	84.5 (20.9)	82.6 (21.2)	0.0009
Prior myocardial infarction	774 (10.3%)	757 (14.4%)	382 (18.5%)	<0.0001
Congestive heart failure	1971 (26.1%)	1771 (33.6%)	865 (41.8%)	<0.0001
Prior stroke, TIA, or systemic embolism	1344 (17.8%)	1067 (20.2%)	475 (23.0%)	<0.0001
Diabetes	1746 (23.1%)	1319 (25.0%)	615 (29.8%)	<0.0001
Hypertension	6550 (86.8%)	4625 (87.7%)	1853 (89.6%)	<0.0001
Prior clinically relevant or spont. bleeding	1161 (15.4%)	841 (16.0%)	423 (20.5%)	<0.0001
History of fall within previous year				<0.0001
Type of atrial fibrillation				
Paroxysmal	1317 (17.5%)	708 (13.4%)	225 (10.9%)	<0.0001
Persistent or permanent	6225 (82.5%)	4564 (86.6%)	1842 (89.1%)	
Vitamin K antagonist naïve	4135 (54.9%)	2839 (53.9%)	1024 (49.7%)	0.0001
$CHADS_2$ (mean, SD)	1.9 (1.0)	2.2 (1.1)	2.5 (1.2)	<0.0001
$CHADS_2$ score				
1	3093 (41.0%)	1561 (29.6%)	400 (19.4%)	<0.0001
2	2641 (35.0%)	1980 (37.6%)	744 (36.0%)	
≥3	1811 (24.0%)	1731 (32.8%)	923 (44.7%)	
Medications at time of randomization				
ACE inhibitor or ARB	5215 (69.1%)	3770 (71.5%)	1546 (74.8%)	<0.0001
Amiodarone	892 (11.8%)	599 (11.4%)	220 (10.6%)	0.3073
β-Blocker	4659 (61.7%)	3388 (64.3%)	1364 (66.0%)	0.0003
Aspirin	2263 (30.0%)	1620 (30.7%)	716 (34.6%)	0.0003
Clopidogrel	115 (1.5%)	99 (1.9%)	51 (2.5%)	0.0129
Digoxin	2256 (29.9%)	1805 (34.2%)	764 (37.0%)	<0.0001
Calcium blocker	2265 (30.0%)	1639 (31.1%)	646 (31.3%)	0.3331
Lipid-lowering agents	3347 (44.4%)	2303 (43.7%)	993 (48.0%)	0.0027
Non-steroidal anti-inflammatory agent	590 (7.8%)	419 (7.9%)	243 (11.8%)	<0.0001

Discussion

Main findings

The main findings of the trial were that the primary endpoint of stroke or systemic embolism occurred less frequently in patients assigned to apixaban than warfarin, regardless of renal function. Also major bleeding occurred less frequently in the apixaban group, irrespective of renal function. The present analysis represents the largest experience of anticoagulation therapy in patients with AF and impaired renal function including 7587 patients with an eGFR of >50–80 mL/min and 3017 subjects with an eGFR of ≤50 mL/min. The findings in patients with different degrees of renal dysfunction were consistent with the results of the overall trial. In addition, patients with impaired renal function (≤50 mL/min) seemed to have the greatest reduction in major bleeding with apixaban, when using creatinine-based estimates of GFR such

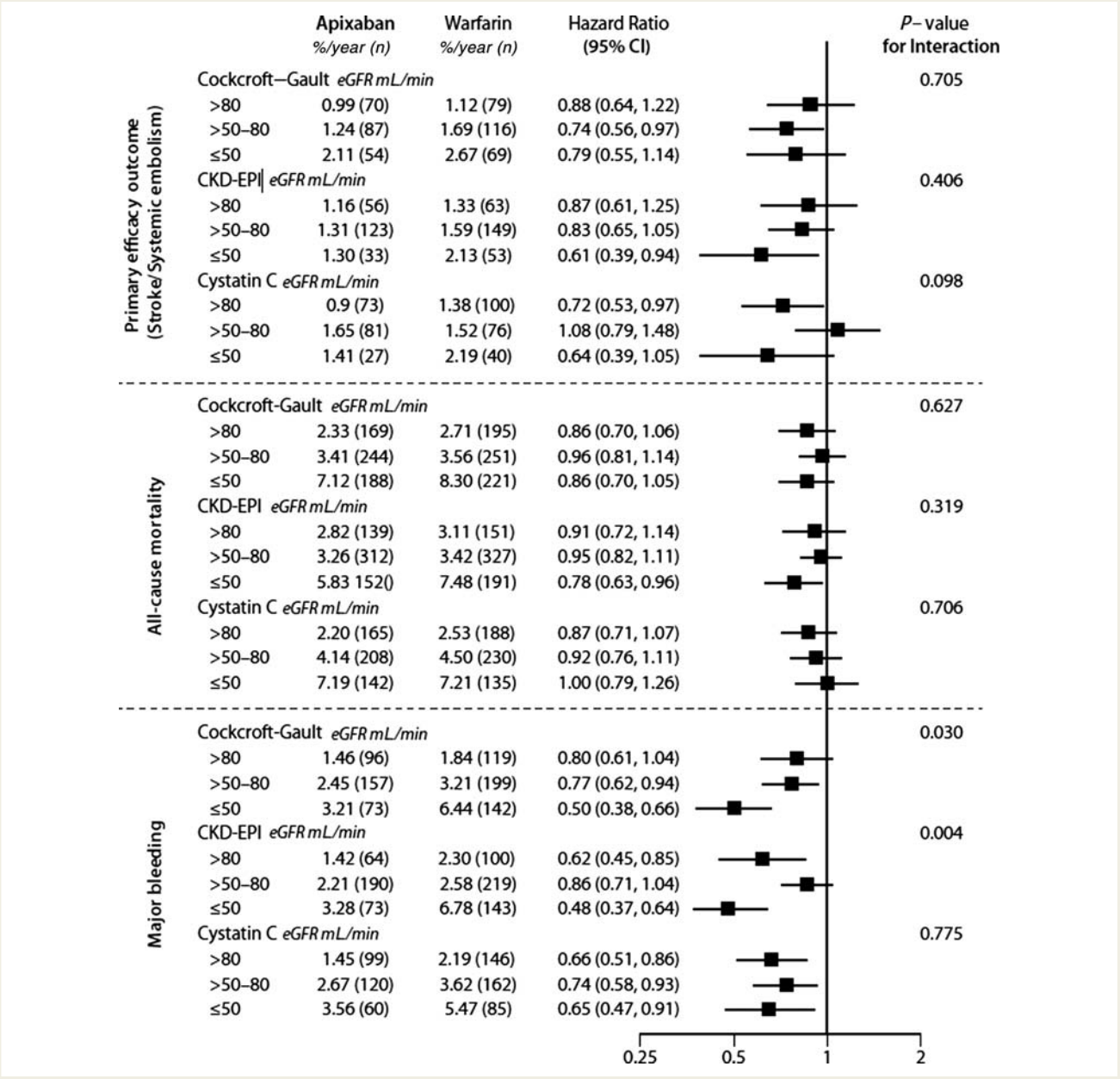

Figure 1 Forrest plot for effect of apixaban vs. warfarin for outcomes of stroke or systemic embolism, mortality, and major bleed according to renal function estimated with the Cockcroft–Gault, CKD-EPI, and cystatin C. Interaction *P*-values are based on categorical estimated glomerular filtration rates.

as the widely used Cockcroft–Gault or the newer CKD-EPI equations.

Stroke prevention in patients with renal dysfunction

The incidence of renal impairment increases with age, particularly in patients with cardiovascular co-morbidities. As AF is also a disease of the elderly, AF and renal dysfunction often coexist. Based on the recent results from a large administrative database of 10 908 AF patients, impaired renal function seemed to be associated with a particularly high risk of ischaemic stroke or systemic embolism.[5] The results from the present study confirm these findings and clearly display the increased stroke rate with decreasing renal function in a large global AF population. Both the annual rates of stroke or systemic embolism and ischaemic strokes were more than doubled in patients with moderate/severe renal impairment when compared with normal renal function. There was no significant interaction between randomized treatment and renal dysfunction for stroke outcomes. Accordingly, with a consistent relative reduction in the rate of stroke or systemic embolism, apixaban provided the largest absolute benefits in patients with renal impairment (*Figure 1*). It should be noted that the confidence intervals in *Figure 2A* are not sufficiently narrow to rule out

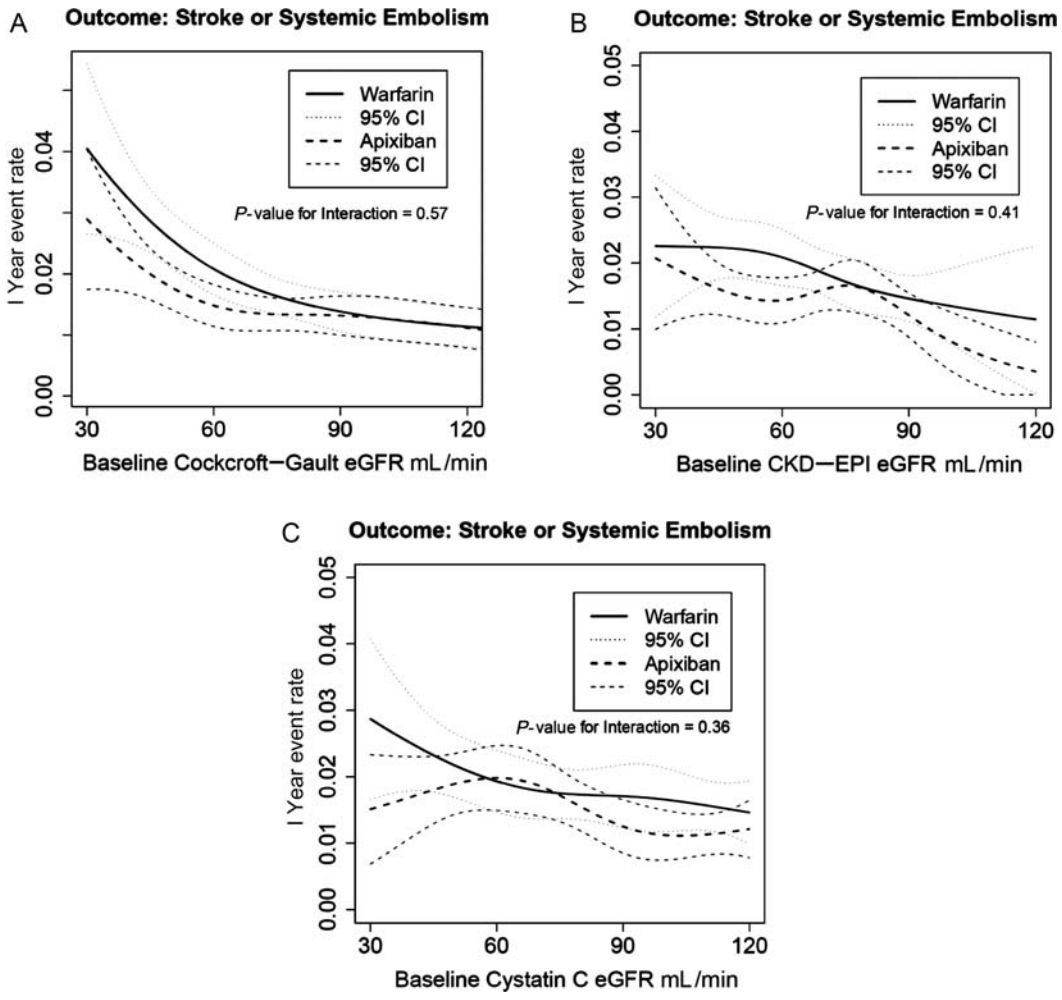

Figure 2 (*A*) Apixaban vs. warfarin for stroke or systemic embolism with continuous analysis of estimated renal function with Cockcroft–Gault. (*B*) Apixaban vs. warfarin for stroke or systemic embolism with continuous analysis of estimated renal function with CKD-EPI. (*C*) Apixaban vs. warfarin for stroke or systemic embolism with continuous analysis of estimated renal function with cystatin C. All interaction *P*-values are based on continuous estimated glomerular filtration rates.

a clinically relevant interaction. In our sample, the benefits of apixaban were mainly in those with an eGFR below 90 mL/min. However, this observed heterogeneity was also consistent with chance.

Renal function and mortality

Atrial fibrillation and impaired renal function have both been demonstrated to be independently associated with increased mortality in various clinical settings.[14–16] This relation remained highly significant in the ARISTOTLE trial. Despite oral anticoagulation and regular follow-up, all-cause mortality remained the most common major outcome event in this AF cohort. The mortality rates increased even further with decreasing renal function and the annual all-cause mortality rate was three-fold higher in patients with moderate/severe renal dysfunction compared with normal renal function. There was no significant interaction between treatment effects and renal dysfunction with respect to all-cause mortality and accordingly apixaban was more effective than warfarin also for this outcome irrespective of degree of renal impairment (*Figure 1*).[8]

Major bleeding in patients with renal dysfunction

Despite this increased risk for AF-associated thrombo-embolism, many patients with renal dysfunction are not receiving oral anticoagulation therapy,[7] mostly because of fear of bleeding with warfarin. In fact, it has been shown that the risk of bleeding associated with warfarin therapy is particularly high in patients with renal dysfunction.[17] The present results verify the increased rates of major bleeding events with decreasing renal function during oral anticoagulation with warfarin treatment in accordance with published reports.[17–19] Our findings show both that the overall rate of major bleeding is lower and also that the increase in the rate of bleeding by renal dysfunction is less with apixaban than warfarin.

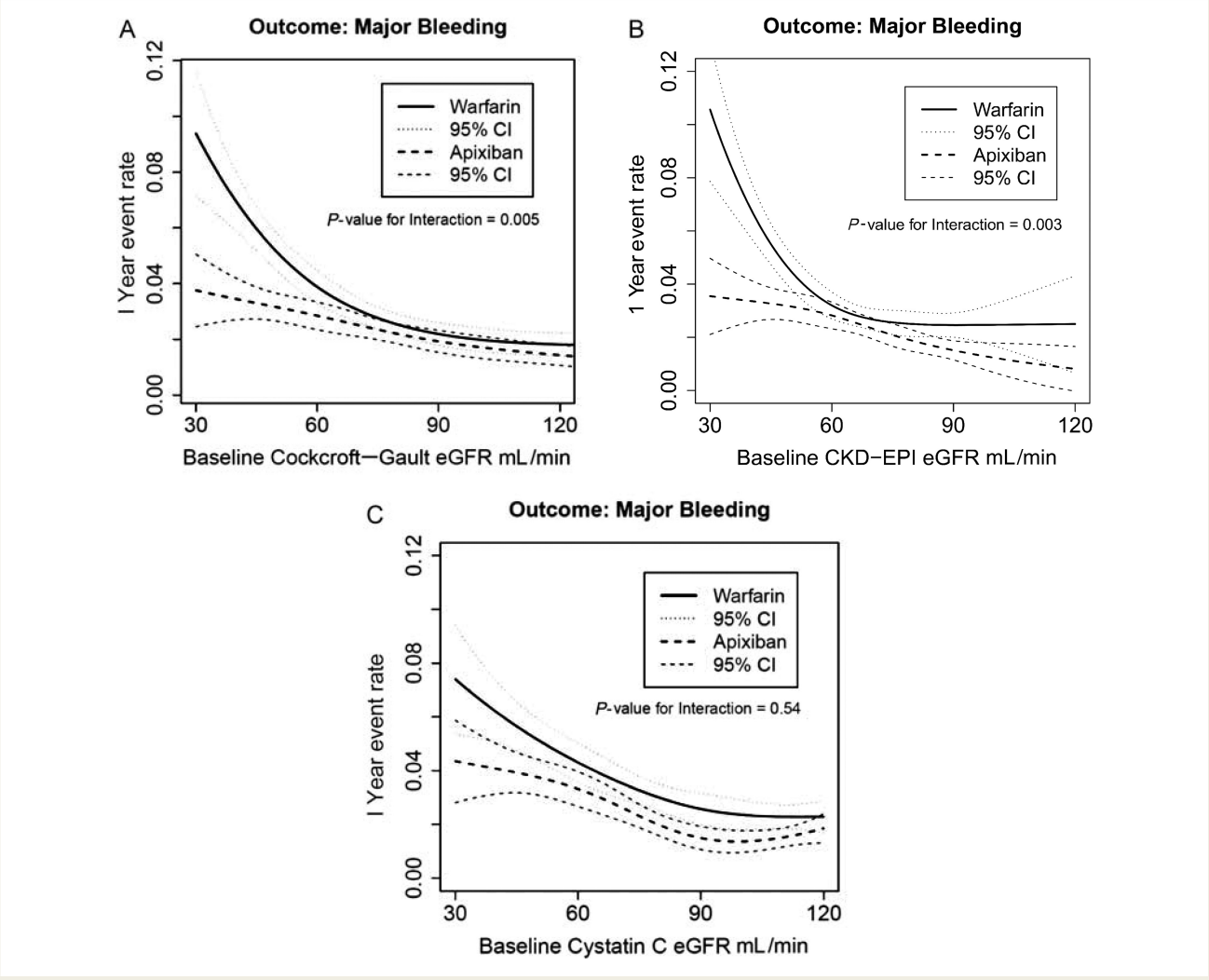

Figure 3 (*A*) Apixaban vs. warfarin for major bleed with continuous analysis of estimated renal function with Cockcroft–Gault. (*B*) Apixaban vs. warfarin for major bleed with continuous analysis of estimated renal function with CKD-EPI. (*C*) Apixaban vs. warfarin for major bleed with continuous analysis of estimated renal function with cystatin C. All interaction *P*-values are based on continuous estimated glomerular filtration rates.

Table 3 Sensitivity analyses of apixaban dose and bleeding

Outcome	*P*-value for interaction between randomized treatment and continuous eGFR (Cockcroft–Gault)		
	Main analysis	Sensitivity 1	Sensitivity 2
Stroke or systemic embolism	0.57	0.65	0.50
Major bleeding	0.005	0.02	0.04

Sensitivity 1, adjustment for dose (low/standard) by including dose as a covariate, both as a main effect and as an interaction between dose and treatment; sensitivity 2, exclusion of all patients on low dose apixaban (see text for details).

Accordingly, apixaban appears as safer for oral anticoagulation in AF patients across the full range of renal function and especially in those with renal impairment. Specifically, when impairment of renal function was assessed according to creatinine-based estimations, the largest reduction in bleeding complications with apixaban when compared with warfarin was seen in patients with the most pronounced renal impairment defined as eGFR below 50 mL/min.

Estimated glomerular filtration rate and treatment interaction

The CKD-EPI is a new equation for the estimation of GFR. CKD-EPI was specifically developed to outperform existing creatinine-based GFR estimates, in particular preserving a high accuracy in a chronic kidney disease population and simultaneously improving accuracy in the range of normal to mild GFR

impairments.[10] Cystatin C is a small protein, synthesized at a constant rate in all nucleated cells.[20] It is freely filtered by the glomerulus, does not return to the blood flow, is minimally influenced by disease states, and is therefore believed to be a better endogenous marker of eGFR than creatinine.[11] Cystatin C has been proposed as a more reliable marker of renal function than serum creatinine,[11] in particular for the detection of small reductions in eGFR.[21]

The Cockcroft–Gault and CKD-EPI are, as described, both serum creatinine-based estimations of GFR. With cystatin C, a higher proportion of patients were classified as having normal renal function in the present study, 51%, compared with 42 and 29% for Cockcroft–Gault and CKD-EPI, respectively. These differences may originate from disparities in the glomerular filtration of the biomarker or within the equations used, as both the Cockcroft–Gault and CKD-EPI take age and gender into account while cystatin C does not. This may explain the discrepancies between the treatment interaction analyses for major bleeding regarding Cockcroft–Gault and CKD-EPI compared with cystatin C. Although cystatin C in several studies has been described as a more reliable marker of renal function, it should be noted that in the elderly population, GFR estimated with cystatin C is not well described. In the few studies available, cystatin C has been described to yield a significantly lower prevalence of chronic kidney disease compared with creatinine-based estimates.[22] Since actual eGFR was not measured in the ARISTOTLE trial and the direct comparison among different methods to estimate GFR was not the main objective of our study, no general assumptions can be made in regard neither to preferable methods nor regarding superiority for estimating true eGFR with either the Cockcroft–Gault, CKD-EPI, or cystatin C equations in this population. Nonetheless, our findings may add to further improvement of tailoring oral anticoagulant treatment in AF patients by estimating renal function with Cockcroft–Gault or CKD-EPI.

Conclusions

The high risk of both stroke and of major bleeding in AF patients with impaired renal function defines an important group with a need for therapy that current treatments may not adequately address. When compared with warfarin, apixaban treatment reduced the rate of stroke, death, and major bleeding, regardless of renal function. Patients with impaired renal function seemed to have the greatest reduction in major bleeding with apixaban, when using creatinine-based estimates of GFR. Our findings suggest that apixaban may be particularly suited to address the unmet need for a more effective and safe stroke prevention in patients with AF and renal dysfunction.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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