Original Investigation

Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation in Relation to Renal Function Over Time

Insights From the ARISTOTLE Randomized Clinical Trial

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IMPORTANCE Renal impairment confers an increased risk of stroke, bleeding, and death in patients with atrial fibrillation. Little is known about the efficacy and safety of apixaban in relation to renal function changes over time.

OBJECTIVES To evaluate changes of renal function over time and their interactions with outcomes during a median of 1.8 years of follow-up in patients with atrial fibrillation randomized to apixaban vs warfarin treatment.

DESIGN, SETTING, AND PARTICIPANTS The prospective, randomized, double-blind Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) clinical trial randomized 18 201 patients with atrial fibrillation to apixaban or warfarin. Serial creatinine measurements were available in 16 869 patients. Worsening of renal function was defined as an annual decrease in estimated glomerular filtration more than 20%. The relations between treatment, outcomes, and renal function were investigated using Cox regression models, with renal function as a time-dependent covariate.

MAIN OUTCOMES AND MEASURES Stroke or systemic embolism (primary outcome), major bleeding (safety outcome), and mortality were examined in relation to renal function over time estimated with both the Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration equations.

RESULTS Among 16 869 patients, the median age was 70 years and 65.2% of patients were men. Worsening in estimated glomerular filtration more than 20% was observed in 2294 patients (13.6%) and was associated with older age and more cardiovascular comorbidities. The risks of stroke or systemic embolism, major bleeding, and mortality were higher in patients with worsening renal function (HR, 1.53; 95% CI, 1.17-2.01 for stroke or systemic embolism; HR, 1.56; 95% CI, 1.27-1.93 for major bleeding; and HR, 2.31; 95% CI, 1.98-2.68 for mortality). The beneficial effects of apixaban vs warfarin on rates of stroke or systemic embolism and major bleeding were consistent in patients with normal or poor renal function over time and also in those with worsening renal function.

CONCLUSIONS AND RELEVANCE In patients with atrial fibrillation, declining renal function was more common in elderly patients and those with cardiovascular comorbidities. Worsening renal function was associated with a higher risk of subsequent cardiovascular events and bleeding. The superior efficacy and safety of apixaban as compared with warfarin were similar in patients with normal, poor, and worsening renal function.

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Oral anticoagulation with non–vitamin K antagonist oral anticoagulants (NOACs) and vitamin K antagonists are associated with substantially reduced risk of stroke in atrial fibrillation (AF).[1-4] Assessment of renal function in this setting is important because the risks of thromboembolic complications and major bleeding are elevated in patients with renal impairment during NOAC as well as vitamin K antagonists treatment.[5-8] Although fixed daily doses of NOACs have demonstrated favorable efficacy and safety compared with warfarin, the influence of renal elimination on their plasma levels necessitates control of renal function over time because renal function gradually decreases with aging and also might be affected by comorbidities.[9] The importance of renal function in AF has also been emphasized becuase it was observed that 1 NOAC (edoxaban, an oral factor Xa inhibitor) was associated with decreased efficacy in patients with AF and high renal function as defined by creatinine clearance greater than 95 mL/min (US Food and Drug Administration Advisory Committee on Edoxaban [to convert to milliliters per second per meters squared, multiply by 0.0167]), highlighting the importance of investigating the efficacy in relation to renal function over time for all of these agents.[10,11]

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban compared with warfarin was associated with reduced risk of stroke, mortality, and major bleeding.[12] Subsequent analyses showed that the subgroup of patients with impaired renal function at randomization had similar results, with a trend towards even larger relative reduction in major bleeding with apixaban compared with warfarin.[8] Our aim in this study was to evaluate the efficacy and safety of apixaban vs warfarin in relation to changes in renal function over time. The specific objectives were to (1) assess the development of renal dysfunction throughout follow-up and its association with efficacy and safety outcomes, and (2) compare apixaban vs warfarin in patients with high renal function over time and in those with worsening renal function during follow-up.

Key Points

Question In patients with atrial fibrillation, how is variability in renal function over time affected by treatment with apixaban or warfarin and how does the change in renal function over time influence outcomes and interact with the efficacy and safety of apixaban compared with warfarin?

Findings Based on serial measurements from 16 869 patients with atrial fibrillation in the ARISTOTLE clinical trial who were randomized to apixaban vs warfarin, a more than 20% worsening of renal function was observed in 13.6% patients and was associated with an increased risk of cardiovascular events. The change in renal function was similar, but the relative risk of both stroke and major bleeding was lower in participants randomized to apixaban irrespective of level and changes in renal function.

Meaning There was a similar variability and decline in renal function over time with both apixaban and warfarin treatment, a worsening more than 20% was associated with higher risk of events, and a better efficacy and safety of apixaban in patients with normal, poor, and worsening renal function.

Methods

Patient Population and Trial Design

Details of the ARISTOTLE trial have been published previously.[13] Briefly, ARISTOTLE was a double-blind, double-dummy, randomized clinical trial that enrolled 18 201 patients with AF and at least 1 $CHADS_2$ risk factor for stroke or systemic embolism. Patients were randomized to warfarin (n = 9081) or apixaban (n = 9120). Apixaban was dosed at 5 mg twice daily or 2.5 mg twice daily for a subset of patients with 2 or more of the following criteria: age 80 years or older, body weight 60 kg or less, and/or serum creatinine level at least 1.5 mg/dL (to convert to micromoles per liter, multiply by 76.25). Exclusion criteria included conditions other than AF that required anticoagulation (eg, prosthetic heart valve) and severe renal insufficiency (serum creatinine level >2.5 mg/dL or calculated creatinine clearance <25 mL/min). Ethics committee approval was obtained for all investigational sites, and all patients provided written informed consent.

Outcome Assessment

The primary efficacy end point in ARISTOTLE was stroke or systemic embolism.[13] Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and categorized as ischemic, hemorrhagic, or unspecified. Hemorrhagic transformation of ischemic stroke was not considered to be hemorrhagic stroke. The primary safety end point was major bleeding.[13] This definition was adapted from the International Society on Thrombosis and Hemostasis. Major bleeding was defined as acute or subacute clinically overt bleeding accompanied by at least 1 of the following[13]: decrease in hemoglobin level of greater than 0.20 g/dL (to convert to grams per liter squared, multiply by 10); a transfusion of at least 2 units of packed red blood cells; and/or bleeding that was fatal or occurred in a critical area or organ (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, or retroperitoneal). A blinded Clinical Events Committee reviewed and adjudicated all suspected thromboembolic and bleeding events.

Laboratory Methods

Venous blood samples were scheduled for collection at the time of randomization and every 3 months thereafter for determination of creatinine levels. Plasma creatinine measurements were performed in a core laboratory using a Roche Modular analyzer with a kinetic colorimetric compensated Jaffe assay (Roche Modular). The creatinine assays were isotope dilution mass spectrometry standardized.

Glomerular Filtration Rate Estimation

Cockcroft-Gault estimated glomerular filtration rate (eGFR) (milliliters per minute per 1.73 m^2) was derived from the following equation: (140−age) × (Weight in kilograms) × (0.85 if female)/(72 × Creatinine in milligrams per decileter). The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR (milliliters per minute per 1.73 m^2) was derived from

the following equation[14]: 141 × min (Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if African American), where κ is 0.7 for women and 0.9 for men, α is −0.329 for women and −0.411 for men, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1, and Scr indicates serum creatinine levels, expressed in milligrams per deciliters.

Worsening renal function was defined as a decrease of greater than 20% in eGFR based on its clinical relevance in previous studies.[15,16]

Statistical Analyses

A total of 18 126 patients receiving treatment had baseline creatinine levels available, of which 16 869 had serial measurements (93%). The reasons for lack of serial measurement were mainly owing to patients requesting to discontinue study treatment, serious adverse events, or death. Cockcroft-Gault and CKD-EPI were calculated with creatinine measured every 3 months during the trial to evaluate eGFR over time. In the analysis of estimated annual change in eGFR over 12 months as a categorical variable, the change was estimated at each time point (3 months apart) by fitting a linear regression model for each patient using the actual and 4 preceding measurements (corresponding to 12 months). In the analysis of the eGFR as a continuous measure, the value was updated at each new creatinine measurement.

Associations between baseline characteristics and the change in eGFR over the first 12 months were examined in a linear regression model, including 14 913 patients with available 12-month measurement, where the change in eGFR over 12 months was the response variable with baseline characteristics, randomized treatment, and the eGFR at baseline as explanatory variables. Model-adjusted means with 95% CIs were compared.

All analyses were based on the receiving-treatment population including all randomized patients who had at least 1 dose of study drug. Analyses of bleeding events included all events from the first dose of study drug until 2 days after the last dose of study drug. Efficacy analyses included events from randomization until the efficacy cutoff date (predefined as January 30, 2011).

Hazard ratios (HRs) with 95% CIs comparing apixaban with warfarin were derived from Cox proportional hazards models including renal function as a time dependent covariate, as 2 different categorical variables (<50, 50-80, and >80 mL/min and <50, 50-95, and >95 mL/min), and as a continuous variable using restricted cubic splines. Treatment effects were compared according to renal function by adding interactions to the model. Hazard ratios comparing treatments were reported at varying levels of renal function, regardless of the significance of interaction. Worsening renal function over time according to an estimated annual 20% decrease over 12 months (yes/no) was also analyzed as a time-dependent covariate, excluding patients from analysis with events occurring before the month 3 measurement. Because changes from and to very high levels of eGFR were not of interest, all values of eGFR greater than 95 mL/min were in this analysis set to 95 mL/min. Annual event rate for a renal function category was calculated as the number of events connected to a renal function category divided by the sum of the patients time (in years) within the renal function category.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc). A 2-sided *P* value of less than .05 was considered statistically significant, and because all analyses were exploratory, there were no adjustments for multiple comparisons.

Results

Renal Function Over Time and Factors Associated With Declining Renal Function

At 12 months, the median eGFR decline was 1.02 mL/min (25th to 75th percentile, −6.72 to 4.52 mL/min). Assessment of renal function using linear regression from randomization to 12 months' follow-up identified a total of 4374 patients (26%) with sustained good renal function (eGFR >80 mL/min) and 1038 patients (6.2%) using the higher cutoff (eGFR >95 mL/min), 8112 patients (48.1%) with stable moderate renal function (eGFR, 50-80 mL/min), 2089 patients (12.4%) with a stable poor eGFR (<50 mL/min), and 2294 patients (13.6%) in whom eGFR declined more than 20%. Worsening renal function was associated with several baseline characteristics (**Table**). Adjusted for baseline renal function, older age, low hematocrit level, presence of heart failure, vascular disease, and diabetes were most strongly associated with deterioration in eGFR. There was no clinically relevant difference in the change in renal function over time in the groups randomized to apixaban vs warfarin. Patients without serial data were slightly older and had more comorbities (eTable in the Supplement).

Outcomes in Patients With Stable Renal Function Over Time

There were 367 events of the primary outcome of stroke or systemic embolism, 261 ischemic or unspecified stroke events, 628 major bleeding events, and 994 deaths occurring after month 3 (time of first repeated eGFR measurement). The annual stroke rate in patients without worsening renal function over time was 0.90% in patients with eGFR at or greater than 80 mL/min at randomization (n = 97), 1.31% in patients with eGFR between 50 and 80 mL/min (n = 126), and 2.03% in patients with eGFR at or less than 50 mL/min (n = 70) during the study according to the Cockcroft-Gault equation (**Figure 1**A). The annual rate of ischemic or unspecified strokes in patients with stable eGFR at or less than 50 mL/min was double that of patients with stable eGFR greater than 80 mL/min during follow-up (1.44% vs 0.69%). All-cause mortality was almost 3-fold higher in patients with stable eGFR at or less than 50 mL/min than in patients with stable eGFR greater than 80 mL/min during follow-up (6.64% vs 2.14%). Similarly, the incidence of major bleeding showed a similar pattern with increased annual event rates in those with stable eGFR at or less than 50 mL/min compared with stable eGFR greater than 80 mL/min (3.81% vs 1.34%). The associations between renal function status and the risk of cardiovascular and bleeding events were consistent using

Table. Baseline Characteristic of 14 913 Patients With Significant Associations With Estimated Change Renal Function (by CKD-EPI) at 12 Months' Follow-Up in Multivariable Adjusted Model

Variable Value at Baseline	No.	Change in Renal Function, mL/min			*P* Value[a]
		Mean (SD)	Model Adjusted Mean[a] (95% CI)	Difference in Means[a] (95% CI)	
Age category, y					
<65	4586	−0.89 (11.20)	0.78 (0.47 to 1.09)	1 [Reference]	<.001
65-<75	5870	−1.26 (9.96)	−1.43 (−1.68 to −1.18)	−2.21 (−2.67 to −1.76)	
≥75	4457	−1.35 (9.39)	−2.83 (−3.14 to −2.52)	−3.61 (−4.14 to −3.08)	
Type of atrial fibrillation					
Paroxysmal	2253	−1.79 (10.47)	−1.77 (−2.19 to −1.35)	1 [Reference]	.002
Persist/perm	12657	−1.06 (10.14)	−1.06 (−1.23 to −0.89)	0.71 (0.25 to 1.17)	
Heart rate class, beats/min					
<50	226	−3.26 (9.28)	−2.54 (−3.81 to −1.26)	1 [Reference]	.05
50-100	13 825	−1.17 (10.14)	−1.17 (−1.34 to −1.01)	1.36 (−0.03 to 2.76)	
>100	828	−0.48 (11.19)	−0.71 (−1.38 to −0.03)	1.83 (0.26 to 3.40)	
Heart failure					
No	10535	−1.19 (9.78)	−0.94 (−1.13 to −0.75)	1 [Reference]	<.001
Yes	4378	−1.14 (11.13)	−1.72 (−2.02 to −1.41)	−0.78 (−1.14 to −0.41)	
Diabetes mellitus					
No	11210	−1.00 (10.03)	−1.02 (−1.20 to −0.83)	1 [Reference]	.002
Yes	3703	−1.69 (10.66)	−1.62 (−1.94 to −1.30)	−0.61 (−0.98 to −0.23)	
Prior use warfarin/ vitamin K antagonist					
No	6141	−0.75 (10.94)	−0.82 (−1.07 to −0.56)	1 [Reference]	<.001
Yes	8772	−1.47 (9.63)	−1.41 (−1.62 to −1.20)	−0.59 (−0.94 to −0.25)	
Vascular disease					
No	11 377	−1.09 (10.20)	−0.98 (−1.17 to −0.80)	1 [Reference]	<.001
Yes	3536	−1.43 (10.17)	−1.75 (−2.09 to −1.42)	−0.77 (−1.16 to −0.38)	
Hematocrit level, %					
>46	3317	−0.24 (10.00)	−0.27 (−0.62 to 0.08)	1 [Reference]	<.001
>43-46	3755	−0.86 (9.73)	−0.69 (−1.00 to −0.37)	−0.42 (−0.97 to 0.13)	
>40-43	3679	−1.42 (10.25)	−1.31 (−1.62 to −0.99)	−1.04 (−1.60 to −0.47)	
≤40	4079	−1.99 (10.62)	−2.21 (−2.53 to −1.89)	−1.94 (−2.54 to −1.35)	
ACEi or ARB treatment					
No	4333	−1.02 (9.65)	−0.79 (−1.09 to −0.48)	1 [Reference]	.005
Yes	10 580	−1.24 (10.41)	−1.32 (−1.51 to −1.13)	−0.54 (−0.91 to −0.16)	
Randomized treatment					
Warfarin	7363	−0.92 (10.27)	−0.96 (−1.18 to −0.74)	1 [Reference]	.01
Apixaban	7550	−1.42 (10.12)	−1.37 (−1.59 to −1.15)	−0.41 (−0.72 to −0.10)	

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; NA, not applicable.

[a] Linear regression model including 14 913 patients with available 12-month measurement with the estimated change in eGFR over 12 months as response variable and baseline characteristics, randomized treatment, and the eGFR at baseline as explanatory variables. Nonsignificant baseline characteristics ($P > .05$) in the model were sex, body mass index (calculated as weight in kilograms divided by height in meters squared), current smoker, prior stroke/systemic embolism/transient ischemic attack, congestive heart failure, hypertension, history of anemia, history of spontaneous or clinically relevant bleeding, treatment with nonsteroidal anti-inflamatory drugs/antiplatelets, and treatment with amiodarone. The model was also adjusted for continuous baseline renal function and geographic region.

both the Cockcroft-Gault and CKD-EPI equations for GFR estimation (Figure 1B).

Outcomes in Patients With Worsening Renal Function Over Time

The annual rate of stroke or systemic embolism, ischemic or unspecified stroke, major bleeding, and mortality was consistently higher in patients with a worsening renal function (eGFR deterioration >20%) compared with patients with no worsening during follow-up, irrespective of the baseline renal function (Figure 1A and B). Worsening renal function during follow-up conveyed HRs of 1.53 (95% CI, 1.17-2.01) for stroke or systemic embolism, 1.56 (95% CI, 1.27-1.93) for major bleeding, and 2.31 (95% CI, 1.98-2.68) for all-cause mortality, compared with patients who had no worsening (Figure 1A). The results were consistent using both the Cockcroft-Gault and CKD-EPI equations for GFR estimation (Figure 1B).

Efficacy and Safety of Apixaban Compared With Warfarin by Renal Function Over Time

The relative risk of stroke or systemic embolism was lower in participants randomized to apixaban compared with warfarin in the whole trial, and this difference was consistent and without any significant interaction with changes in renal function during the study (**Figure 2**). These results were similar for the ischemic or unspecified stroke outcome. The relative risk of major bleeding was lower in participants randomized to apixaban compared with warfarin, and these findings were consistent without any significant interaction with changes in renal function (Figure 2). Using a higher cutoff for normal renal

Figure 1. Outcomes According to Categories of Change in Renal Function Over Time by Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equations

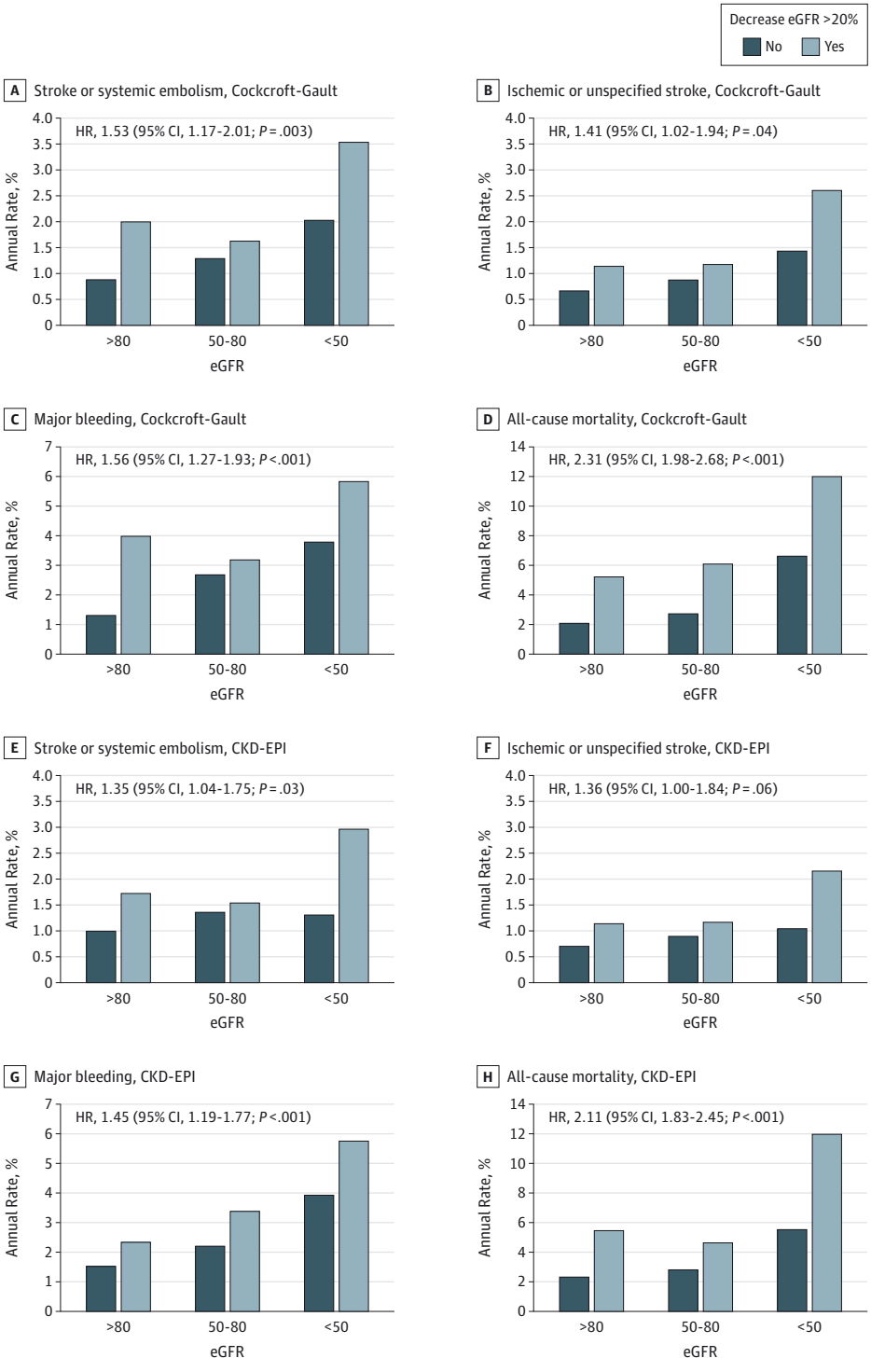


Figure illustrates the annual rate of events according to renal function at randomization and whether renal function deteriorated greater than 20% over 12 months. The hazard ratio (HR) is based on a Cox proportional hazards model including treatment group, change category (20% decrease per 12 months yes/no) as a time-dependent covariate, and baseline renal function category (estimated glomerular filtration rate [eGFR] <50 mg/dL, 50-80 mg/dL, and >80 mg/dL). eGFR indicates estimated glomerular filtration rate.

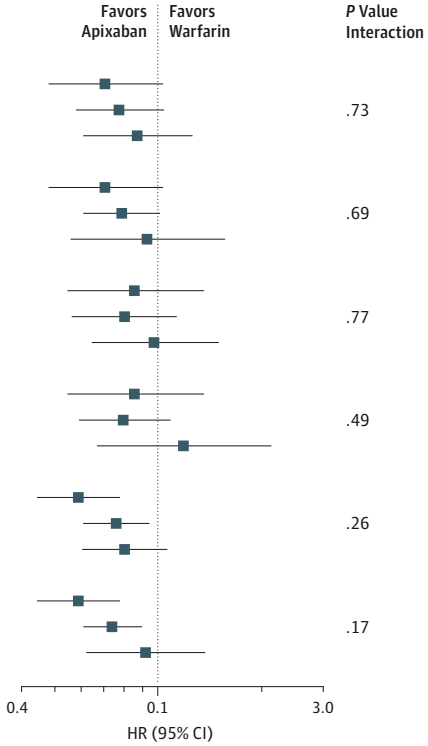
function (eGFR >95 mL/min instead of >80 mL/min) yielded similar results (Figure 2). Analyses based on the continuous eGFR data demonstrated similar results with lower relative risk of stroke or systemic embolism, ischemic or unspecified stroke, and major bleeding with apixaban compared with warfarin (**Figure 3**).

In patients with worsening of renal function over time during 12 months, apixaban, compared with warfarin, consistently demonstrated lower relative risk of stroke or systemic embolism (HR, 0.80; 95% CI, 0.51-1.24; P = .86), ischemic or unspecified stroke (HR, 0.88; 95% CI, 0.52-1.48; P = .94), and major bleeding (HR, 0.76; 95% CI, 0.54-1.07;

Figure 2. Apixaban vs Warfarin According to Category of Renal Function Over Time by Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration Equations

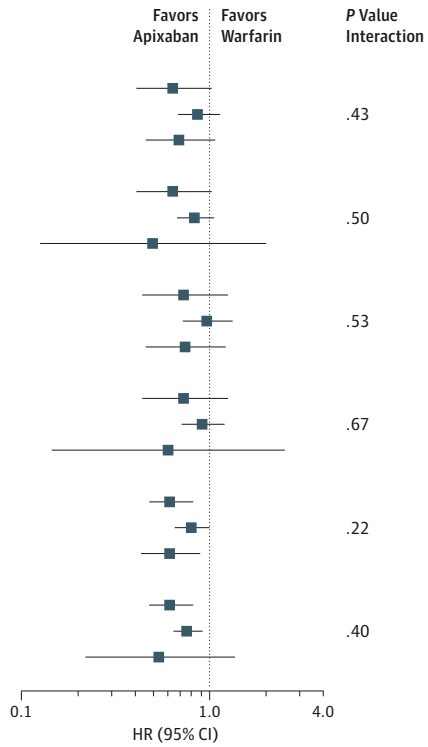
A Cockcroft-Gault equation

Estimated Glomerular Filtration Rate	No. of Person-Years		No. of Events (%/y)		HR (95% CI)	P Value Interaction
	Apixaban	Warfarin	Apixaban	Warfarin		
Stroke/systemic embolism						
<50 mL/min	2772.8	2656.1	45 (1.62)	61 (2.30)	0.70 (0.48-1.03)	
50-80 mL/min	6640.5	6552.4	77 (1.16)	98 (1.50)	0.78 (0.58-1.04)	.73
>80 mL/min	6457.4	6478.0	53 (0.82)	61 (0.94)	0.87 (0.60-1.26)	
Higher renal function cutoff						
<50 mL/min	2772.8	2656.1	45 (1.62)	61 (2.30)	0.70 (0.48-1.03)	
50-95 mL/min	9145.6	9083.2	102 (1.12)	129 (1.42)	0.79 (0.61-1.02)	.69
>95 mL/min	3952.3	3947.1	28 (0.71)	30 (0.76)	0.93 (0.56-1.56)	
Ischemic/unspecified stroke						
<50 mL/min	2779.0	2665.8	35 (1.26)	39 (1.46)	0.86 (0.54-1.35)	
50-80 mL/min	6649.0	6562.2	56 (0.84)	69 (1.05)	0.80 (0.56-1.14)	.77
>80 mL/min	6464.6	6484.6	42 (0.65)	43 (0.66)	0.98 (0.64-1.50)	
Higher renal function cutoff						
<50 mL/min	2779.0	2665.8	35 (1.26)	39 (1.46)	0.86 (0.54-1.35)	
50-95 mL/min	9158.3	9096.1	73 (0.80)	91 (1.00)	0.80 (0.59-1.09)	.49
>95 mL/min	3955.2	3950.7	25 (0.63)	21 (0.53)	1.19 (0.67-2.12)	
Major bleeding						
<50 mL/min	2603.0	2428.7	82 (3.15)	130 (5.35)	0.59 (0.45-0.77)	
50-80 mL/min	6347.0	6203.0	136 (2.14)	176 (2.84)	0.76 (0.60-0.94)	.26
>80 mL/min	6235.5	6187.9	83 (1.33)	103 (1.66)	0.80 (0.60-1.07)	
Higher renal function cutoff						
<50 mL/min	2603.0	2428.7	82 (3.15)	130 (5.35)	0.59 (0.45-0.77)	
50-95 mL/min	8773.7	8573.6	173 (1.97)	229 (2.67)	0.74 (0.61-0.90)	.17
>95 mL/min	3808.8	3817.3	46 (1.21)	50 (1.31)	0.92 (0.62-1.38)	



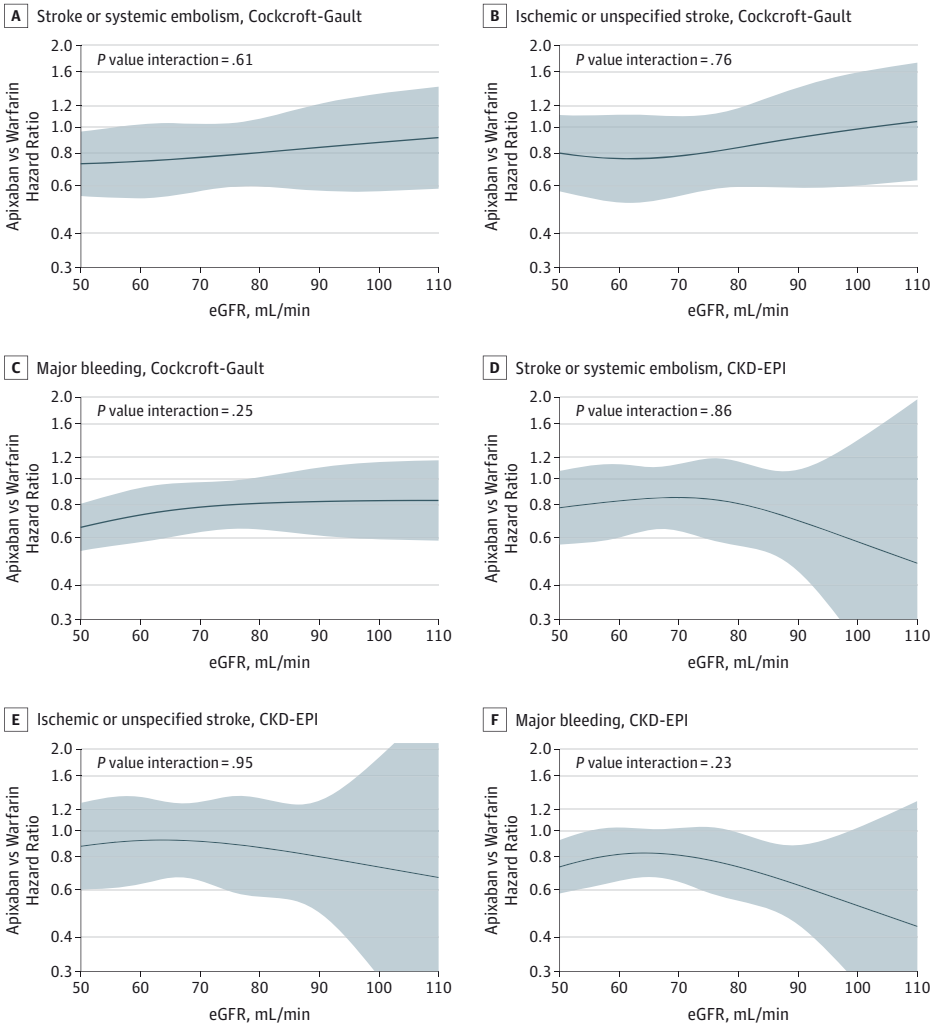
B Chronic Kidney Disease Epidemiology equation

Estimated Glomerular Filtration Rate	No. of Person-Years		No. of Events (%/y)		HR (95% CI)	P Value Interaction
	Apixaban	Warfarin	Apixaban	Warfarin		
Stroke/systemic embolism						
<50 mL/min	2702.2	2600.2	30 (1.11)	45 (1.73)	0.64 (0.41-1.02)	
50-80 mL/min	8918.3	8766.8	111 (1.24)	125 (1.43)	0.87 (0.68-1.13)	.43
>80 mL/min	4310.2	4367.2	35 (0.81)	51 (1.17)	0.70 (0.45-1.07)	
Higher renal function cutoff						
<50 mL/min	2702.2	2600.2	30 (1.11)	45 (1.73)	0.64 (0.41-1.02)	
50-95 mL/min	12 287.0	12 189.0	143 (1.16)	170 (1.39)	0.83 (0.67-1.04)	.50
>95 mL/min	941.6	945.0	3 (0.32)	6 (0.63)	0.50 (0.12-2.00)	
Ischemic/unspecified stroke						
<50 mL/min	2706.3	2604.9	25 (0.92)	33 (1.27)	0.73 (0.44-1.23)	
50-80 mL/min	8931.8	8780.0	80 (0.90)	81 (0.92)	0.97 (0.71-1.32)	.53
>80 mL/min	4314.6	4375.4	28 (0.65)	38 (0.87)	0.75 (0.46-1.21)	
Higher renal function cutoff						
<50 mL/min	2706.3	2604.9	25 (0.92)	33 (1.27)	0.73 (0.44-1.23)	
50-95 mL/min	12 304.7	12 208.6	105 (0.85)	114 (0.93)	0.91 (0.70-1.19)	.67
>95 mL/min	941.7	946.8	3 (0.32)	5 (0.53)	0.60 (0.14-2.51)	
Major bleeding						
<50 mL/min	2504.9	2348.7	82 (3.27)	124 (5.28)	0.62 (0.47-0.82)	
50-80 mL/min	8544.3	8348.2	172 (2.01)	209 (2.50)	0.80 (0.66-0.98)	.22
>80 mL/min	4195.1	4170.5	48 (1.14)	78 (1.87)	0.61 (0.43-0.88)	
Higher renal function cutoff						
<50 mL/min	2504.9	2348.7	82 (3.27)	124 (5.28)	0.62 (0.47-0.82)	
50-95 mL/min	11 833.8	11 607.5	213 (1.80)	274 (2.36)	0.76 (0.64-0.91)	.40
>95 mL/min	905.6	911.2	7 (0.77)	13 (1.43)	0.54 (0.22-1.36)	



Cox proportional hazards model including randomized treatment, estimated glomerular filtration rate as a time dependent covariate, and treatment interaction. For each outcome estimated glomerular filtration rates categories with different definitions of normal renal function (>80 mL/min and >95 mL/min, respectively) are presented.

Figure 3. Apixaban vs Warfarin According to Continuous Renal Function Over Time According to the Cockcroft-Gault and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equations



Cox proportional hazards model included randomized treatment, renal function as a time dependent continuous covariate, and treatment interaction. eGFR indicates estimated glomerular filtration rate.

P = .73) (eFigure in the Supplement). Estimated glomerular filtration rate according to the Cockcroft-Gault equation showed similar results for all the interaction analyses (eFigure in the Supplement).

Discussion

The results from this study verified a mean slow gradual reduction of renal function over time in patients with AF treated with oral anticoagulants. The study highlighted that the rate of deterioration was variable, with a more rapid reduction at older age and with comorbidities such as heart failure, vascular disease, or diabetes. The 2294 patients (13.6%) with a more pronounced (>20%) worsening of renal function had a higher risk of both cardiovascular events and bleeding. Apixaban compared with warfarin treatment was associated with lower risk of stroke, death, and major bleeding in patients, regardless of baseline and changes of renal function.

Worsening Renal Function Over Time and Risk of Cardiovascular Events

These results on serial changes of renal function are in accordance with previous results based on baseline measurements on renal function from this and other trials.[5,7,8] In AF, the risks related to a worsening of renal function over time have, to our knowledge, previously only been described in smaller, registry-based cohorts and have primarily been composed of increased rates of mortality and composite cardiovascular events.[17,18] The results in this study demonstrate similar associations and further extend the results to the individual outcomes of stroke or systemic embolism and of major bleeding. Apart from the direct consequences on the renal clearance of NOACs, renal dysfunction is a state associated with several mechanisms of an increased risk of thromboembolic and bleeding complications, such as aging, hypertension, comorbidities, concomitant medications, and general frailty, in addition to more specific mechanism such as platelet dysfunction and coagulopathy.[19-21] The relation between renal

dysfunction and poorer prognosis both concerning thromboembolic and major bleeding risk poses a concrete dilemma in clinical practice because better protection against stroke is often counterbalanced by more bleeding.[20] However, in this study, apixaban demonstrated lower rates of both efficacy outcomes (stroke/systemic embolism and ischemic or unspecified stroke) and safety outcomes (major bleeding) irrespective of renal function over time, which provides useful information and may facilitate an informed decision regarding anticoagulation treatment in clinical practice.

Risk of Progressive Renal Dysfunction and Implications for Monitoring

In most of the 16 869 patients with repeated measurements in the ARISTOTLE trial (86.5%), overall renal function declined very slowly over time. The finding is reassuring and indicates that, in general, there is little need for close monitoring of renal function for dose adjustments of NOACs. However, in the selected group of patients with AF with older age, low hematocrit level, presence of heart failure, vascular disease, or diabetes, there was a risk for a more rapid decline in renal function over time. Patients at risk for more rapid decline and patients with initially poor renal function may be considered for more frequent monitoring of renal function when treated with oral anticoagulants. In the ARISTOTLE trial, renal function was assessed at the time of randomization and every 3 months thereafter. It might therefore be suggested that renal function should be reevaluated initially after 3 months to estimate the individual rate of decline in renal function and thereafter at least on a yearly basis.[22] In patients with reduced kidney function (eGFR <60 mL/min), a more rapid decline (>20%/year), or with any of the previously mentioned risk factors, shorter recheck intervals seem reasonable. Although the dose reduction criteria (≥2 of the following: age ≥80 years, body weight ≤60 kg, and/or serum creatinine level ≥1.5 mg/dL) in the ARISTOTLE trial were used only at the time of randomization, it seems reasonable to decrease the dose in those who fulfill these criteria during follow-up, a preventive measure also suggested in the 2015 guidelines.[22] Among other variables associated with declining renal function during the trial was prior (prestudy) use of vitamin K antagonists such as warfarin. This may be indicative of an increased vascular calcification owing to vitamin K antagonist treatment, as has recently been reported.[23] However, it may also be owing to confounding because prior warfarin treatment also identifies patients with higher burden of cardiovascular disease, the initial reason for prescribing the anticoagulant. Exploratory post hoc analyses concerning the effect of apixaban or warfarin study treatment on renal function during the trial only showed small differences, possibly affected by confounding factors because apixaban overall significantly reduced mortality compared with warfarin.[12]

Efficacy and Safety in Patients With Normal Renal Function

The potential concern of adequate dosing of NOACs in patients with AF and high normal renal function has been highlighted by the US Food and Drug Administration because edoxaban was believed by the Food and Drug Administration to have reduced efficacy in patients with high creatinine clearance (>95 mL/min) at baseline. Although the risk of adverse events in patients with normal renal function is generally low, these observations emphasize the potential hazard and consequence of underdosing NOACs. Concerning apixaban, a prior analysis of outcomes in relation to renal function at randomization demonstrated consistent efficacy and safety compared with warfarin, irrespective of baseline renal function.[8] This study provides additional insight by showing similar superior outcomes with apixaban compared with warfarin, regardless of renal function over time, enabling a better identification of patients with normal, worsening, or reduced renal function during up to 4 years of follow-up. Both apixaban and edoxaban are direct factor Xa inhibitors with fairly similar pharmacokinetic half-lives: 12 hours for apixaban and 9 to 11 hours for edoxaban.[9,11,13] However, apixaban is used twice daily, compared with the once-daily dosing of edoxaban. Renal clearance is less, approximately 27%, for apixaban compared with 50% for edoxaban. Besides the possibility of underdosing of edoxaban, these differences in dose intervals and renal elimination may contribute to the different relative efficacy compared with warfarin in patients with normal renal function.

Limitations

The findings in this study are limited by being a retrospective analysis based on a study population from the ARISTOTLE trial in which eGFR of less than 25 mL/min constituted an exclusion criterion. Comparisons between compounds tested in different studies always need to be interpreted with great caution because of differences in patient populations and follow-up periods and also owing to more specific matters such as different eGFR methods applied and different classifications of worsening renal function over time. The analyses regarding the association between abnormal renal function and increased rates of bleeding, stroke, and mortality were based on observational data in subgroups and not adjusted for confounders. The strength of these analyses of the ARISTOTLE trial is the fairly complete serial information on renal function over time based on 16 869 patients and a total of 135 564 measurements of creatinine. In addition, eGFR was assessed by 2 different equations with similar results.

Conclusions

In patients with AF, the decline in renal function was more rapid in those with older age or presence of comorbidities, such as heart failure, diabetes, or vascular disease, as opposed to slow, age-related decline. Worsening renal function was associated with a higher risk of subsequent cardiovascular events. Treatment with apixaban compared with warfarin had no effect on renal function and the advantages in efficacy and safety of apixaban compared with warfarin were similar among patients with normal, poor, or worsening renal function.

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