

Apixaban 5 mg Twice Daily and Clinical Outcomes in Patients With Atrial Fibrillation and Advanced Age, Low Body Weight, or High Creatinine

A Secondary Analysis of a Randomized Clinical Trial

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IMPORTANCE In the Apixaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation (ARISTOTLE) trial, the standard dose of apixaban was 5 mg twice daily; patients with at least 2 dose-reduction criteria—80 years or older, weight 60 kg or less, and creatinine level 1.5 mg/dL or higher—received a reduced dose of apixaban of 2.5 mg twice daily. Little is known about patients with 1 dose-reduction criterion who received the 5 mg twice daily dose of apixaban.

OBJECTIVE To determine the frequency of 1 dose-reduction criterion and whether the effects of the 5 mg twice daily dose of apixaban on stroke or systemic embolism and bleeding varied among patients with 1 or no dose-reduction criteria.

DESIGN, SETTING, AND PARTICIPANTS Among 18 201 patients in the ARISTOTLE trial, 17 322 were included in this analysis. Annualized event rates of stroke or systemic embolism and major bleeding and hazard ratios (HRs) and 95% CIs were evaluated. Interactions between the effects of apixaban vs warfarin and the presence of 1 or no dose-reduction criteria were assessed. The first patient was enrolled in the ARISTOTLE trial on December 19, 2006, and follow-up was completed on January 30, 2011. Data were analyzed from January 2015 to May 30, 2016.

MAIN OUTCOMES AND MEASURES Analysis of major bleeding included events during study drug treatment. Analysis of stroke or systemic embolism was based on intention to treat.

RESULTS Of the patients with 1 or no dose-reduction criteria assigned to receive the 5 mg twice daily dose of apixaban or warfarin, 3966 had 1 dose-reduction criterion; these patients had higher rates of stroke or systemic embolism (HR, 1.47; 95% CI, 1.20-1.81) and major bleeding (HR, 1.89; 95% CI, 1.62-2.20) compared with those with no dose-reduction criteria ($n = 13\,356$). The benefit of the 5 mg twice daily dose of apixaban ($n = 8665$) compared with warfarin ($n = 8657$) on stroke or systemic embolism in patients with 1 dose-reduction criterion (HR, 0.94; 95% CI, 0.66-1.32) and no dose-reduction criterion (HR, 0.77; 95% CI, 0.62-0.97) were similar (P for interaction = .36). Similarly, the benefit of 5 mg twice daily dose of apixaban compared with warfarin on major bleeding in patients with 1 dose-reduction criterion (HR, 0.68; 95% CI, 0.53-0.87) and no dose-reduction criterion (HR, 0.72; 95% CI, 0.60-0.86) were similar (P for interaction = .71). Similar patterns were seen for each dose-reduction criterion and across the spectrum of age, body weight, creatinine level, and creatinine clearance.

CONCLUSIONS AND RELEVANCE Patients with atrial fibrillation and isolated advanced age, low body weight, or renal dysfunction have a higher risk of stroke or systemic embolism and major bleeding but show consistent benefits with the 5 mg twice daily dose of apixaban vs warfarin compared with patients without these characteristics. The 5 mg twice daily dose of apixaban is safe, efficacious, and appropriate for patients with only 1 dose-reduction criterion.

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In patients with atrial fibrillation (AF) at risk for stroke, oral anticoagulation is recommended to reduce the risk of thromboembolism. Although non-vitamin K antagonist oral anticoagulants (NOACs) have been developed with a single dose for most patients, reduced doses are recommended in patients with increased predicted exposure and a related increased risk of bleeding.¹⁻⁵ Prescription data from around the world suggest higher than expected use of the reduced doses of NOACs, presumably because of concerns about bleeding in higher-risk populations (IMS MIDAS Standard Units Report, unpublished data, November 2015). In trials that have randomized patients with AF to different doses of a NOAC, higher doses have consistently been associated with greater reductions in ischemic stroke and more bleeding, whereas lower doses have been associated with smaller reductions or increases in stroke and less bleeding.^{1,4}

In the Apixaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation (ARISTOTLE) trial that compared the oral direct factor Xa inhibitor apixaban with warfarin in patients with AF, the standard dose of apixaban was 5 mg twice daily. A reduced dose of apixaban—2.5 mg twice daily—was used in patients with 2 or more of the following criteria: 80 years or older, weight 60 kg or less, and creatinine level 1.5 mg/dL or more (to convert to micromoles per liter, multiply by 88.4).^{2,6-8} Little is known about the subgroup of patients with only 1 of 3 dose-reduction criteria receiving the 5 mg twice daily dose of apixaban vs warfarin. Our objectives were (1) to determine whether the effects of the 5 mg twice daily dose of apixaban compared with warfarin on stroke or systemic embolism and bleeding varied among patients who had 1 or no dose-reduction criteria; and (2) to assess the safety of the 5 mg twice daily dose of apixaban compared with warfarin with respect to bleeding across the range of observed individual dose-reduction criteria.

Methods

Study Procedure

The design and results of the ARISTOTLE trial have been published previously.^{2,9} Briefly, the ARISTOTLE trial was a double-blind, double-dummy, randomized clinical trial of 18 201 patients with AF and at least 1 additional risk factor for stroke or systemic embolism. Risk factors included being 75 years or older and having hypertension, diabetes, heart failure or reduced left ventricular systolic function, and prior stroke or systemic embolism. Appropriate ethics committees at all sites approved the study, and all patients provided written informed consent.

Patients were randomized to warfarin and apixaban placebo (n = 9081) or apixaban and warfarin placebo (n = 9120). Most of the patients randomized to apixaban were assigned to receive the 5 mg twice daily dose; however, patients with 2 or 3 dose-reduction criteria at baseline were assigned the reduced 2.5 mg twice daily dose. Dose-reduction criteria included being 80 years or older, weighing 60 kg or less, and having a creatinine level 1.5 mg/dL or higher. These characteristics, particularly in combination, predict greater expo-

Key Points

Question Does the effect of apixaban dosing—5 mg twice daily—on bleeding or stroke vary in patients with advanced age, low body weight, or elevated creatinine levels?

Findings In this secondary analysis of the ARISTOTLE trial, the subgroup of patients with advanced age, low body weight, or elevated creatinine had higher rates of bleeding and stroke than those without these characteristics. The effects of the 5 mg twice daily dose of apixaban compared with warfarin on bleeding and stroke were similar in patients with and without these characteristics.

Meaning The 5 mg twice daily dose of apixaban is appropriate for patients with advanced age, low body weight, or an elevated creatinine level.

sure to apixaban.⁶⁻⁸ Warfarin was dose adjusted to achieve a target international normalized ratio of 2.0 to 3.0 using a blinded, encrypted, point-of-care international normalized ratio device.

The median duration of follow-up in the ARISTOTLE trial was 1.8 years. The first patient was enrolled on December 19, 2006, and final follow-up was completed on January 30, 2011. The primary focus of this analysis was safety, and thus the primary outcome was major bleeding as defined by the International Society on Thrombosis and Haemostasis.¹⁰ Other outcomes include stroke or systemic embolism, ischemic or unspecified stroke, intracranial hemorrhage, cardiovascular death, and all-cause death. All end points were adjudicated by a clinical events committee that was unaware of treatment assignment, using prespecified criteria.

Statistical Analysis

Data were analyzed from January 2015 to May 2016. Participants in the ARISTOTLE trial randomized to the 5 mg twice daily dose of apixaban or warfarin were stratified by dose-reduction criteria. Patients with 2 or 3 dose-reduction criteria were excluded from the present analysis. Patients with 1 of the 3 dose-reduction criteria were then compared with patients with none of the 3 criteria; all patients included in the analysis were assigned to receive the 5 mg twice daily dose of apixaban or warfarin. Baseline categorical variables are presented as counts with associated percentages and continuous variables as medians (25th, 75th percentiles). We evaluated annualized event rates of stroke or systemic embolism and major bleeding and derived hazard ratios (HRs) and 95% CIs from Cox proportional hazards models. Analyses of bleeding outcomes included only events occurring during study drug treatment, whereas stroke or systemic embolism and other efficacy outcomes were analyzed using intention-to-treat methods. Interactions between the effects of apixaban compared with warfarin and the presence of 1 or no dose-reduction criteria and for each dose-reduction criterion were assessed. The estimated 1-year probability and associated 95% CI of a major bleeding event among patients randomized to the 5 mg twice daily dose of apixaban or warfarin were plotted using restricted cubic splines across the range of

age, weight, creatinine level, and estimated creatinine clearance. Estimated creatinine clearance was calculated using the Cockcroft-Gault equation.¹¹ The analyses presented herein were performed at the Uppsala Clinical Research Center (Uppsala, Sweden) using SAS software (version 94; SAS Institute, Inc).

Results

Among the 18 201 patients enrolled in the ARISTOTLE trial, 17 370 (95.4%) were randomized to receive the 5 mg twice daily dose of apixaban or warfarin. Of these, 13 356 (76.9%) had no dose-reduction criteria and 3966 (22.8%) had only 1 dose-reduction criterion. Forty-eight patients (0.3%) with 2 dose-reduction criteria who received the 5 mg twice daily dose of apixaban were excluded from this analysis. Among patients with only 1 dose-reduction criterion, 1636 (41.3%) were 80 years or older, 1426 (36.0%) weighed 60 kg or less, and 904 (22.8%) had creatinine levels 1.5 mg/dL or higher (Table 1).

The baseline characteristics of those randomized to the 5 mg twice daily dose of apixaban or warfarin with 1 and no dose-reduction criteria are shown in Table 2. Patients with 1 dose-reduction criterion were older, weighed less, were more frequently female, were more likely to be from the Asia Pacific region, had worse renal function, and had higher CHADS₂ (Congestive Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus [1 point for presence of each], and Stroke/TIA [2 points])¹² and HAS-BLED scores (represents bleeding risk and assigns 1 point for the presence of each of the following: hypertension [uncontrolled systolic blood pressure >160 mm Hg], abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, being elderly, and concomitant use of drugs and/or excessive alcohol)¹³ than patients with no dose-reduction criteria. Among the patients with 1 dose-reduction criterion, baseline characteristics were well matched between those randomized to apixaban and those randomized to warfarin (eTable in the Supplement). Patients with 1 dose-reduction criterion had higher rates of stroke or systemic embolism (HR, 1.47; 95% CI, 1.20-1.81), ischemic stroke (HR, 1.54; 95% CI, 1.21-1.96), major bleeding (HR, 1.89; 95% CI, 1.62-2.20), intracranial hemorrhage (HR, 1.72; 95% CI, 1.23-2.39), all-cause death (HR, 2.01; 95% CI, 1.78-2.28), and cardiovascular death (HR, 1.88; 95% CI, 1.58-2.23) than patients with no dose-reduction criteria.

The effect of the 5 mg twice daily dose of apixaban causing less major bleeding than warfarin was consistent among patients with 1 and no dose-reduction criteria (*P* for interaction = .71) (Figure 1). Similarly, the effect of the 5 mg twice daily dose of apixaban compared with warfarin on major bleeding was consistent among patients with each dose-reduction criterion (Figure 1). Although the HR for ischemic stroke, cardiovascular death, and all-cause death was greater than 1 among patients with 1 dose-reduction criterion and less than 1 among patients with no dose-reduction criteria, we found no evidence of statistical heterogeneity in the effect of apixaban com-

Table 1. Dose-Reduction Criteria Among Patients Randomized to Apixaban or Warfarin in the ARISTOTLE Trial^a

No. of Dose-Reduction Criteria	No. (%) of Patients (n = 17 370)
None	13 356 (76.9)
1	3966 (22.8)
Age ≥80 y	1636 (41.3)
Weight ≤60 kg only	1426 (36.0)
Creatinine ≥1.5 mg/dL only	904 (22.8)
2	48 (0.3)

Abbreviation: ARISTOTLE, Apixaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation.

SI conversion factor: To convert creatinine to micromoles per liter, multiply by 88.4.

^a Includes patients randomized to apixaban 5 mg twice daily (standard dose).

pared with warfarin on stroke or systemic embolism (*P* for interaction = .36), ischemic stroke (*P* for interaction = .14), intracranial hemorrhage (*P* for interaction = .26), all-cause death (*P* for interaction = .054), or cardiovascular death (*P* for interaction = .26) or among patients with 1 and those with no dose-reduction criteria (Table 3).

The effects of the 5 mg twice daily dose of apixaban compared with warfarin on the risk of major bleeding across the range of age, weight, creatinine level, and creatinine clearance observed in the ARISTOTLE population are shown in Figure 2. Apixaban was consistently associated with a numerically lower risk of major bleeding than warfarin across the spectrum of age, weight, creatinine level, and creatinine clearance. Patients who were older, weighed less, had an elevated creatinine level, and had lower creatinine clearance tended to have greater relative reductions in major bleeding with apixaban compared with warfarin than patients who were younger, weighed more, had lower creatinine levels, and had higher creatinine clearance.

Discussion

Patients with AF and 1 apixaban dose-reduction criterion—80 years or older, weight 60 kg or less, and creatinine level 1.5 mg/dL or higher—had more bleeding and thromboembolic events during follow-up than patients without these dose-reduction criteria. In patients with 1 or no dose-reduction criteria, the 5 mg twice daily dose of apixaban compared with warfarin resulted in similar benefits with respect to stroke or systemic embolism, major bleeding, and intracranial hemorrhage. Even at extremes of older age, lower body weight, and renal dysfunction, the 5 mg twice daily dose of apixaban was associated with substantially less bleeding than warfarin. These findings, that the bleeding benefits are preserved with the 5 mg twice daily dose of apixaban in patients with only 1 dose-reduction criterion, suggest that this apixaban dose should be used in this population. Patients should be treated with the effective doses as studied, because using the reduced 2.5 mg twice daily dose of apixaban in this population could result in preventable strokes.¹⁻⁴

Table 2. Baseline Characteristics of Patients With 1 and No Dose-Reduction Criteria in the ARISTOTLE Trial^a

Baseline Characteristic	No. (%) of Patients	
	1 Dose-Reduction Criterion (n = 3966)	No Dose-Reduction Criterion (n = 13 356)
Age, median (25th, 75th percentile), y	77.0 (69.0, 82.0)	68.0 (61.0, 73.0)
Weight, median (25th, 75th percentile), kg	70.0 (57.6, 83.9)	86.0 (75.0, 99.0)
BMI, median (25th, 75th percentile)	25.9 (22.7, 29.4)	29.5 (26.4, 33.5)
Female sex	1824 (46.0)	4129 (30.9)
Region		
Asia Pacific	1028 (25.9)	1722 (12.9)
Europe	1120 (28.2)	6023 (45.1)
Latin America	813 (20.5)	2429 (18.2)
North America	1005 (25.3)	3182 (23.8)
Smoker	195 (4.9)	1272 (9.5)
Creatinine level, median (25th, 75th percentile), mg/dL	1.06 (0.86, 1.42)	1.00 (0.87, 1.15)
Calculated CrCl, median (25th, 75th percentile), mL/min/1.73 m ²	53.4 (43.9, 64.3)	82.8 (67.3, 104.1)
Type of AF		
Paroxysmal	521 (13.1)	2173 (16.3)
Permanent or persistent	3444 (86.8)	11 181 (83.7)
VKA naive	1737 (43.8)	5653 (42.3)
Prior stroke, TIA, or SE	952 (24.0)	2361 (17.7)
CHF within 3 mo	1190 (30.0)	4067 (30.5)
Diabetes	892 (22.5)	3501 (26.2)
Hypertension	3254 (82.0)	11 914 (89.2)
Myocardial infarction	560 (14.1)	1650 (12.4)
History of anemia	390 (9.8)	717 (5.4)
History of bleeding	742 (18.7)	2122 (15.9)
Fall within previous year	219 (5.5)	469 (3.5)
CHADS ₂ score ^b		
≤1	938 (23.7)	5165 (38.7)
2	1477 (37.2)	4684 (35.1)
≥3	1551 (39.1)	3507 (26.3)
HAS-BLED score ^c		
≤1	1826 (46.0)	7923 (59.3)
2	1459 (36.8)	4019 (30.1)
≥3	681 (17.2)	1414 (10.6)

Abbreviations: AF, atrial fibrillation; ARISTOTLE, Apixaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation; BMI, body mass index (calculated as weight in kilograms divided by square of height in meters); CHADS₂, Congestive Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus (1 point for presence of each), and Stroke/TIA (2 points); CHF, congestive heart failure; CrCl, creatinine clearance; SE, systemic embolism; TIA, transient ischemic attack; VKA, vitamin K antagonist.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; creatinine clearance to milliliters per second per square meter, by 0.0167.

^a Percentages have been rounded and may not total 100.

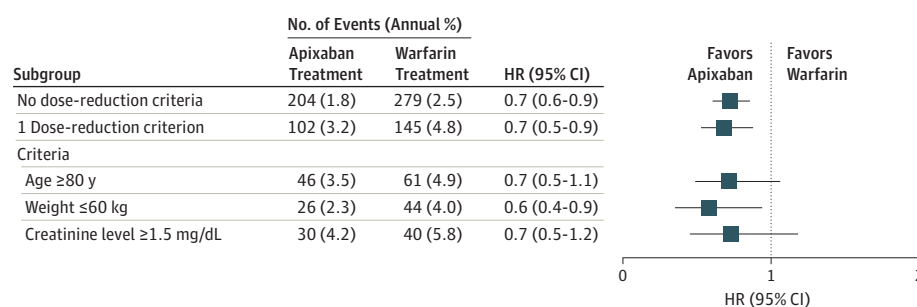
^b Scores range from 0 to 6, with higher scores indicating higher risk of stroke.

^c Represents bleeding risk factors and assigns 1 point for the presence of each of the following: hypertension (uncontrolled systolic blood pressure >160 mm Hg), abnormal renal and/or liver function, previous stroke, bleeding history or predisposition, labile international normalized ratios, being elderly, and concomitant use of drugs and/or excessive alcohol. Scores for the present study were calculated without information on labile international normalized ratio. Scores range from 0 to 9, with scores of 3 or greater indicating a high risk of bleeding.

Although these same criteria predict risk of bleeding and stroke, the dose-reduction criteria used in the ARISTOTLE trial were chosen because, particularly in combination, they predict increased apixaban exposure based on pharmacokinetic modeling.⁶⁻⁸ Patients in the ARISTOTLE trial with 2 or 3 dose-reduction criteria were assigned to the 2.5 mg twice daily dose of apixaban to minimize the potential for higher exposures in a population that may be at increased risk for bleeding. Based on population pharmacokinetic data, the median (5th, 95th percentiles) predicted peak and trough apixaban concentrations at a steady state with the 2.5 mg twice daily dose are 123 (69, 221) ng/mL and 79 (34, 162) ng/mL; and with the 5 mg twice daily dose, 171 (91, 321) ng/mL and 103 (41, 230) ng/mL, respectively.¹⁴ In the ARISTOTLE trial,² 831 patients (4.6%) had 2 or 3 dose-reduction criteria and were randomized to the 2.5 mg twice daily dose

of apixaban or warfarin. In these patients, the 2.5 mg twice daily dose of apixaban had a similar effect on stroke or systemic embolism (*P* for interaction = .22) and major bleeding (*P* for interaction = .21) as the 5 mg twice daily dose of apixaban in patients without 2 dose-reduction criteria. Similar dose-reduction strategies were used in selected populations in the ROCKET AF (Rivaroxaban Once-daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) and ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction Study 48) trials.^{3,4,15} These reduced doses of apixaban (2.5 mg twice daily) and rivaroxaban (15 mg/d) have only been compared with warfarin in patients with AF and the relevant dose-reduction criteria. The 2.5 mg twice daily dose of apixaban was directly compared with the

Figure 1. Rates of Major Bleeding and the Effect of Apixaban Compared With Warfarin



Annualized event rates of major bleeding defined according to the International Society of Thrombosis and Haemostasis. Patients with 1 and no dose-reduction criteria and patients with each individual dose-reduction criterion are compared by treatment. HR indicates hazard ratio; error bars, 95% CI. *P* value for interaction compares the effect of apixaban vs warfarin among patients with 1 and no dose-reduction criteria. To convert creatinine to micromoles per liter, multiply by 88.4.

Table 3. Rates of Events Among Patients With 1 and No Dose-Reduction Criteria and the Effect of Apixaban Compared With Warfarin

Outcome by No. of Dose-Reduction Criteria	No. of Events (Annual %)		Apixaban vs Warfarin, HR (95% CI)	P Value for Interaction
	Apixaban (n = 8665) ^a	Warfarin (n = 8657)		
Stroke or SE				
1	63 (1.80)	67 (1.93)	0.94 (0.66-1.32)	.36
None	137 (1.10)	176 (1.42)	0.77 (0.62-0.97)	
Ischemic or unspecified stroke				
1	52 (1.49)	43 (1.23)	1.21 (0.81-1.81)	.14
None	100 (0.80)	118 (0.95)	0.84 (0.65-1.10)	
Major bleeding				
1	102 (3.24)	145 (4.79)	0.68 (0.53-0.87)	.71
None	204 (1.77)	279 (2.46)	0.72 (0.60-0.86)	
Intracranial hemorrhage				
1	13 (0.41)	39 (1.26)	0.32 (0.17-0.60)	.26
None	37 (0.32)	74 (0.64)	0.49 (0.33-0.73)	
All-cause death				
1	205 (5.74)	197 (5.50)	1.04 (0.86-1.27)	.054
None	322 (2.52)	390 (3.07)	0.82 (0.71-0.95)	
CV death				
1	101 (2.83)	97 (2.71)	1.04 (0.79-1.38)	.26
None	173 (1.35)	201 (1.58)	0.86 (0.70-1.05)	

Abbreviations: CV, cardiovascular; HR, hazard ratio; SE, systemic embolism.

^a Includes patients randomized to apixaban 5 mg twice daily (standard dose).

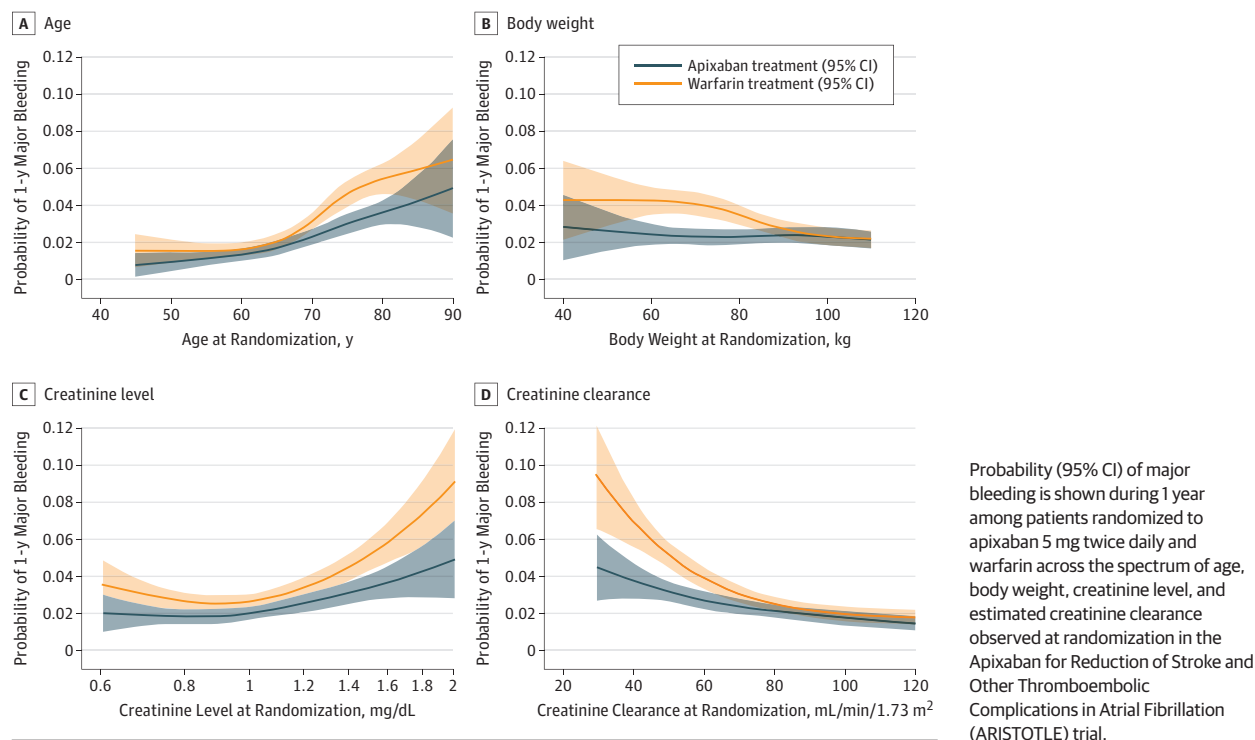
5 mg twice daily dose in the extended treatment of patients with acute venous thromboembolism.¹⁶ In this setting, the reduced apixaban dose resulted in similar rates of recurrent venous thromboembolism and bleeding compared with standard apixaban dose. How these data from patients with remote venous thromboembolism are applicable to patients with AF is unknown. At this point, the efficacy and safety of reduced-dose apixaban or rivaroxaban in patients with AF without appropriate dose-reduction criteria are unknown, and the use of the reduced dose should be discouraged.

Pharmacologically, it is intuitive that oral anticoagulation should be dosed to obtain an optimal plasma concentration and corresponding anticoagulant effect. To reach such a target level might necessitate individualized dosing in different patients. Although not widely available, blood tests exist to monitor the level of anticoagulation with the direct throm-

bin inhibitor dabigatran, or the factor Xa inhibitors apixaban, rivaroxaban, and edoxaban.¹⁷ The NOACs, however, have not been developed with a strategy of routine therapeutic monitoring but rather with standard fixed dosing for most patients. The rationale behind the dose-reduction strategies in the ARISTOTLE, ROCKET AF, and ENGAGE AF-TIMI 48 trials was only to avoid overdosing in patients with renal dysfunction, advanced age, and/or low body weight.

Compared with the dose-reduction strategies used in the ARISTOTLE, ROCKET AF, and ENGAGE AF-TIMI 48 trials, the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy)¹⁸ and ENGAGE AF-TIMI 48 trials¹⁹ randomized patients to higher and lower doses of dabigatran and edoxaban, respectively. In both of these trials,^{1,4} the lower dose of oral anticoagulant resulted in lower rates of bleeding and higher rates of stroke or systemic embolism than the higher

Figure 2. Dose-Reduction Criteria and Probability of Major Bleeding During 1 Year of Treatment



dose. In the ENGAGE AF-TIMI 48 trial,⁴ investigators found a 41% increase in ischemic stroke with low-dose edoxaban compared with warfarin. In the RE-LY trial,¹ dabigatran 150 mg twice daily was superior to warfarin, whereas dabigatran 110 mg twice daily was only noninferior to warfarin for stroke prevention. In both these cases, anticoagulant efficacy was dose related and underdosing resulted in potentially preventable strokes.⁴ No data currently exist on the effect of the 2.5 mg twice daily dose of apixaban on clinical outcomes in patients with AF without 2 or more dose-reduction criteria. In the absence of data to the contrary, we can reasonably presume that similar lower rates of bleeding and higher rates of stroke would be seen. Therefore, limiting the use of the 2.5 mg twice daily dose of apixaban to patients who meet 2 or more of the 3 dose-reduction criteria used in the ARISTOTLE trial seems most appropriate. Our findings support the safety of the 5 mg twice daily dose of apixaban compared with warfarin among patients with only 1 dose-reduction criterion, even at the extremes of advanced age, low body weight, and renal dysfunction among patients included in the ARISTOTLE trial.

The availability of anticoagulation alternatives to warfarin offers the potential to provide more patients with AF at risk for stroke more effective and safer stroke prevention. Quality improvement programs for patients with AF should include systematic approaches to ensure that patients with AF are not

only taking an oral anticoagulant, but also that they are receiving the correct dose on the basis of available evidence from clinical trials.²⁰

These data are from the ARISTOTLE trial population and may not be generalizable to other populations of patients with AF, some of whom may have greater extremes of age, body weight, or renal dysfunction. To date, no study has been conducted comparing the efficacy of the 5 vs 2.5 mg twice daily doses of apixaban in any population of patients with AF; therefore, the effect of the 2.5 mg twice daily dose of apixaban on stroke or bleeding in patients without 2 or more dose-reduction criteria is unknown.

Conclusions

Patients with AF and isolated advanced age, low body weight, or renal dysfunction have a higher risk of stroke or systemic embolism and major bleeding and consistent benefits with the 5 mg twice daily dose of apixaban vs warfarin compared with patients without these characteristics. The 5 mg twice daily dose of apixaban is safe, efficacious, and in the absence of additional data on the efficacy and safety of reduced apixaban doses compared with warfarin, should be the preferred dose of apixaban for patients with 1 dose-reduction criterion.

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