History of bleeding and outcomes with apixaban versus warfarin in patients with atrial fibrillation in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial

Raffaele De Caterina, MD, PhD,[a] Ulrika Andersson, MSc,[b] John H. Alexander, MD, MHS,[c] Sana M. Al-Khatib, MD, MHS,[c] M. Cecilia Bahit, MD,[d] Shinya Goto, MD, PhD,[e] Michael Hanna, MD,[f] Claes Held,[b,g] Stefan Hohnloser, MD,[h] Elaine M. Hylek, MD, MPH,[i] Fernando Lanas, MD,[j] Renato D. Lopes, MD, PhD,[c] José López-Sendón, MD, PhD, FESC,[k] Giulia Renda, MD,[a] John Horowitz, MD, PhD,[l] Christopher B. Granger, MD,[c] and Lars Wallentin, MD, PhD[b,g], on behalf of the ARISTOTLE Investigators *Chieti, Italy; Uppsala, Sweden; Durham, NC; Santa Fe, Argentina; Isehara, Japan; Princeton, NJ; Frankfurt, Germany; Boston, MA; Temuco, Chile; IdiPaz Madrid, Spain; and Adelaide, Australia*

Aims History of bleeding strongly influences decisions for anticoagulation in atrial fibrillation (AF). We analyzed outcomes in relation to history of bleeding and randomization in ARISTOTLE trial patients.

Methods and results The on-treatment safety population included 18,140 patients receiving at least 1 dose of study drug (apixaban) or warfarin. Centrally adjudicated outcomes in relation to bleeding history were analyzed using a Cox proportional hazards model adjusted for randomized treatment and established risk factors. Efficacy end points were analyzed on the randomized (intention to treat) population. A bleeding history was reported at baseline in 3,033 patients (16.7%), who more often were male, with a history of prior stroke/transient ischemic attack/systemic embolism and diabetes; higher $CHADS_2$ scores, age, and body weight; and lower creatinine clearance and mean systolic blood pressure. Major (but not intracranial) bleeding occurred more frequently in patients with versus without a history of bleeding (adjusted hazard ratio 1.35, 95% CI 1.14-1.61). There were no significant interactions between bleeding history and treatment for stroke/systemic embolism, hemorrhagic stroke, death, or major bleeding, with fewer outcomes with apixaban versus warfarin for all of these outcomes independent of the presence/absence of a bleeding history.

Conclusion In patients with AF in a randomized clinical trial of oral anticoagulants, a history of bleeding is associated with several risk factors for stroke and portends a higher risk of major—but not intracranial—bleeding, during anticoagulation. However, the beneficial effects of apixaban over warfarin for stroke, hemorrhagic stroke, death, or major bleeding remains consistent regardless of history of bleeding. (Am Heart J 2016;175:175-83.)

A history of bleeding is important in decision making for anticoagulation in atrial fibrillation (AF), as it may limit the use of anticoagulants in favor of the less effective antiplatelet agents or no antithrombotic agents.[1] Both approaches have been shown to be associated with worse outcomes.[2,3] A history of bleeding is the clinical factor most commonly used in evaluating future bleeding risk in patients with AF in predictive algorithms such as the $HEMORR_2HAGES$ (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke),[4] HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol),[5] and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)[6]

From the [a]Institute of Cardiology and Center of Excellence on Aging, G. d'Annunzio University, Chieti, Italy, [b]Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden, [c]Duke Clinical Research Institute, Duke Medicine, Durham, NC, [d]INECO Neurociencias Oroño, Rosario, Santa Fe, Argentina, [e]Tokai University School of Medicine, Isehara, Japan, [f]Bristol-Myers Squibb, Princeton, NJ, [g]Department of Medical Sciences, Cardiology, Uppsala University, Uppsala, Sweden, [h]J.W. Goethe-University, Frankfurt, Germany, [i]Boston University Medical Center, Boston, MA, [j]Universidad de La Frontera, Temuco, Chile, [k]Hospital Universitario La Paz, IdiPaz Madrid, Spain, and [l]Queen Elizabeth Hospital, Adelaide, Australia.

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Reprint requests: Raffaele De Caterina, MD, PhD, Institute of Cardiology, "G. d'Annunzio" University–Chieti, c/o Ospedale SS. Annunziata, Via dei Vestini, 66013 Chieti, Italy.
E-mail: rdecater@unich.it

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scores. These are recommended in the evaluation of patients with AF before the initiation of treatment.[7,8]

It is possible that a history of bleeding is associated with a higher risk of future thromboembolic events, perhaps as a result of lesser adherence to the prescribed antithrombotic therapy or because of the overlap between risk factors for bleeding and those for thromboembolism in AF.

The ARISTOTLE trial[9] compared apixaban with warfarin in patients with AF at increased risk for stroke. Using data from the 18,201 patients enrolled in ARISTOTLE, we evaluated outcomes in relation to a history of bleeding and randomization treatments. We hypothesized that a history of bleeding is associated with future bleeding events and, secondarily, to ischemic events. We also assessed whether the favorable association of apixaban versus warfarin with stroke and systemic embolism (SE), hemorrhagic stroke, major bleeding, and death[9] was similar in patients with or without a history of bleeding.

Methods

The design and results of the ARISTOTLE trial have been published previously (Lopes AHJ 2012 and Granger NEJM 2011). The on-treatment safety population included 18,140 patients (of the 18,201 randomized in ARISTOTLE) who received at least 1 dose of study drug. Patients were randomly assigned to treatment with either apixaban 5 mg twice daily (2.5 mg twice daily with 2 of the following: age ≥80 years, body weight ≤60 kg, or creatinine ≥133 μmol/L) or warfarin (target international normalized ratio 2.0-3.0, with a median time in therapeutic range of 66%), for a median of 1.8 years. Patients were excluded if they had an increased bleeding risk believed to be a contraindication to oral anticoagulation (eg, documented peptic ulcer disease within 6 months, previous intracranial hemorrhage).

Bleeding history was captured in the screening case report form as the answer to the question: "Does the subject have a history of clinically relevant (CR) or spontaneous bleeding?" with details collected about the timing and the location of prior bleeding. The prior bleeding events were subcategorized as history of major bleeding, history of minor bleeding, and history of gastrointestinal (GI) bleeding based on the information on location of prior bleeding. Bleeding definitions used in the trial are summarized in online Appendix Supplementary Table I. History of peptic ulcer disease and date were also collected because this is a determinant of upper GI bleeding and a frequent specific deterrent to the use of anticoagulants.

Statistical analysis

Baseline characteristics for the 18,137 of 18,140 patients in the on-treatment population who had nonmissing bleeding history were examined by group according to bleeding history. Continuous variables were presented as means and either SD or 95% CIs, with between-group comparisons tested by t test. Categorical variables were presented as counts and percentages and compared by χ^2 tests.

Analyses of bleeding end points were based on the on-treatment population, including all randomized patients who received at least 1 dose of the study drug, and included all events from receipt of the study drug until 2 days after the last dose. Primary and secondary efficacy analyses included all randomized patients (intention to treat) and included all events from randomization until the efficacy cutoff date (predefined as January 30, 2011).

Outcomes in relation to study treatments and bleeding history were analyzed using a Cox proportional hazards model including treatment group, bleeding history group, and treatment by bleeding history group interaction as covariates. Hazard ratios (HRs) with 95% CI for treatment comparisons were reported by bleeding history group, regardless of the significance of interaction. The effect of bleeding history was analyzed in Cox regression models including bleeding history category and randomized treatment as covariates and in models also adjusting for prior warfarin/vitamin K antagonist (VKA) status; geographic region; age (continuous); sex; glomerular filtration rate according to the CKD-EPI formula (continuous); smoking status; systolic blood pressure (BP) (continuous); heart rate (continuous); AF type; diabetes; heart failure; previous stroke/SE/transient ischemic attack (TIA); hypertension, previous myocardial infarction (MI); previous peripheral arterial disease/coronary artery bypass grafting/percutaneous coronary interventions; and treatment at randomization with aspirin, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), amiodarone, and statins. For bleeding events, history of anemia, anemic at baseline (defined as hemoglobin <13.0 g/dL in men and hemoglobin <12.0 g/dL in women), hematocrit, chronic liver disease, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) at randomization were also included. Restricted cubic splines were used to allow for nonlinear relationship between continuous variables and outcomes.

Event rates per 100 patient-years of follow-up were reported, and Kaplan-Meier estimates of the cumulative risk were calculated and plotted. All analyses were performed using the SAS version 9.4 software (SAS Institute, Inc, Cary, NC). A 2-sided P value of .05 was considered statistically significant, and because all analyses were exploratory, there were no adjustments for multiple comparisons.

Results

Demographic and clinical characteristics

History of bleeding was reported in 3,033 (16.7%) of the 18,137 on-treatment patients. Patients reporting a

history of bleeding, compared with those with no history of bleeding, were more often male (67.5% vs 64.2%, $P < .0005$), with a history of prior stroke/TIA/SE (22.7% vs 18.8%, $P < .0001$) and diabetes (27.3% vs 24.5%, $P = .0010$, with trends to longer diabetes duration for the minority [37%] of patients having such information and a significantly higher percentage of insulin use, altogether suggesting a higher severity of diabetes); had higher $CHADS_2$ scores ($CHADS_2$ >3: 35.2% vs 29.2%), age (mean [SD] 70.9 [9.1] vs 68.7 [9.7], $P < .0001$), and body weight (85.8 [21.2] vs 83.7 [20.6], $P < .0001$); had a lower calculated creatinine clearance (77.4 [32.7] vs 79.6 [32.3], $P = 0.0007$) and mean systolic BP (130.5 [17.1] vs 131.5 [16.2], $P = .0027$); and had a higher HAS-BLED score, also here calculated without the component of bleeding history. Such patients were also more frequently reporting alcohol abuse and history of anemia and were more frequently anemic at baseline (Table I).

Calcium-channel blockers and statins were used slightly more, and NSAIDs and proton pump inhibitors were used substantially more in patients with versus those without a history of bleeding. Conversely, ACE inhibitors, amiodarone, and digoxin were used slightly less in patients with versus those without a history of bleeding (Table II). Specifically, however, the use of aspirin in patients with a history of bleeding was similar (30.3%), compared with those without (31.0%, $P = .4222$).

Outcomes in patients with or without a history of bleeding

Of the primary and secondary efficacy/safety events assessed in the ARISTOTLE trial (as detailed in Granger et al[9] and online Appendix Supplementary Table I), a history of CR or spontaneous bleeding was associated with a 35% increase in risk for major bleeding (adjusted HR 1.35, 95% CI 1.14-1.61) and a 48% increase in risk for major bleeding/CR nonmajor bleeding (adjusted HR 1.48, 95% CI 1.31-1.68). Other types of bleeding not included in the primary safety end points, that is, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) mild bleeding and International Society on Thrombosis and Haemostasis (ISTH) minor bleeding, were more frequent, and the risk was statistically higher in patients with a history of bleeding (Table III). However, a history of previous bleeding did not significantly entail a higher risk of hemorrhagic stroke or intracranial bleeding during the trial (Table III). In addition, a history of bleeding was not associated with an increased risk of stroke (Table III).

Out of the broad category of history of clinically significant or spontaneous bleeding (online Appendix Supplementary Table I), the ARISTOTLE data base captured a distinction between history of major and history of minor bleeding. A history of major bleeding (online Appendix Supplementary Table II), for which we had only 270 patients in the overall cohort, was not

Table I. Baseline demographic and clinical characteristics of patients with and without a history of bleeding

Baseline characteristic	History of CR or spontaneous bleeding? Yes (n = 3033)	No (n = 15,104)	P^*
Age			
n	3033	15,104	<.0001
Mean (SD)	70.9 (9.1)	68.7 (9.7)	
Weight			
n	3026	15,051	<.0001
Mean (SD)	85.8 (21.2)	83.7 (20.6)	
Male sex, n (%)	2048 (67.5%)	9696 (64.2%)	.0005
Region, n (%)			
Asia/Pacific	459 (15.1%)	2445 (16.2%)	
Europe	915 (30.2%)	6398 (42.4%)	<.0001
Latin America	480 (15.8%)	2978 (19.7%)	
North America	1179 (38.9%)	3283 (21.7%)	
Calculated CrCL, mL/min			
n	3025	15,038	.0007
Mean (SD)	77.4 (32.7)	79.6 (32.3)	
Level of renal impairment, n (%)			
Normal	1174 (38.7%)	6321 (41.8%)	<.0001
Mild	1254 (41.3%)	6309 (41.8%)	
Moderate	547 (18.0%)	2190 (14.5%)	
Severe	50 (1.6%)	218 (1.4%)	
Not reported	8 (0.3%)	66 (0.4%)	
Systolic BP			
n	3030	15,071	.0027
Mean (SD)	130.5 (17.1)	131.5 (16.2)	
Prior stroke/TIA/SE, n (%)	690 (22.7%)	2833 (18.8%)	<.0001
CHF within 3 m or LVEF ≤40%, n (%)	977 (32.2%)	5457 (36.1%)	<.0001
CHF within 3 m, n (%)	818 (27.0%)	4708 (31.2%)	<.0001
Diabetes mellitus, n (%)	828 (27.3%)	3697 (24.5%)	.001
Insulin at randomization	168 (5.5%)	657 (4.3%)	.0041
$CHADS_2$ score, n (%)			
≤1	953 (31.4%)	5214 (34.5%)	<.0001
2	1012 (33.4%)	5479 (36.3%)	
≥3	1068 (35.2%)	4411 (29.2%)	
HAS-BLED score†, n (%)			
≤1	1727 (56.9%)	9875 (65.4%)	<.0001
2	1096 (36.1%)	4459 (29.5%)	
≥3	210 (6.9%)	770 (5.1%)	
Mean (SD)	2.4 (0.8)	1.2 (0.8)	
Prior warfarin/VKA status, n (%)			
Warfarin/VKA experienced	2247 (74.1%)	8127 (53.8%)	<.0001
Warfarin/VKA naive	786 (25.9%)	6977 (46.2%)	
Alcohol abuse, n (%)	101 (3.3%)	352 (2.3%)	.0013
History of anemia, n (%)	474 (15.6%)	769 (5.1%)	<.0001
Anemic at baseline, n (%)	460 (15.2%)	1822 (12.1%)	<.0001

No statistically significant differences ($P > .05$) between groups according to history of bleeding were found regarding type of AF and hypertension.
Abbreviations: *CHF*, Congestive heart failure; *CrCl*, creatinine clearance; *LVEF*, left ventricular ejection fraction, SD, standard deviation; TIA, transient ischemic attack; VKA, vitamin K antagonist.
* *P* value is for the comparison between groups according to history of bleeding and is based on the χ^2 test for categorical variables and *t* test for continuous variables.
† Mean (SD) for HAS-BLED score was calculated excluding labile international normalized ratio. Summary and χ^2 test comparing groups across HAS-BLED score categories were also excluding history of CR or spontaneous bleeding.

Table II. Differential treatment characteristics (medications) at randomization of patients with or without a previous history of bleeding

	History of CR or spontaneous bleeding?		
Drug	Yes (n = 3033)	No (n= 15,104)	*P**
ACE inhibitor or ARB	2080 (68.6%)	10,709 (70.9%)	.0105
Amiodarone	282 (9.3%)	1764 (11.7%)	.0002
Aspirin	919 (30.3%)	4688 (31.0%)	.4222
Digoxin	931 (30.7%)	4948 (32.8%)	.0267
Calcium-channel blocker	1099 (36.2%)	4446 (29.4%)	<.0001
Statins	1502 (49.5%)	5938 (39.3%)	<.0001
NSAIDs	419 (13.8%)	1098 (7.3%)	<.0001
Proton pump inhibitors	668 (22.0%)	1868 (12.4%)	<.0001

Values are presented as number (percentage). No statistically significant differences (p-value >0.05) between groups according to history of bleeding were found regarding treatment with clopidogrel, aspirin and beta blockers at randomization.
* *P* value is based on the χ^2 test.

associated with a significantly higher risk of any type of future bleeding. However, a history of major bleeding had HR estimates for future major bleeding and major/CR bleeding that were similar to the HRs that history of CR or spontaneous bleeding had for future bleeds (1.28 vs 1.35 for future major bleeds, 1.36 vs 1.48 for major or CR bleed), although wider CIs for those estimates due to the small number of patients with such a history of major bleeding.

For a history of minor bleeding (n = 2,880), results were similar to the results for the broad category of history of clinically significant or spontaneous bleeding (online Appendix Supplementary Table III).

Outcomes in patients with or without a history of GI bleeding

A history of GI bleeding was associated with an increased risk of bleeding during the trial: major bleeding (adjusted HR 1.97 [95% CI 1.28-3.02]) or major or CR nonmajor bleeding (adjusted HR 1.79 [95% CI 1.29-2.50]). Of note, a history of previous GI bleeding was not associated with the use of aspirin at randomization (28.5% used aspirin in the group with history of GI bleeding vs 30.9% in the group without a history).

Outcomes in patients with or without a history of bleeding by treatment group

Despite higher rates of major bleeding in patients with a history of bleeding, we found no significant differences in the relative efficacy of apixaban and warfarin as a function of the presence or absence of a history of previous bleeding. There were no significant ($P > .05$) interactions between bleeding history and treatment in relation to outcomes for stroke/SE, hemorrhagic stroke, death, or major bleeding. The event rates for the outcomes of stroke/SE, hemorrhagic stroke, death, or major bleeding were lower in patients receiving apixaban as compared with those receiving warfarin. In particular, despite a history of any previous CR or spontaneous bleeding being associated with more major bleeding occurring consistently throughout the trial, apixaban was consistently associated with lower rates of major bleeding compared with warfarin in both patients with and without a history of bleeding (Figure 1D). The only exception was the category of major/CR nonmajor bleeding, for which the interaction *P* value was of borderline significance (with a lower HR for apixaban vs warfarin for this outcome in patients without versus those with a history of bleeding) (Figure 2). We found no significant interaction of treatment with history of GI bleeding or history of major bleeding. For history of minor bleeding, there was a significant interaction for major/CR nonmajor bleeding, consistent with the overall history of CR or spontaneous bleeding (with a lower HR for apixaban vs warfarin for this outcome in patients without vs those with a history of bleeding) (online Appendix Supplementary Tables IV to VII).

Discussion

This study shows that, in patients with AF who were selected by their physicians for enrollment in ARISTOTLE, a history of bleeding was associated with several clinical risk factors for stroke and bleeding and—the main clinical thrust of the present investigation—with a higher risk of subsequent bleeding during anticoagulation. A history of bleeding did not, however, translate into an increased risk of intracranial hemorrhage or any thromboembolic complications or death. In addition, this study shows that the benefits of apixaban over warfarin were consistent with regard to stroke/SE, intracranial hemorrhage, mortality, and major bleeding, irrespective of the bleeding history. Novelties of this study are a careful dissection of the impact of history of bleeding on future outcomes and an assessment of the similar impact of apixaban versus warfarin on outcomes, independent of the bleeding history.

A history of bleeding is an important element in the medical history of a patient with AF when his/her candidacy for life-long oral anticoagulation is being considered and has been found to be a clear deterrent to the initiation or continuation of oral anticoagulation in several reports.[10-13] A history of bleeding is also likely to explain the still large underutilization of antithrombotic therapy or antiplatelet therapy in AF.[14] Although major current guidelines[7,8] do not discourage the use of anticoagulation in patients with risk factors for bleeding, of which a history of bleeding is a common component,[4-6] they do encourage evaluation of the risk of bleeding to implement special surveillance protocols. However, the association between a history of bleeding and the risk for

Table III. Outcomes according to history of CR or spontaneous bleeding

Outcome	Bleeding history	No. of patients	Events (%/y)	Adjusted HR (95% CI) Yes vs no	*P**
Stroke or SE	No	15,156	397 (1.4)		
	Yes	3040	80 (1.5)	0.97 (0.75-1.24)	.7791
Hemorrhagic stroke	No	15,156	101 (0.4)		
	Yes	3040	17 (0.3)	0.88 (0.52-1.49)	.6215
Death	No	15,156	1045 (3.7)		
	Yes	3040	227 (4.1)	1.08 (0.93-1.25)	.3274
Cardiovascular death	No	15,156	537 (1.9)		
	Yes	3040	115 (2.1)	1.14 (0.93-1.41)	.2124
MI	No	15,156	150 (0.5)		
	Yes	3040	42 (0.8)	1.05 (0.74-1.50)	.7722
Major bleeding	No	15,104	602 (2.4)		
	Yes	3033	186 (3.8)	1.35 (1.14-1.61)	.0008
Major or CR nonmajor bleeding	No	15,104	1124 (4.5)		
	Yes	3033	365 (7.8)	1.48 (1.31-1.68)	<.0001
GUSTO severe bleeding	No	15,104	207 (0.8)		
	Yes	3033	45 (0.9)	1.11 (0.79-1.55)	.5629
GUSTO moderate/severe bleeding	No	15,104	416 (1.6)		
	Yes	3033	110 (2.2)	1.11 (0.89-1.39)	.3487
GUSTO mild bleeding	No	15,104	1851 (7.7)		
	Yes	3033	618 (14.2)	1.60 (1.46-1.77)	<.0001
ISTH minor bleeding	No	15,104	1265 (5.2)		
	Yes	3033	424 (9.3)	1.58 (1.41-1.78)	<.0001
Intracranial bleeding	No	15,104	147 (0.6)		
	Yes	3033	27 (0.5)	0.90 (0.59-1.36)	.6027

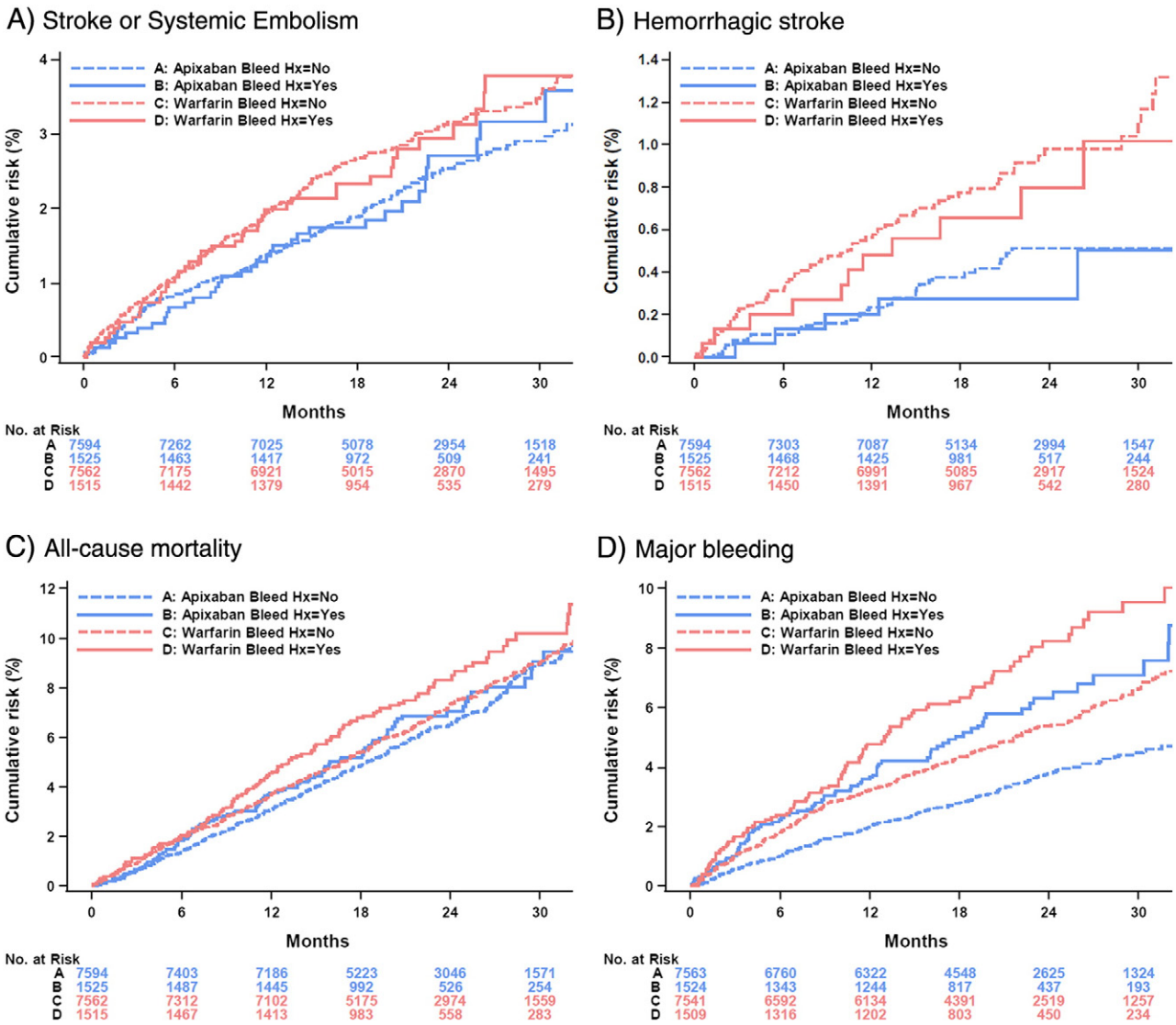
Cox proportional hazards model adjusted for randomized treatment, geographic region, prior VKA status, and established risk factors—age (continuous); sex; glomerular filtration rate CKD-EPI (continuous); smoking status; systolic BP (continuous); heart rate (continuous); AF type; diabetes; heart failure; previous stroke/SE/TIA; hypertension; previous MI; previous peripheral arterial disease/coronary artery bypass grafting/percutaneous coronary interventions; and treatment at randomization with aspirin, ACE inhibitors or ARBs, amiodarone, and statins. For bleeding events, history of anemia, anemia at baseline, chronic liver disease, hematocrit, and use of NSAIDS at randomization were also included. Hazard ratios for comparisons bleeding history (yes vs no).
* *P* value for effect of bleeding history.

future bleeding as well as the risk for future ischemic outcomes is largely unknown. In theory, a history of bleeding, because it may prompt health care providers to underdose anticoagulants or avoid them altogether, might translate into an increased risk of ischemic events, as clearly shown in the setting of acute coronary syndromes.[15] Our study specifically addressed the unmet need of assessing the prognostic implications of a history of bleeding and distinguishing between a history of any bleeding and a history of major, minor, or GI bleeding.

We found that patients with a history of bleeding have baseline characteristics different from patients without such a history, being—as expected—older, more frequently with impaired renal function or diabetes and with features of higher diabetes severity; more often, they were also anemic at baseline or with a history of anemia or prior stroke and more frequently reporting alcohol abuse, but also with lesser prevalence in Europe. In comparing such baseline characteristics (as reported in Tables I and II) with those of patients who actually bled (ISTH major bleeding) during the course ARISTOTLE trial while on anticoagulants, on which we have also reported recently[16] (see Table I in that study), most of such characteristics are similar. It seems, therefore, that baseline characteristics of previous bleeders and of bleeders on anticoagulants are relatively similar.

We found that a history of bleeding translates into more future bleeding episodes. Importantly, a higher risk of bleeding also occurs in the presence of a history of minor bleeding. On the contrary, history of major bleeding (for which data are scarce) was not found to be such a predictor, but this may simply be due to the statistical uncertainty of the estimates due to the small number of major bleeding observed, as the HRs for the predictive ability of a history of minor and major bleeding appear to be quite similar. These findings imply that not only previous major bleeding, but also previous minor bleeding should be incorporated into scores for predicting the risk of future bleeding events.[4-6] This is currently the case for the ATRIA bleeding risk score,[6] but not for the $HEMORR_2HAGES$ score, in which the severity of previous bleeding is not specified,[4] or for the HAS-BLED score, which only takes previous major bleeding into account.[5] Currently, we do not know what subtype of minor bleeding in the patients' medical history is really predictive of future bleeding events. Such additional information may be important for improving bleeding scores in the future.

Figure 1

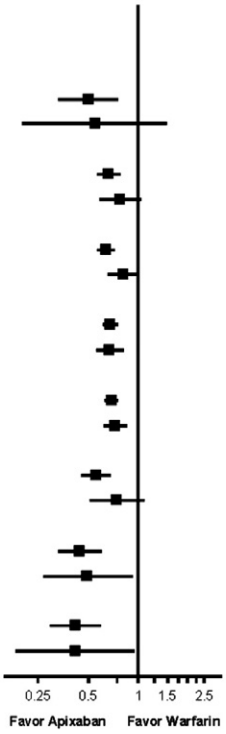


Kaplan-Meier curves depicting the accumulation of events as a function of time, divided according to the presence (continuous line) or absence of a history of bleeding (dotted line) and of the randomized treatment (apixaban in blue) or warfarin (red). **A**, Stroke and SE. **B**, Hemorrhagic stroke. **C**, Death. **D**, Major bleeding.

Of note, the association of a history of bleeding with future bleeding outcomes in our study remains significant independent of the presence of anemia at baseline, with *P* value for interaction of bleeding history and being anemic at baseline always nonsignificant ($P > .05$). This is noteworthy, in the light of our recent report on the prognostic role of anemia in bleeding (and mortality, but not stroke), in the ARISTOTLE cohort.[17] We have also recently reported on a characterization of major bleeding in the trial based on the components of the major bleeding definition; explored major bleeding by location; defined 30-day mortality after a major bleeding event; and identified factors associated with major bleeding.[16] In that article, we have reported that, compared with warfarin, apixaban was associated with fewer intracranial hemorrhages, less adverse consequences after extracranial hemorrhage, and a 50% reduction in fatal consequences at 30 days in cases of major hemorrhage. That article also found that previous hemorrhage was a predictor of future bleeding.[16] That article, however, did not report on the implications of a bleeding history for subsequent types of bleeding and for ischemic events, which is, therefore, the aim of the current study.

Figure 2

Outcomes according to history of clinically relevant or spontaneous bleeding	Apixaban *No of patients*	Warfarin *No of patients*	Apixaban *Events (%/year)*	Warfarin *Events (%/year)*	HR (95%CI)	p-value *Interaction*
Hemorrhagic stroke						
Bleeding History=No	7594	7562	34 (0.2)	67 (0.5)	0.50 (0.33-0.76)	0.8798
Bleeding History=Yes	1525	1515	6 (0.2)	11 (0.4)	0.55 (0.20-1.48)	
ISTH Major bleeding						
Bleeding History=No	7563	7541	244 (1.9)	358 (2.9)	0.66 (0.56-0.78)	0.3278
Bleeding History=Yes	1524	1509	82 (3.4)	104 (4.3)	0.78 (0.59-1.05)	
Major or CR Non-Major bleeding						
Bleeding History=No	7563	7541	447 (3.5)	677 (5.5)	0.64 (0.57-0.72)	0.0455
Bleeding History=Yes	1524	1509	165 (7.0)	200 (8.6)	0.82 (0.66-1.00)	
ISTH Minor bleeding						
Bleeding History=No	7563	7541	526 (4.2)	739 (6.2)	0.68 (0.61-0.76)	0.9314
Bleeding History=Yes	1524	1509	175 (7.5)	249 (11.2)	0.67 (0.56-0.82)	
GUSTO Mild bleeding						
Bleeding History=No	7563	7541	776 (6.3)	1075 (9.2)	0.69 (0.63-0.75)	0.5599
Bleeding History=Yes	1524	1509	267 (11.9)	351 (16.5)	0.73 (0.62-0.85)	
GUSTO Moderate/Severe bleeding						
Bleeding History=No	7563	7541	151 (1.2)	265 (2.1)	0.55 (0.45-0.68)	0.1795
Bleeding History=Yes	1524	1509	47 (1.9)	63 (2.6)	0.74 (0.51-1.09)	
GUSTO Severe bleeding						
Bleeding History=No	7563	7541	65 (0.5)	142 (1.1)	0.45 (0.33-0.60)	0.7652
Bleeding History=Yes	1524	1509	15 (0.6)	30 (1.2)	0.50 (0.27-0.92)	
Intracranial Bleeding						
Bleeding History=No	7563	7541	44 (0.3)	103 (0.8)	0.42 (0.29-0.59)	0.9933
Bleeding History=Yes	1524	1509	8 (0.3)	19 (0.8)	0.42 (0.18-0.96)	



Bleeding outcomes in ARISTOTLE in relation to randomized treatment and absence or presence of a history of CR or spontaneous bleeding. No significant interaction of treatment with history of any type of bleeding examined is found, with the exception of a marginally significant interaction for the cluster of major/CR nonmajor bleeding.

In the ROCKET-AF study with rivaroxaban in nonvalvular AF, an analysis of predictors of bleeding has also been done. Here increasing age, baseline diastolic BP ≥90 mm Hg, history of chronic obstructive pulmonary disease or GI bleeding, prior acetylsalicylic acid use, and anemia were independently associated with major bleeding risk.[18] Such data, therefore, reporting that a history of GI bleeding—in a completely independent study cohort—predicts future bleeding reinforce and complement data here presented. Those data were, however, only related to history of GI bleeding.

We found that a history of bleeding (of any kind) is not associated with an increased risk of the most ominous complication of anticoagulant therapy, namely, intracranial hemorrhage. Possible reasons for this are (1) the rarity of such condition; (2) the exclusion of patients with previous intracranial hemorrhage from the trial[9,19]; and/or (3) the etiology of intracranial hemorrhage, different from that of (major or minor) extracranial bleeding.[20,21]

We also found no association between a history of bleeding and the risk of ischemic events, including ischemic stroke. One could expect a higher risk of stroke in these patients because there could be a tendency to undertreat or underdose them. It is possible that participation in a clinical trial has protected these patients from being undertreated or underdosed. Real-world data on this point would be, therefore, important to confirm or not such data. Should these be confirmed, history of bleeding would appear as a main discriminating factor between bleeding and thrombotic risks and lend support to the suggestion to start anticoagulant therapy in most patients with nonvalvular AF, irrespective of the bleeding risk assessment.[7,22] This would be even more supported by the use of NOACs, given that the net clinical benefit from starting a non-vitamin K antagonist oral anticoagulant (NOAC) in such patients is largely favorable compared with VKAs and particularly favorable with apixaban.[23]

Indeed, we found an overall benefit of apixaban over warfarin, irrespective of the presence or absence of a history of bleeding. We found no significant interaction of treatment (apixaban vs warfarin) with history of major bleeding (online Appendix Supplementary Table V), minor bleeding (online Appendix Supplementary Table VI), or GI

bleeding (online Appendix Supplementary Table VII). In other words, the prognostic impact of history of bleeding on major, minor, or GI bleeding was not significantly different for the patients being on apixaban or warfarin. For history of minor bleeding, there was one significant interaction for the outcome of major/CR nonmajor bleeding, suggesting that the impact of history of minor bleeding might be prognostically more relevant in predicting major/CR nonmajor bleeding in patients treated with apixaban than in those treated with warfarin (online Appendix Supplementary Table VI). Previous reports of the ARISTOTLE study did not report whether the benefits of apixaban versus warfarin are consistent with regard to stroke/SE, intracranial hemorrhage, mortality, and major bleeding, irrespective of the bleeding history. In that, this information now provided is another novelty of our study. Indeed, by knowing that history of bleeding predicts future bleeding, then physicians, by using this knowledge, may choose among the various anticoagulant options now available, and select drugs associated with less bleeding compared with warfarin, such as apixaban.

In conclusion, this study shows that a history of even minor bleeding, including GI bleeding, is a risk factor for all future bleeding events, with the notable exception of intracranial hemorrhage. A history of bleeding does not appear to be associated with the risk of subsequent ischemic events. Finally, the overall better efficacy and safety of apixaban versus warfarin demonstrated in the ARISTOTLE trial appears to apply broadly to both patients with and without a history of bleeding. This information is important information able to inform physicians' behavior in prescribing anticoagulants for nonvalvular AF.

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References

1. Levine MN, Raskob G, Beyth RJ, et al. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl): 287S-310S.
2. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67.
3. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. Ann Intern Med 2007;147(8):590-2.
4. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J 2006;151(3):713-9.
5. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010;138(5): 1093-100.
6. Fang MC, Go AS, Chang Y, et al. A new risk scheme to predict warfarin-associated hemorrhage: the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol 2011;58(4):395-401.
7. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33(21):2719-47.
8. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130(23): 2071-104.
9. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365: 981-92.
10. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290:2685-92.
11. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26(22): 2422-34.
12. Birman-Deych E, Radford MJ, Nilasena DS, et al. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37(4):1070-4.
13. Gussoni G, Di Pasquale G, Vescovo G, et al. Decision making for oral anticoagulants in atrial fibrillation: the ATA-AF study. Eur J Intern Med 2013;24(4):324-32.
14. De Caterina R, Ammentorp B, Darius H, et al. Frequent and possibly inappropriate use of combination therapy with an oral anticoagulant and antiplatelet agents in patients with atrial fibrillation in Europe. Heart 2014;100(20):1625-35.
15. Steg PG, Huber K, Andreotti F, et al. Bleeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J 2011;32(15):1854-64.
16. Hylek EM, Held C, Alexander JH, et al. 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. J Am Coll Cardiol 2014;63(20):2141-7.
17. Westenbrink BD, Alings M, Granger CB, et al. Anemia predicts bleeding and mortality, but not stroke, in patients with AF: insights from the ARISTOTLE trial. Circulation 2014;130, A16800.
18. Goodman SG, Wojdyla DM, Piccini JP, et al. Factors associated with major bleeding events: insights from the ROCKET AF trial (rivaroxaban once-daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation). J Am Coll Cardiol 2014;63(9):891-900.
19. Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for reduction in stroke and other ThromboembolLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010;159(3):331-9.
20. Lacroix P, Portefaix O, Boucher M, et al. The causes of intracranial hemorrhagic complications induced by antivitamins K. Arch Mal Coeur Vaiss 1994;87(12):1715-9.
21. Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007;120(8):700-5.
22. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31(19):2369-429.
23. Renda G, di Nicola M, De Caterina R. Net clinical benefit of non-vitamin K antagonist oral anticoagulants versus warfarin in phase III atrial fibrillation trials. Am J Med 2015;128(9):1007-14. [e2].