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Major Bleeding in Patients With Atrial Fibrillation Receiving Apixaban or Warfarin

The ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): Predictors, Characteristics, and Clinical Outcomes

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Objectives This study sought to characterize major bleeding on the basis of the components of the major bleeding definition, to explore major bleeding by location, to define 30-day mortality after a major bleeding event, and to identify factors associated with major bleeding.

Background Apixaban was shown to reduce the risk of major hemorrhage among patients with atrial fibrillation in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.

Methods All patients who received at least 1 dose of a study drug were included. Major bleeding was defined according to the criteria of the International Society on Thrombosis and Haemostasis. Factors associated with major hemorrhage were identified using a multivariable Cox model.

Results The on-treatment safety population included 18,140 patients. The rate of major hemorrhage among patients in the apixaban group was 2.13% per year compared with 3.09% per year in the warfarin group (hazard ratio [HR] 0.69, 95% confidence interval [CI]: 0.60 to 0.80; $p < 0.001$). Compared with warfarin, major extracranial hemorrhage associated with apixaban led to reduced hospitalization, medical or surgical intervention, transfusion, or change in antithrombotic therapy. Major hemorrhage followed by mortality within 30 days occurred half as often in apixaban-treated patients than in those receiving warfarin (HR 0.50, 95% CI: 0.33 to 0.74; $p < 0.001$). Older age, prior hemorrhage, prior stroke or transient ischemic attack, diabetes, lower creatinine clearance, decreased hematocrit, aspirin therapy, and nonsteroidal anti-inflammatory drugs were independently associated with an increased risk.

Conclusions Apixaban, compared with warfarin, was associated with fewer intracranial hemorrhages, less adverse consequences following extracranial hemorrhage, and a 50% reduction in fatal consequences at 30 days in cases of major hemorrhage. (J Am Coll Cardiol 2014;63:2141–7) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

AF = atrial fibrillation

CI = confidence interval

HR = hazard ratio

INR = international normalized ratio

ISTH = International Society on Thrombosis and Haemostasis

TIA = transient ischemic attack

Atrial fibrillation (AF) is a potent risk factor for stroke. Warfarin is highly efficacious in reducing this risk, but its effectiveness in clinical practice is challenged by its variable dose response, need for frequent monitoring, and associated risk of hemorrhage. Among patients age 65 years or older, warfarin was noted to be the drug most often implicated in medication-related adverse events leading to emergency hospital stay (1). Apixaban, a factor Xa inhibitor, was shown to reduce the risk of major hemorrhage by 31% compared with warfarin among patients with AF in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (2). In this report, we sought to: 1) define 30-day mortality after a major bleeding event and determine whether this factor differed between warfarin- and apixaban-treated patients; 2) identify predictors of major bleeding and determine whether predictors of major bleeding varied between warfarin- and apixaban-treated patients; 3) further characterize the reduction in major bleeding based on the components of the major bleeding definition and determine whether these components varied between warfarin- and apixaban-treated patients; and 4) explore major bleeding by location and determine whether bleeding locations varied between warfarin- and apixaban-treated patients.

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Methods

The ARISTOTLE trial design has been reported previously (3). Patients with AF and at least 1 risk factor for stroke were randomized to receive either dose-adjusted warfarin or apixaban, 5 mg twice daily. A reduced dose of apixaban, 2.5 mg twice daily, was designated for participants with 2 or more of the following criteria: age $\geq$80 years, weight $\leq$60 kg, or serum creatinine concentration $\geq$1.5 mg/dl (133 μmol/l). The reduced dose of apixaban was administered to 428 patients (4.7%). To enhance the quality of warfarin management, a dosage algorithm was provided, and a program implemented to provide regular feedback to sites regarding their level of international normalized ratio (INR) control.

The analyses of bleeding events included all patients who received at least 1 dose of a study drug and included all events from the time of the first dose until 2 days after the last dose was received. Major bleeding was defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dl or transfusion of at least 2 units of packed red cells, occurring at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial, retroperitoneal), or resulting in death (4). No time restrictions were applied to this definition. Laboratory and transfusion data coupled with clinical event details were used to identify and adjudicate potential bleeding events. Routine collection of hemoglobin occurred every 3 months. Location of bleeding was extracted from the case report form. Additional source documents were collected when necessary. The primary safety outcomes were adjudicated on the basis of pre-specified criteria by a clinical events committee whose members were not aware of study group assignments.

Severity of hemorrhage and 30-day mortality following first ISTH major hemorrhage. Parameters to assess the severity of major hemorrhage, in addition to anatomic location, for apixaban and warfarin were determined and compared. Metrics relevant for major extracranial hemorrhage included decrease of hemoglobin of at least 2 g/dl, hospitalization because of bleeding, transfusion of packed red cells, number of units transfused, medical or surgical consultation or evaluation, medical or surgical intervention to stop the bleeding, hemodynamic compromise, and change in antithrombotic therapy. Thirty-day mortality rates following first ISTH major hemorrhage were evaluated and compared between warfarin- and apixaban-treated patients.

Statistical analyses. Categorical variables were summarized as frequencies and percentages and continuous variables as medians and 25th and 75th percentiles. p Values representing comparisons between patients with and without major bleeding were based on Cox regression models with ISTH criteria first major hemorrhage as a dependent variable. p Values for the interactions between randomized treatment and each covariate were derived using Cox models. Factors associated with the first ISTH major hemorrhage were identified using a multivariable Cox model. Candidate variables included demographics and clinical characteristics, medications, and laboratory values at baseline. Randomized treatment and region of enrollment were also included as candidate variables. Missing values in predictors were imputed using multiple imputations.

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Table 1 Baseline Characteristics

	ISTH Major Bleeding = Yes			ISTH Major Bleeding = No				
	Overall (n = 789)	Apixaban (n = 327)	Warfarin (n = 462)	Overall (n = 17,351)	Apixaban (n = 8761)	Warfarin (n = 8590)	p Value*	Interaction p Value†
Age, yrs	74 (68, 79)	74 (67, 79)	74 (68, 79)	70 (62, 76)	70 (63, 76)	70 (62, 76)	<0.001	0.50
Female (%)	270 (34.2)	102 (31.2)	168 (36.4)	6,123 (35.3)	3,118 (35.6)	3,005 (35.0)	0.84	0.084
Systolic BP, mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	0.16	0.36
Weight, kg	80 (68, 93)	83 (70, 94)	78 (67, 91)	82 (70, 96)	82 (70, 96)	82 (70, 96)	<0.001	0.012
Prior MI (%)	143 (18.1)	61 (18.7)	82 (17.8)	2,437 (14.1)	1,257 (14.4)	1,180 (13.8)	0.003	0.78
Prior clinically relevant or spontaneous bleeding episodes (%)	186 (23.6)	82 (25.2)	104 (22.5)	2,847 (16.4)	1,442 (16.5)	1,405 (16.4)	<0.001	0.33
History of falls within previous year (%)	57 (7.9)	26 (8.7)	31 (7.4)	695 (4.4)	360 (4.5)	335 (4.3)	<0.001	0.57
Type of AF (%)							0.078	0.75
Paroxysmal	104 (13.2)	44 (13.5)	60 (13.0)	2,672 (15.4)	1,327 (15.1)	1,345 (15.7)		
Persistent or permanent	685 (86.8)	283 (86.5)	402 (87.0)	14,676 (84.6)	7,432 (84.9)	7,244 (84.3)		
Qualifying risk factors (%)								
Age ≥75 yrs	375 (47.5)	151 (46.2)	224 (48.5)	5,280 (30.4)	2,685 (30.7)	2,595 (30.2)	<0.001	0.39
Prior stroke, TIA, or SE	188 (23.8)	80 (24.5)	108 (23.4)	3,335 (19.2)	1,660 (18.9)	1,675 (19.5)	0.001	0.61
HF or reduced LVEF	275 (34.9)	112 (34.2)	163 (35.3)	6,160 (35.5)	3,115 (35.6)	3,045 (35.4)	0.75	0.74
Diabetes	226 (28.6)	112 (34.2)	114 (24.7)	4,300 (24.8)	2,164 (24.7)	2,136 (24.9)	0.0056	0.0034
Hypertension requiring treatment	671 (85.0)	277 (84.7)	394 (85.3)	15,188 (87.5)	7,655 (87.4)	7,533 (87.7)	0.028	0.96
Medications at randomization (%)								
Amiodarone	82 (10.6)	31 (9.6)	51 (11.4)	1,965 (11.5)	974 (11.3)	991 (11.7)	0.63	0.49
Aspirin	254 (32.2)	115 (35.2)	139 (30.1)	4,159 (24.1)	2,107 (24.1)	2,052 (24.0)	<0.001	0.19
Clopidogrel	25 (3.2)	11 (3.4)	14 (3.0)	312 (1.8)	158 (1.8)	154 (1.8)	0.0026	0.80
Statin	381 (46.8)	157 (48.5)	204 (45.5)	7,081 (41.5)	3,579 (41.6)	3,502 (41.3)	0.0043	0.36
NSAIDs	100 (13.0)	40 (12.3)	60 (13.4)	1,418 (8.3)	711 (8.3)	707 (8.3)	<0.001	0.69
Gastric antacid drugs	197 (25.5)	86 (26.5)	111 (24.8)	3,139 (18.4)	1,589 (18.5)	1,550 (18.3)	<0.001	0.62
Renal function covariates (%)							<0.001	0.042
Normal (>80 ml/min)	215 (27.3)	96 (29.5)	119 (25.9)	7,281 (42.1)	3,654 (41.9)	3,627 (42.4)		
Mild impairment (>50–80 ml/min)	356 (45.3)	157 (48.2)	199 (43.3)	7,209 (41.7)	3,650 (41.8)	3,559 (41.6)		
Moderate impairment (>30–50 ml/min)	189 (24.1)	66 (20.2)	123 (26.7)	2,548 (14.8)	1,291 (14.8)	1,257 (14.7)		
Severe impairment (≤30 ml/min)	26 (3.3)	7 (2.1)	19 (4.1)	242 (1.4)	129 (1.5)	113 (1.3)		
Liver dysfunction (%)	8 (1.0)	4 (1.2)	4 (0.9)	505 (2.9)	261 (3.0)	244 (2.8)	0.0024	0.68
Hematocrit	42.0 (38.6, 45.0)	42.0 (38.2, 45.0)	42.0 (38.9, 45.0)	43.0 (40.0, 46.0)	43.0 (40.0, 46.0)	43.0 (40.0, 46.0)	<0.001	0.60
Platelet count, $\times 10^9$/l	211 (176, 253)	207 (172, 249)	213 (180, 255)	211 (178, 250)	210 (177, 249)	212 (179, 251)	0.83	0.45

Values are median (25th, 75th percentile) or n (%). *p value comparing patients with and without ISTH major bleeding. †p value for treatment by covariable interaction.

AF = atrial fibrillation; BP = blood pressure; HF = heart failure; ISTH = International Society on Thrombosis and Haemostasis; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs; SE = systemic embolism; TIA = transient ischemic attack.

Missing values were uncommon (<3%) for all predictors, except for history of fall (9%). Twenty-five imputed datasets were generated, and a stepwise selection method was used in each dataset. Predictors selected in more than 80% of the imputed datasets were included in the final model. We tested for interactions between variables in the final model and randomized treatment.

Four additional endpoints were defined according to the consequences of hemorrhage, including major extracranial hemorrhage, followed by hospitalization, medical or surgical intervention, transfusion, and change in antithrombotic therapy. These endpoints were summarized overall and by randomized treatment as rates (except for the number of units of packed cells transfused), number of events, and hazard ratios (HR) comparing all patients randomized to apixaban versus those to warfarin. All statistical analyses were performed using SAS version 9.2 software (SAS Institute, Inc., Cary, North Carolina).

Results

As previously reported, the ARISTOTLE trial enrolled 18,201 patients from 1,034 clinical sites in 39 countries. The on-treatment safety population included 18,140 patients. The median follow-up time was 20.5 months. Major hemorrhage occurred in 789 patients (4.3%) overall; 327 in the apixaban group (2.13% per year) compared with 462 in the warfarin group (3.09% per year; HR 0.69, 95% confidence interval [CI]: 0.60 to 0.80; $p < 0.001$). Patients who sustained a major bleed were older (74 vs. 70 years, respectively), more commonly had a history of myocardial infarction, prior hemorrhage, impaired renal function, and a fall within the previous year compared with patients without ISTH major hemorrhage (Table 1). They also weighed less and had a lower hematocrit level at baseline. Among the qualifying risk factors, patients who sustained a major hemorrhage were more likely to have a history of stroke, transient ischemic attack (TIA) or systemic embolism, diabetes, or hypertension. They were also more likely to use aspirin, clopidogrel, nonsteroidal anti-inflammatory drugs, statins, and gastric antacid drugs at baseline.

Location of hemorrhage. The most frequent sites of major hemorrhage were gastrointestinal (31%; n = 248), intracranial (22%; n = 171), and soft tissue (10%; n = 75) (Table 2). Two-thirds of the gastrointestinal bleeds involved the upper tract. Apixaban was associated with fewer gastrointestinal hemorrhages than warfarin, but this difference did not achieve statistical significance (HR 0.89, 95% CI: 0.70 to 1.14). There were also fewer soft tissue hematomas associated with apixaban that met the criteria for ISTH major hemorrhage (HR 0.46, 95% CI: 0.29 to 0.74). In addition, apixaban was associated with fewer major hemorrhages related to trauma: 37 in the apixaban group (0.24% per year) compared with 60 in the warfarin group (0.40% per year; HR 0.60, 95% CI: 0.40 to 0.91; $p = 0.015$). As previously reported, apixaban was associated with fewer intracranial hemorrhages than warfarin (HR 0.42, 95% CI: 0.30 to 0.58).

Severity and short-term consequences of hemorrhage. Major extracranial hemorrhage-associated adverse consequences occurred less frequently in the apixaban group than in the warfarin group, including fewer hospitalizations (HR: 0.75, 95% CI: 0.61 to 0.92), fewer medical or surgical interventions to stop the bleeding (HR: 0.72, 95% CI: 0.56 to 0.93), fewer transfusions (HR: 0.71, 95% CI: 0.57 to 0.89), and fewer changes in antithrombotic therapy (HR: 0.78, 95%

Table 2 Major Bleeding by Location (First Major Hemorrhage at Each Location)

Location	Overall (n = 18,140)	Apixaban (n = 9088)	Warfarin (n = 9052)	Apixaban vs. Warfarin HR (95% CI)	p Value*
Intracranial	0.57 (174)	0.33 (52)	0.80 (122)	0.42 (0.30–0.58)	<0.001
Intra-articular	0.05 (16)	0.04 (6)	0.07 (10)	0.59 (0.21–1.61)	0.30
Digestive tract	0.83 (254)	0.78 (121)	0.88 (133)	0.89 (0.70–1.14)	0.35
Upper gastrointestinal	0.49 (151)	0.43 (66)	0.56 (85)	0.76 (0.55–1.05)	0.094
Lower gastrointestinal	0.24 (75)	0.25 (39)	0.24 (36)	1.06 (0.67–1.67)	0.80
Hemorrhoidal	0.02 (7)	0.03 (4)	0.02 (3)	1.31 (0.29–5.83)	0.73
Rectal	0.08 (26)	0.09 (14)	0.08 (12)	1.14 (0.53–2.47)	0.74
Hemoptysis	0.01 (4)	0.01 (1)	0.02 (3)	0.33 (0.03–3.15)	0.33
Hemothorax	0.02 (5)	0.01 (2)	0.02 (3)	0.66 (0.11–3.92)	0.64
Intramuscular	0.01 (2)	0.01 (1)	0.01 (1)	0.98 (0.06–15.60)	0.99
Bruising/ecchymosis	0.04 (11)	0.02 (3)	0.05 (8)	0.37 (0.10–1.38)	0.14
Epistaxis	0.07 (23)	0.08 (12)	0.07 (11)	1.06 (0.47–2.41)	0.88
Retroperitoneal	0.02 (7)	0.01 (2)	0.03 (5)	0.39 (0.08–2.02)	0.26
Intraspinal	0.01 (4)	0.01 (2)	0.01 (2)	0.98 (0.14–6.97)	0.99
Vaginal	0.02 (7)	0.03 (5)	0.01 (2)	2.46 (0.48–12.68)	0.28
Hematoma	0.25 (78)	0.16 (25)	0.35 (53)	0.46 (0.29–0.74)	0.0015
Hematuria	0.14 (42)	0.13 (20)	0.14 (22)	0.89 (0.49–1.63)	0.71
Intraocular	0.15 (47)	0.18 (28)	0.13 (19)	1.45 (0.81–2.59)	0.21

Values are rate (per 100 patient-years of follow-up) (number of events). *p values compare apixaban to warfarin rates of bleeding.
CI = confidence interval; HR = hazard ratio.

CI: 0.64 to 0.95) (Table 3). Major ISTH hemorrhage criteria followed by death within 30 days occurred half as often in the apixaban group compared with the warfarin group, with 36 and 71 events, respectively (HR: 0.50, 95% CI: 0.33 to 0.74; $p < 0.001$) (Fig. 1).

Independent factors associated with first major hemorrhage. Older age, prior hemorrhage, prior stroke or TIA, diabetes, lower creatinine clearance (5), and decreased hematocrit level were independently associated with an increased risk of major hemorrhage (Table 4). Use of aspirin and nonsteroidal anti-inflammatory drugs also independently increased the risk of major bleeding by approximately 30%. In the multivariable models, randomization to apixaban, compared with warfarin, was associated with a lower risk of major hemorrhage (HR: 0.69, 95% CI: 0.60 to 0.72), as was female sex and liver disease.

In an exploratory analysis of subgroup by treatment interactions, we found a differential effect by treatment according to 3 variables: baseline renal function, weight, and diabetes. For patients with renal dysfunction and low body weight, the reduction in bleeding with apixaban appeared to be greater than in patients with normal renal function and higher body weight than in patients taking warfarin. For patients with diabetes, the reduction in bleeding with apixaban appeared to be less than for patients without diabetes.

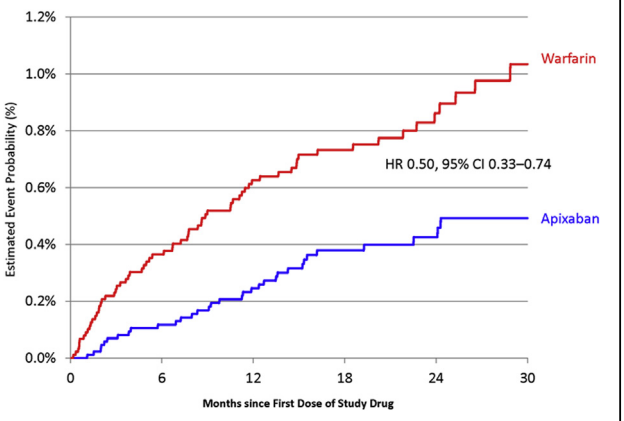

Figure 1 Major Bleeding Following by Death Within 30 Days

CI = confidence interval; HR = hazard ratio.

Discussion

In the ARISTOTLE trial, there were fewer intracranial hemorrhages on apixaban, fewer adverse consequences of extracranial hemorrhages, and fewer trauma-related hemorrhages. Apixaban, compared with warfarin, was associated with 50% less ISTH major hemorrhage leading to death within 30 days after the event. Warfarin treatment was more often associated with bleeding requiring hospitalization, transfusion, procedures to stop bleeding, and change in antithrombotic therapy, all of which may have contributed to the differences in severity and mortality. Although the mechanisms underlying these differences are unknown, the prolonged half-life of warfarin and warfarin's suppression of factor VIIa may be implicated; an active factor VIIa and tissue factor complex are necessary to initiate hemostasis (6). Although reversal of warfarin with vitamin K, fresh frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa has been shown to reduce the INR, the effects of these interventions on clinical outcomes are uncertain. Delays in presentation, infusion delays, incomplete INR correction, and prothrombotic risk all undermine the effectiveness of these agents in routine practice (7–9). In the ARISTOTLE trial, warfarin-associated major hemorrhage also more often triggered a change in antithrombotic therapy. Cessation of warfarin therapy was recently shown to increase the risk of thrombosis and death among individuals who had sustained a gastrointestinal hemorrhage (10). A better understanding of the sequelae of major hemorrhage in terms of intervention, treatment, and attendant complications would inform its optimal management in clinical practice.

Our findings for independent factors associated with major hemorrhage underscore the challenge of shared risk factors for stroke and hemorrhage among individuals with AF, especially those who are older and have had prior stroke and renal dysfunction (11–16). Our findings also highlight

Table 3 Characteristics of Major Extracranial Hemorrhage

	Overall (n = 18,140)	Apixaban (n = 9088)	Warfarin (n = 9052)	Apixaban vs. Warfarin HR (95% CI)	p Value*
Led to hospitalization	1.23 (374)	1.05 (162)	1.41 (212)	0.75 (0.61–0.92)	0.0052
Fall in hemoglobin ≥2 g/dl	1.25 (381)	1.06 (164)	1.44 (217)	0.74 (0.60–0.91)	0.0035
Led to transfusion	1.06 (325)	0.89 (137)	1.25 (188)	0.71 (0.57–0.89)	0.0025
Required medical or surgical consultation	1.74 (527)	1.54 (236)	1.94 (291)	0.79 (0.67–0.94)	0.0080
Required medical or surgical intervention to stop	0.77 (236)	0.65 (100)	0.90 (136)	0.72 (0.56–0.93)	0.012
Associated with hemodynamic compromise	0.32 (97)	0.26 (40)	0.38 (57)	0.69 (0.46–1.029)	0.069
Caused changed in antithrombotic therapy	1.31 (398)	1.14 (176)	1.47 (222)	0.78 (0.64–0.95)	0.012

Values are rate (per 100 patient-years of follow-up) (number of events). *p values compare apixaban to warfarin rates of bleeding.
Abbreviations as in Table 2.

Table 4 Baseline Factors Independently Associated With Major Hemorrhage*

Parameter	Chi-Square Value	p Value	HR Represents	HR (95% CI)
Hematocrit (<45%)	38.5	<0.001	5-U decrease (under 45)	1.38 (1.24–1.52)
Age	35.3	<0.001	10-yr increase	1.36 (1.23–1.51)
Randomized treatment	26.8	<0.001	Apixaban vs. warfarin	0.69 (0.60–0.79)
Creatinine clearance (<85 ml/min/1.73 m^2)	16.9	<0.001	10-U decrease (under 85)	1.11 (1.058–1.17)
Sex	14.2	0.002	Female vs. male	0.74 (0.63–0.87)
History of bleeding	14.2	0.002	Yes vs. no	1.38 (1.17–1.63)
Aspirin at randomization	13.5	0.002	Yes vs. no	1.31 (1.14–1.52)
Diabetes	7.3	0.0067	Yes vs. no	1.24 (1.062–1.45)
NSAIDs at randomization	6.7	0.0096	Yes vs. no	1.33 (1.072–1.65)
Prior stroke/TIA/SE	5.8	0.016	Yes vs. no	1.23 (1.038–1.45)
Liver disease	5.4	0.020	Yes vs. no	0.44 (0.22–0.88)

*C-index: 0.68. Region of enrollment was included in the model.
NSAIDs = nonsteroidal anti-inflammatory drugs; SE = systemic embolism; TIA = transient ischemic attack; other abbreviations as in Table 2.

the challenges of implementing anticoagulant therapy among individuals with a propensity for hemorrhage, as those individuals with a prior episode are at highest risk for recurrence. Because of the substantial overlap in risk factors and the major disability related to ischemic stroke, reliance on currently available hemorrhage risk scores for decisions regarding anticoagulant therapy is problematic. These scores were not derived to predict intracranial hemorrhage but rather a wide spectrum of hemorrhagic complications, most of which do not render permanent sequelae. The inability to account for aspirin and nonprescription nonsteroidal anti-inflammatory drugs is another limitation (13,17). Use of these tools to identify modifiable risk factors amenable to intervention will translate into fewer hemorrhages and improved long-term persistence with anticoagulant therapy. The potent deleterious effects of antiplatelet drugs and nonsteroidal anti-inflammatory agents urge caution with concomitant use and vigilance regarding indication and duration of therapy (18,19). Alternative analgesic medications without the attendant effects on platelets and gastric mucosa are needed for this patient population. Ascertainment of any protective effect of gastric acid suppressants in this setting requires randomized assessment. Similar to the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial and the studies by Beyth et al. (12) and Shireman et al. (20), we also found diabetes mellitus to be an independent risk factor for major hemorrhage (15). The independent contribution of diabetes mellitus may be obscured by renal dysfunction, given their expected high degree of correlation. Microalbuminuria has been associated with both intracerebral hemorrhage and hematuria (21,22). Hypertension was not found to be an independent predictor of major hemorrhage in ARISTOTLE, which may reflect the degree of blood pressure control achieved among trial participants. The lower rate of major bleeding in females has not been previously reported and warrants further study. Only 8 patients with liver dysfunction experienced a major hemorrhage, precluding any definitive conclusion regarding this patient subgroup.

Study limitations. The objective of a randomized trial is to provide the most valid, unbiased estimate of medication effect. For this reason, individuals with anticipated difficulty with study protocols or with heightened risk of short exposures (adherence, excessive risk of hemorrhage) may be underrepresented. Thus, extrapolation of trial results to these populations should be done cautiously. However, rates of major hemorrhage associated with warfarin in contemporary AF trials are 2- to 3-fold higher than the rates reported in earlier studies, likely reflecting the older age of today's trial participants, the higher prevalence of chronic disease and concomitant aspirin use, and the overall broader prescription of anticoagulant medications in current AF populations (23–27). Thus, we believe our trial participants are representative of most patients with AF in clinical practice.

Conclusions

Compared with warfarin, apixaban was associated with a 31% reduction in risk of first major ISTH hemorrhage. Apixaban was associated with fewer intracranial hemorrhages, fewer adverse consequences following extracranial hemorrhages, fewer trauma-associated hemorrhages, and a 50% reduction in fatal consequences at 30 days in case of a major hemorrhage. Therefore, concerns for complications in case of hemorrhage during anticoagulant treatment are fewer during apixaban than warfarin treatment.

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