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Major Bleeding With Apixaban vs Aspirin
A Subanalysis of the ARTESiA Randomized Clinical Trial

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IMPORTANCE The Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation (ARTESiA) randomized clinical trial showed that in patients with subclinical atrial fibrillation (SCAF) apixaban, compared with aspirin, reduced stroke/systemic embolism but increased major bleeding.

OBJECTIVES To characterize major bleeding events (site and severity) and identify factors associated with major bleeding.

DESIGN, SETTING, AND PARTICIPANTS This was a prespecified subanalysis of the ARTESiA population who received treatment. This was an international, double-blind, double-dummy randomized clinical trial. Included were patients with 1 or more episodes of SCAF lasting 6 minutes to 24 hours with stroke risk factors (CHA_2DS_2-VASc score ≥3) or prior stroke without other risk factors. Study data were analyzed from August to November 2024.

INTERVENTIONS Apixaban, 5 mg, twice daily (2.5 mg twice daily when indicated) or aspirin, 81 mg, once daily.

MAIN OUTCOMES AND MEASURES Major bleeding adjudicated by a blinded committee according to International Society on Thrombosis and Hemostasis criteria.

RESULTS A total of 3961 patients (mean [SD] age, 76.8 [7.6] years; 2535 male [64%]) were included in this analysis. After a mean (SD) follow-up of 3.5 (1.8) years, 1 or more major bleeding episodes occurred in 133 patients, 86 of 1989 taking apixaban and 47 of 1972 taking aspirin (1.71 vs 0.94 per 100-patient-years; hazard ratio [HR], 1.80; 95% CI, 1.26-2.57). The rates of intracranial (0.33 vs 0.40 per 100 patient-years; HR, 0.82; 95% CI, 0.43-1.57) and fatal (0.10% vs 0.16% per 100 patient-years; HR, 0.63; 95% CI, 0.20-1.91) bleeding were similar in the apixaban and aspirin groups, whereas the rate of gastrointestinal bleeding was higher in the apixaban group (0.89% vs 0.40% per 100 patient-years; HR, 2.23; 95% CI, 1.32-3.78). Among 133 index major bleeding events, those that occurred with apixaban were less likely to occur at critical sites (27.9% [24 of 86] vs 46.8% [22 of 47]; *P* = .03) including intracranial (18.6% [16 of 86] vs 42.6% [20 of 47]; *P* = .003). Most major bleeding events were nonemergencies characterized by decreased hemoglobin greater than or equal to 2 g/dL. Factors associated with major bleeding included nonsteroidal anti-inflammatory drug (NSAID) use (HR, 10.25; 95% CI, 6.57-15.99), cancer (HR, 2.87; 95% CI, 1.49-5.53), randomization to apixaban (HR, 1.84; 95% CI, 1.29-2.63), and age (HR, 1.47; 95% CI, 1.28-1.67, per 5-year increase).

CONCLUSIONS AND RELEVANCE Results of this subanalysis of the ARTESiA randomized clinical trial found that although the rate of major gastrointestinal bleeding was higher in patients with SCAF who were treated with apixaban vs aspirin, rates of fatal and intracranial bleeding were not different. Most major bleeding events were nonemergencies characterized by a decrease in hemoglobin level greater than or equal to 2 g/dL. NSAID use, cancer, randomization to apixaban, and increasing age were associated with an increased risk of major bleeding.

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Visual Abstract

Supplemental content

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Patients with subclinical atrial fibrillation (SCAF), identified through implanted rhythm devices including pacemakers, implantable cardioverter-defibrillators, or cardiac monitors, have an elevated risk of stroke or systemic embolism.[1] Although oral anticoagulation (OAC) is recommended for patients with clinical AF at high stroke risk (>2% per year) and considered for those at intermediate stroke risk (1%-2% per year), the role of OAC in the management of SCAF is less clear given the lower absolute stroke rates in this population and the risk of bleeding.[2-5]

In the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation (ARTESiA) randomized clinical trial, apixaban reduced the risk of stroke or systemic embolism by 37% compared with aspirin in patients with SCAF, an effect that was accompanied by an increased risk of major bleeding.[6] These findings were confirmed by a meta-analysis with the Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH AFNET 6) randomized clinical trial, in which OAC reduced the risk of stroke by 32% risk reduction compared with aspirin/placebo accompanied by an increase in major bleeding in patients with SCAF.[7]

A comprehensive evaluation of the potential benefits and harms of OAC requires not only consideration of the absolute risks of stroke and major bleeding but also an understanding of the type and severity of these events. In the ARTESiA trial, there were more strokes in the aspirin group, 45% of which resulted in permanent disability or death.[6] Compared with aspirin, apixaban reduced the risk of disabling or fatal stroke by 49% (hazard ratio [HR], 0.51; 95% CI, 0.29-0.88), and most bleeding events resolved with conservative/supportive measures with similarly low rates of fatal bleeding (<0.5%) and symptomatic intracranial bleeding (<0.8%) in both groups. Thus, although OAC reduces stroke due to SCAF, further examination of bleeding events is needed to understand the spectrum of bleeding and its consequences to facilitate clinical decision-making by physicians and patients.

We conducted this prespecified subanalysis of the ARTESiA trial to further characterize major bleeding events; determine the cumulative incidence of major bleeding overall and according to randomized treatment, site, severity and clinical course; and determine factors associated with major bleeding.

Key Points

Question In patients with subclinical atrial fibrillation (SCAF) treated with apixaban or aspirin, what are the sites, severity, and factors associated with major bleeding?

Findings In this subanalysis of the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation (ARTESiA) randomized clinical trial including 3961 patients, although the rate of major gastrointestinal bleeding was higher with apixaban compared with aspirin, critical site, intracranial bleeding, and fatal bleeding were similar between arms. Most major bleeding events in both groups were characterized by decreased hemoglobin and were not emergencies.

Meaning This study found that in patients with SCAF, apixaban increased major gastrointestinal bleeding compared with aspirin but intracranial and fatal bleeding events were similar between groups; most bleeding events were nonemergencies characterized by a decrease in hemoglobin.

Methods

Study Design and Population

The ARTESiA randomized clinical trial was conducted at 247 clinical sites in 16 countries between May 7, 2015, and July 30, 2021, as previously described.[6] Research ethics committees at each study site approved the trial protocol (Supplement 1), and all participants provided written informed consent. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

The trial enrolled patients with at least 1 episode of SCAF detected by an implanted pacemaker, defibrillator, or cardiac monitor and lasting between 6 minutes and 24 hours, and risk factors for stroke (CHA_2DS_2-VASc score ≥3, which stands for congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65-74 years, female sex) or previous stroke without other risk factors.[6] In protocol amendments, participant age was raised to 55 years and patients who were 75 years and older or those with a history of stroke and no other risk factors were eligible. Participants were randomized (1:1) in a double-blind double-dummy design to receive 5 mg of apixaban twice daily (2.5 mg twice daily for patients meeting dose reduction criteria) or 81 mg of aspirin daily, using a web-based randomization system. Patients self-identified the following races and ethnicities: Black African, Native Latin, Native North American or Pacific Islander, South Asian, White European, and other (not specified).

Key exclusion criteria included a history of clinical AF, another indication for OAC, need for dual antiplatelet therapy, creatinine clearance less than 25 mL/min, serious bleeding in the last 6 months or at high risk of bleeding (including prior intracranial hemorrhage, active peptic ulcer disease, clinically significant thrombocytopenia or anemia, recent stroke within past 10 days, documented bleeding tendencies or blood dyscrasias), or moderate /severe hepatic impairment. Open-label aspirin was permitted but discouraged. The protocol advised discontinuation of study drug and initiation of open-label OAC in the event of clinical AF or SCAF episodes longer than 24 hours.

Outcomes

The primary outcome of this subanalysis was major bleeding defined according to International Society on Thrombosis and Hemostasis (ISTH) criteria as overt bleeding accompanied by a decrease in hemoglobin of greater than or equal to 2 g/dL (to convert to grams per liter, multiply by 10) or transfusion of greater than or equal to 2 units of packed red cells, occurring at a critical site (eg, intracranial, intraspinal, intraocular retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), or resulting in death.[8] An independent committee of blinded experts adjudicated bleeding events

and classified the severity of the clinical presentation and clinical course using criteria described previously based on review of case report forms and source documents.[9-12] The severity of clinical presentation was classified as follows: (1) category 1, not considered a clinical emergency; (2) category 2, some treatment provided but not considered a clinical emergency; (3) category 3, clinical emergency (eg, hemodynamic instability or intracranial bleeding with neurological symptoms); or (4) category 4, led to death before or almost immediately after the patient presented to hospital. The clinical course was classified as follows: (1) class 1, only measures applied to treat discomfort; (2) class 2, only standard measures (eg, transfusion); (3) class 3, immediate and elaborate measures to avoid death; or (4) class 4, death unavoidable, no lifesaving attempts made.

Statistical Analysis

This subanalysis was conducted in the population receiving treatment, which included all the patients who had undergone randomization and received at least 1 dose of the randomly allocated treatment, with follow-up censored 5 days after permanent discontinuation of allocated treatment. The trial was stopped after enrollment of 4012 patients due to slow recruitment and lower than expected rate of stroke or systemic embolism; although, the data and safety monitoring committee recommended continuation after formal interim analyses.

Baseline characteristics for patients with and without major bleeding were summarized using descriptive statistics with mean and SD or median and IQR for continuous variables and proportions for categorical variables. Major bleeding characteristics, including site of bleeding, severity of clinical presentation, and clinical course, were reported overall and by randomized treatment. To examine the association between randomized treatment and major bleed characteristics for categories with overall cell counts of 5 or more, χ^2 testing of independence was performed. Kaplan-Meier methods were used to calculate cumulative incidences.

We examined the association between baseline covariates and postrandomization aspirin/nonsteroidal anti-inflammatory drug (NSAID) use with major bleeding using univariate Cox regression models stratified by criteria for low dose apixaban. Results are presented as HRs and 95% CIs. A multivariable Cox regression model was selected using backward elimination with significance level to stay in the model set to a 2-sided P value < .05. We used concomitant medications collected at 30 days postrandomization and every 6 months thereafter to derive time-dependent variables for open-label aspirin and NSAID use. All analyses were performed from August to November 2024 using SAS software, version 9.4 (TS1M7) (SAS Institute).

Results

A total of 3961 patients (mean [SD] age, 76.8 [7.6] years; 1426 female [36%]; 2535 male [64%]) were included in this analysis (eFigure in Supplement 2). Patients self-identified with the following races and ethnicities: 87 Black African (2%), 20 Native Latin (0.5%), 14 Native North American or Pacific Islander (0.4%), 17 South Asian (0.4%), 3731 White European (94%), and 92 other (2%). Baseline characteristics of patients with and without major bleeding in the treatment population are presented in **Table 1** and eTable 1 in Supplement 2. Those who experienced major bleeding were older, with lower body weight, and lower creatinine clearance. The distribution of DOAC score categories was statistically different between patients with and without bleeding, with the greatest difference between expected and observed counts for the very high-risk category (DOAC score ≥10).

After a mean (SD) follow-up of 3.5 (1.8) years, at least 1 major bleeding event occurred in 133 patients (142 total bleeding events), 86 of 1989 patients taking apixaban (1.71% per 100 patient-years) and 47 of 1972 patients taking aspirin (0.94% per 100 patient-years; HR, 1.80; 95% CI, 1.26-2.57). The cumulative incidence of major bleeding is shown in **Figure 1**.

After randomization, 12 of 86 patients (14.0%) with apixaban-related bleeding and 6 of 47 patients (12.8%) with aspirin-related bleeding received open-label aspirin (P = .85), whereas 10 of 86 patients (11.6%) with apixaban-related bleeding and 1 of 47 patients (2.1%) with aspirin-related bleeding received NSAIDs (P = .10).

Major Bleed Sites

Noncritical site major bleeding was most frequent (65.4% of index bleeding events) occurring in 87 of 3961 patients (2.2%) overall with a higher risk in apixaban-treated (3.1% [62 of 1989]) vs aspirin-treated (1.3% [25 of 1972]) patients (HR, 2.44; 95% CI, 1.53-3.89; P < .001) (**Table 2**, eTable 2 in Supplement 2, and **Figure 2**). The rates of symptomatic intracranial bleeding (0.33 vs 0.40 per 100 patient-years; HR, 0.82; 95% CI, 0.43-1.57) and fatal bleeding (0.10% vs 0.16% per 100 patient-years; HR, 0.63; 95% CI, 0.20-1.91) were similar in the apixaban and aspirin groups, whereas the rate of gastrointestinal bleeding was higher in the apixaban group (0.89% vs 0.40% per 100 patient-years; HR, 2.23; 95% CI, 1.32-3.78). The cumulative incidences of intracranial bleeding and gastrointestinal bleeding are shown in Figure 1.

Gastrointestinal bleeding was the most common single site of major bleeding (48.9% of index bleeding events) affecting 65 of 3961 patients (1.4%) overall and was more frequent among apixaban-treated (2.3% [45 of 1989]) vs aspirin-treated (1.0% [20 of 1972]) patients (P = .002) (Table 2 and eTable 2 in Supplement 2). Hematuria was also more common among patients taking apixaban vs those taking aspirin (0.4% [9 of 1989] vs 0% [0 of 1972]; P = .004). When considering 133 index major bleeding events, those that occurred in the apixaban group were less likely to be at a critical site compared with those in the aspirin group (27.9% [24 of 86] vs 46.8% [22 of 47]; P = .03), including intracranial (18.6% [16 of 86] vs 42.6% [20 of 47]; P = .003) (eTable 2 in Supplement 2).

Major Bleed Criteria

Hemoglobin decrease of greater than or equal to 2 g/dL was the most frequent adjudicated major bleeding criterion (63.4% [83 of 133] of index bleeding events), occurring in 84 of 3961

Table 1. Baseline Characteristics of Patients Who Experienced 1 or More Major Bleeding Events During Follow-Up

Characteristic	Patients during follow-up		*P* value[b]
	With major bleeding (n = 133)[a]	Without major bleeding (n = 3828)	
Sociodemographic			
Age, median (IQR), y	81 (75-85)	77 (72-82)	<.001
Sex, No. (%)			
Female	47 (35.3)	1379 (36.0)	.52
Male	86 (64.7)	2449 (64.0)	
Race and ethnicity			
Black African	1 (0.8)	86 (2.2)	.23
Native Latin	0	20 (0.5)	
Native North American or Pacific Islander	0	14 (0.4)	
South Asian	0	17 (0.4)	
White European	126 (94.7)	3605 (94.2)	
Other[c]	6 (4.5)	86 (2.2)	
Physical measures			
Body weight, median (IQR), kg	79.0 (65.0-92.0)	81.0 (7.0-92.5)	.02
Body weight category, No. (%)			
<60 kg	18 (13.5)	301 (7.9)	.001
60-120 kg	115 (86.5)	3377 (88.2)	
≥120 kg	0 (0.0)	150 (3.9)	
Body mass index, median (IQR)[d]	27.2 (24.1-31.6)	28.0 (25.1-31.6)	.06
Body mass index category, No. (%)			
<25	44 (33.1)	938 (24.5)	.04
25-30	45 (33.8)	1549 (4.5)	
≥30	44 (33.1)	1339 (35.0)	
Device type, No. (%)			
Pacemaker	95 (71.4)	2649 (69.2)	.33
ICD	12 (9.0)	536 (14.0)	
CRT-ICD or CRT pacemaker	18 (13.5)	443 (11.6)	
ICM	8 (6.0)	200 (5.2)	
Medical history, No. (%)			
Alcohol consumption	51 (45.5)	1408 (41.4)	.38
History of cancer			
No	102 (76.7)	3159 (82.5)	.007
Yes, resolved	21 (15.8)	559 (14.6)	
Yes, chronic/ongoing	10 (7.5)	110 (2.9)	
Chronic liver disease	1 (0.8)	31 (0.8)	.93
Congestive heart failure	30 (22.6)	1098 (28.7)	.24
Coronary arterial disease	50 (37.6)	1418 (37.0)	.57
Diabetes	36 (27.1)	1115 (29.1)	.86
Hypertension	102 (76.7)	3124 (81.6)	.20
Peripheral arterial disease including carotid stenosis	12 (9.0)	314 (8.2)	.39
Stroke, TIA, or systemic embolism	16 (12.0)	340 (8.9)	.13
History of serious bleeding	6 (4.5)	87 (2.3)	.11
CHA_2DS_2-VASc, median (IQR)	4 (3-5)	4 (3-5)	.11
CHA_2DS_2-VASc category, No. (%)			
0-2	12 (9.0)	212 (5.5)	.02
3-5	102 (76.7)	3270 (85.4)	
≥6	19 (14.3)	346 (9.0)	
DOAC score category, No. (%)[e]			

(continued)

patients (2.1%) overall, and was more common in apixaban-treated (3.1% [61 of 1989]) vs aspirin-treated (1.2% [23 of 1972]) patients ($P < .001$) (Table 2 and eTable 2 in Supplement 2). Additional ISTH major bleeding criteria of fatal bleeding (0.2%

Table 1. Baseline Characteristics of Patients Who Experienced 1 or More Major Bleeding Events During Follow-Up (continued)

Characteristic	Patients during follow-up		*P* value[b]
	With major bleeding (n = 133)[a]	Without major bleeding (n = 3828)	
0-3	3 (2.3)	221 (5.8)	<.001
4-5	26 (19.5)	837 (21.9)	
6-7	43 (32.3)	1397 (36.5)	
8-9	44 (33.1)	1115 (29.1)	
≥10	17 (12.8)	258 (6.7)	
Randomized treatment, No. (%)			
Apixaban	86 (64.7)	1903 (49.7)	<.001
Aspirin	47 (35.3)	1925 (5.3)	
Medications, No. (%)			
Aspirin	77 (57.9)	2333 (6.9)	.63
Other single antiplatelet	10 (7.5)	280 (7.3)	.67
Dual antiplatelet therapy	4 (3.0)	129 (3.4)	.89
Calcium channel blockers	38 (28.6)	905 (23.6)	.19
NSAIDs	7 (5.3)	192 (5.0)	.95
Laboratory measures			
Creatinine clearance, median (IQR)	63 (45-79)	67 (53-86)	<.001
Creatinine clearance category, No. (%)			
<50 mL/min	40 (30.1)	804 (21.0)	<.001
50-80 mL/min	61 (45.9)	1834 (47.9)	
>80 mL/min	32 (24.1)	1189 (31.1)	

Abbreviations: $CHA2DS_2$-VASc, congestive heart failure, hypertension, age ≥75 years (doubled), diabetes, stroke, or transient ischemic attack (doubled), vascular disease, age 65-74 years, and sex (female); DOAC, direct oral anticoagulant; ICD, implantable cardioverter-defibrillator; ICM, insertable cardiac monitor; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

[a] 133 Patients experienced 1 or more major bleeding events (142 major bleeding events overall).

[b] *P* values from univariate Cox models.

[c] Other race and ethnicity category not specified.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] DOAC score clinical risk tool is used to estimate bleeding risk for patients with atrial fibrillation treated with DOACs. It includes the following variables: age, creatinine clearance, body weight, history of stroke, transient ischemic attack or systemic embolism, history of diabetes, history of hypertension, antiplatelet use, NSAID use, history of bleeding, history of liver disease.

[5 of 1989] vs 0.4% [8 of 1972]), critical site bleeding (1.3% [25 of 1989] vs 1.1% [22 of 1972]) and transfusion of greater than or equal to 2 red blood cell units (1.4% [28 of 1989] vs 0.9% [18 of 1972]) were similar between the apixaban and aspirin arms.

Major Bleed Severity and Clinical Course

As shown in Table 2, 102 patients (2.6%) were hospitalized for bleeding, 65 (3.3%) in the apixaban arm and 37 (1.9%) in the aspirin arm (*P* = .006). The median (IQR) duration of hospitalization for index major bleeding events was 5 (3-11) days overall (eTable 2 in Supplement 2). The cumulative incidence of bleeding according to severity of clinical presentation is shown in **Figure 3**.

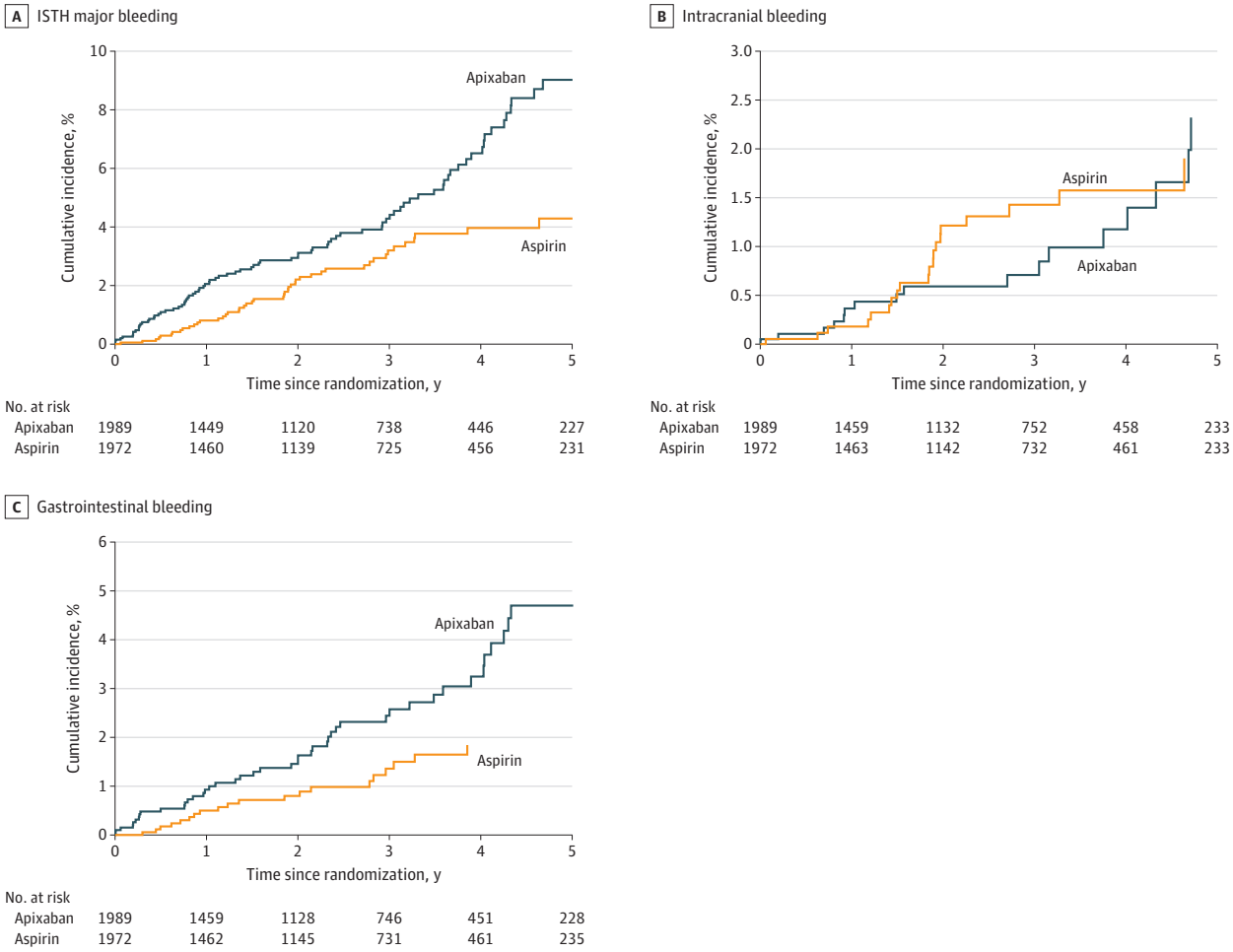
Most patients (2.5% [95 of 3961]) experienced major bleeding events that were adjudicated as nonclinical emergencies (73.3% of index bleeding events), including 63 of 1969 (3.2%) in the apixaban arm and 32 of 1972 (1.6%) in the aspirin arm (HR, 2.01; 95% CI, 1.27-3.19) (Table 2, eTable 2 in Supplement 2, and Figure 2). Rates of death before or almost immediately after presentation to hospital were low among patients with apixaban- and aspirin-related bleeding (0.1% [2 of 1989] vs 0.1% [2 of 1972]). The distribution of severity of clinical presentation was statistically different between treatment groups (*P* = .02), with the largest difference between expected and observed counts for category 2 (not clinical emergency and need for some treatment).

Most patients (0.9% [107 of 3169]) experienced major bleeding that involved conservative management or supportive measures such as transfusion (83.2% of index bleeding events), including 71 of 1969 patients (1.1%) in the apixaban arm and 36 of 1972 patients (1.8%) in the aspirin arm. Bleeding that required immediate measures to avoid death occurred in 0.5% of patients in the apixaban arm vs 0.2% in the aspirin arm, whereas bleeding for which death was unavoidable occurred in 0.1% of patients in the apixaban arm and 0.3% of patients in the aspirin arm. The distribution of clinical course was statistically different between treatment groups (*P* = .005), with the largest difference between expected and observed counts for class 2 (supportive care including transfusion).

Factors Associated With Major Bleeding

In multivariable Cox regression modeling (eTable 3 in Supplement 2), covariates associated with an increased risk of major bleeding included NSAID use (time-dependent variable; HR, 10.25; 95% CI, 6.57-15.99), cancer (HR, 2.87; 95% CI, 1.49-5.53), randomization to apixaban (HR, 1.84; 95% CI, 1.29-2.63), and age (HR, 1.47; 95% CI, 1.28-1.67, per increase of 5

Figure 1. Cumulative Incidence of Major Bleeding



Cumulative incidence of major bleeding (A) overall according to randomized treatment, intracranial bleeding (B), and gastrointestinal bleeding (C). ISTH indicates International Society on Thrombosis and Hemostasis.

years). There were statistically significant interactions with alcohol consumption and randomized treatment (aspirin HR, 2.40; 95% CI, 1.25-4.63 and apixaban HR, 0.83; 95% CI, 0.52-1.34; interaction $P = .01$) and between NSAID use and randomized treatment (aspirin HR, 1.00 and apixaban HR, 13.20; 95% CI, 7.56-23.03; interaction $P < .001$) (eTable 4 in Supplement 2).

Discussion

This prespecified ARTESiA trial subanalysis showed that whereas apixaban increased the risk of major bleeding compared with aspirin in patients with SCAF (absolute risk increase 0.77% per patient-year). Most major bleeding events were not considered clinical emergencies and required only conservative/supportive measures. Gastrointestinal bleeding was most frequent with 2-fold higher rates in apixaban-treated patients. Index major bleeding events that occurred in patients taking apixaban were less likely to occur at a critical site (including intracranial) than in those taking aspirin. Although apixaban increased major gastrointestinal bleeding compared with aspirin, it reduced ischemic stroke by 37% of which more than half were fatal/disabling. Our findings suggest that differences in event severity may be useful for weighing the potential benefits and harms of OAC in this population.

Rates of treatment-related major bleeding in the ARTESiA trial (1.71% per patient-year taking apixaban and 0.94% per patient-year taking aspirin) were lower than those expected for similarly aged patients with clinical AF (detected by surface electrocardiogram). In contrast, in the Apixaban vs Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial, which compared apixaban with aspirin in a younger clinical AF population (average age 70 years vs 77 years in the ARTESiA trial), the rate of treatment-related major bleeding was 1.4% per year in patients receiving apixaban and 0.9% per year in those receiving aspirin (HR, 1.54; 95% CI, 0.96-2.45).[13] However, major

Table 2. Characteristics of Major Bleeding Events Experienced by Study Participants[a]

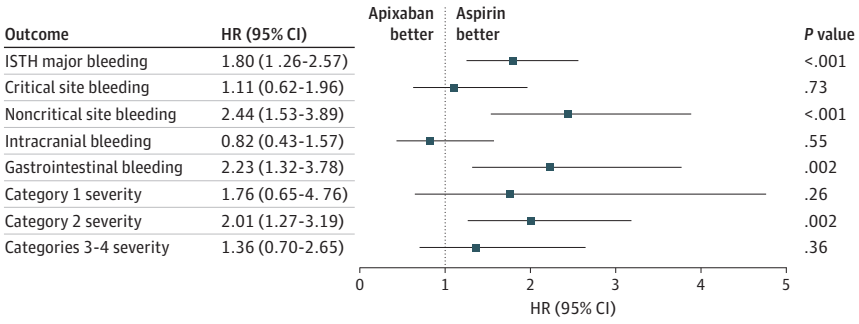
Characteristic, No. (%)	Overall (n = 3961)	Apixaban (n = 1989)	Aspirin (n = 1972)	*P* value
Bleeding site				
Critical site	47 (1.19)	25 (1.26)	22 (1.12)	.68
Intracranial	37 (0.93)	17 (0.85)	20 (1.01)	.60
Intraocular	7 (0.18)	5 (0.25)	2 (0.10)	.45
Pericardial	2 (0.05)	2 (0.10)	0	.50
Intra-articular	1 (0.03)	1 (0.05)	0	>.99
Noncritical site	87 (2.20)	62 (3.12)	25 (1.27)	<.001
Gastrointestinal	65 (1.64)	45 (2.26)	20 (1.01)	.002
Hematuria	9 (0.23)	9 (0.45)	0	.004
Bruising/hematoma	3 (0.08)	2 (0.10)	1 (0.05)	>.99
Surgical site	2 (0.05)	1 (0.05)	1 (0.05)	>.99
Epistaxis	1 (0.03)	1 (0.05)	0	>.99
Intramuscular (without compartment syndrome)	1 (0.03)	1 (0.05)	0	>.99
Other noncritical site	6 (0.15)	3 (0.15)	3 (0.15)	>.99
ISTH major bleeding criteria				
Fatal bleeding	13 (0.33)	5 (0.25)	8 (0.41)	.40
Critical site bleeding	47 (1.19)	25 (1.26)	22 (1.12)	.68
Hemoglobin decrease ≥2 g/dL	84 (2.12)	61 (3.07)	23 (1.17)	<.001
Transfusion ≥2 units of RBCs	46 (1.16)	28 (1.41)	18 (0.91)	.15
Hospitalization for bleeding				
Hospitalization for bleeding	102 (2.58)	65 (3.27)	37 (1.88)	.006
Severity of clinical presentation[a]				
Category 1: not a clinical emergency	14 (0.35)	9 (0.45)	5 (0.25)	.02
Category 2: not a clinical emergency but need for some treatment	81 (2.05)	54 (2.72)	27 (1.37)	
Category 3: clinical emergency (eg, hemodynamic instability or neurological symptoms)	32 (0.81)	19 (0.96)	13 (0.66)	
Category 4: death before or almost immediately after presentation to hospital	4 (0.10)	2 (0.10)	2 (0.10)	
Category 3 or 4	36 (0.91)	21 (1.06)	15 (0.76)	.33
Clinical course of major bleeding[a]				
Class 1: conservative measures	35 (0.88)	21 (1.06)	14 (0.71)	.005
Class 2: supportive care, transfusion	72 (1.82)	50 (2.52)	22 (1.12)	
Class 3: immediate and measures needed to avoid death	15 (0.38)	10 (0.50)	5 (0.25)	
Class 4: death unavoidable	9 (0.23)	3 (0.15)	6 (0.30)	

Abbreviations: ISTH, International Society on Thrombosis and Hemostasis; RBC, red blood cell.

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.

[a] Overall, 133 patients experienced 142 major bleeding events. For patients with more than 1 major bleeding event the highest category or class reported.

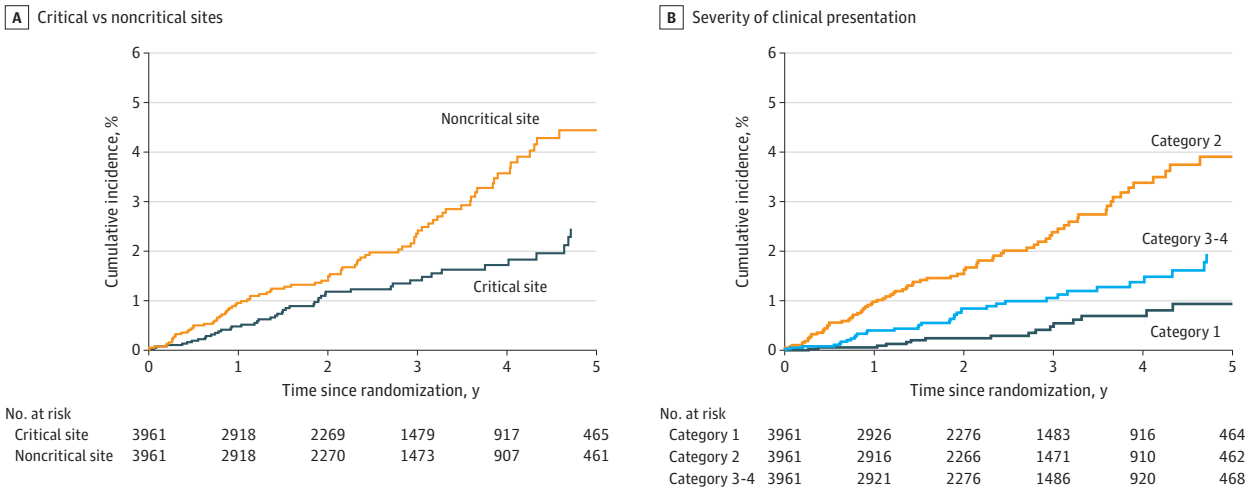
Figure 2. Forest Plot Showing Hazard Ratios and 95% CIs for Categories of Bleeding



Severity of bleeding is graded as follows: category 1, not a clinical emergency; category 2, not a clinical emergency but some treatment; category 3, clinical emergency (eg, hemodynamic instability or neurologic symptoms); and category 4, death before or almost immediately after presentation to hospital. ISTH indicates International Society on Thrombosis and Hemostasis.

bleeding in the AVERROES trial was more frequent among those aged 75 years and older, with a rate of 2.2% per year in patients taking aspirin 2.6% per year in those taking apixaban.[14] Although the risk of treatment-related major bleeding was not statistically different between the apixaban and aspirin groups in the AVERROES trial, a clinically significant difference may

Figure 3. Cumulative Incidence of Bleeding According to Site and Severity of Clinical Presentation



Severity of bleeding is graded as follows: category 1, not a clinical emergency; category 2, not a clinical emergency but some treatment; category 3, clinical emergency (eg, hemodynamic instability or neurologic symptoms); and category 4, death before or almost immediately after presentation to hospital.

not have been excluded given the imprecision of the risk estimate for major bleeding with 95% CI that included both a 4% reduction and a 245% increase in the risk of major bleeding.[13] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial (average age 70 years), the annual rate of treatment-related major bleeding was 2.1% in apixaban-treated patients overall and 3.3% among those aged 75 years and older. In the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, (average age 72 years) the annual rate of bleeding was 2.7% in edoxaban-treated patients (60 mg/30 mg arm) overall and 4.0% among those aged 75 years and older.[15,16] Therefore, despite an increase in the relative risk of major bleeding with apixaban compared with aspirin in the ARTESiA trial, the absolute rates of bleeding appear lower compared with similarly aged patients with clinical AF.

Our findings are consistent with those of the NOAH-AFNET 6 trial in which edoxaban increased the risk of major bleeding by 2-fold compared with aspirin or placebo in patients with device-detected AF (2.1% vs 1.0%; HR, 2.10; 95% CI, 1.30-3.38).[17] A meta-analysis[7] of the ARTESiA and NOAH-AFNET 6 trials confirmed the increase in major bleeding with OAC (relative risk [RR], 1.62; 95% CI, 1.05-2.5) with a small absolute risk increase of 7 major bleeding events per 1000 patient-years (95% CI of 1< to 17<) and no difference in fatal bleeding (RR, 0.79; 95% CI, 0.37-1.69). In evidence-based venous thromboembolism guidelines, an absolute risk increase of this magnitude for major bleeding (23 per 1000) is considered below the trivial/small decision threshold.[18,19]

Our findings suggest that the type and severity of bleeding events, in addition to event rates, may be helpful for understanding the potential harms of OAC, although further data regarding prognosis after the bleeding event are needed. This includes long-term outcomes such as quality of life and dependency for activities of daily living, which are known to be impaired after antithrombotic-related extracranial bleeding.[20,21] In clinical trials, antithrombotic safety is assessed using standard composite outcomes comprised of prognostically heterogeneous criteria (eg, ISTH definition), which may not fully reflect the nature of bleeding events as experienced by patients. In the ARTESiA trial, apixaban prevented strokes, 45% of which were fatal or disabling, with greater benefit in patients with higher CHA_2DS_2-VASc scores and/or prior stroke.[22,23] Most major bleeding events were not emergencies were managed supportively and were attributed primarily to hemoglobin decrease. It appears that the severity of strokes prevented by apixaban is greater than the severity of bleeding caused by apixaban. The importance of differences in severity between stroke and bleeding events is supported by patient preferences regarding OAC for AF. Although patients are generally willing to accept bleeding complications to avoid stroke, physicians may be more averse to bleeding, which is related, at least in part, to concerns about causing harm with provision of treatment vs omission of treatment (as opposed to concerns about bleeding event severity).[24,25] Patient preferences are particularly important in areas of clinical uncertainty in which decisions can have profound consequences. However, to achieve shared decision-making and weigh different treatment options, patients and physicians require a clear understanding about the frequency and severity of both stroke and bleeding events.

We identified 4 factors associated with an increased risk of major bleeding: NSAID use, cancer, randomization to apixaban, and increasing age. Postrandomization NSAID use was associated with a 10-fold increase in major bleeding. However, these findings should be interpreted with caution given the low number of bleeding episodes among NSAID users (particularly in the aspirin arm). A well-established modifiable contributor to anticoagulant-related bleeding, NSAID use increased major bleeding in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial (HR 1.68; 95%

CI, 1.40-2.02) and ARISTOTLE trial (HR, 1.61; 95% CI, 1.11-2.33).[26,27] We showed that the presence of cancer (10.4% of cohort) increased major bleeding by almost 3 fold. The association between cancer and OAC-related bleeding is uncertain among patients with AF due to underrepresentation of patients with cancer in clinical trials (particularly active cancer) and limited data regarding cancer diagnoses and treatments. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial, the risk of major or nonmajor clinically relevant bleeding was higher in patients with a history of cancer at baseline (previous or active) compared with those without cancer (22.6 vs 14.4 per 100 patient-years; HR, 1.22; 95% CI, 1.05-1.41), whereas in the ARISTOTLE trial, the risk of major bleeding was not significantly higher among patients with active/recent cancer at baseline (HR, 0.59; 95% CI, 0.24-1.43).[28,29] Finally, we showed a 1.5-fold higher risk of major bleeding for every 5-year increase in age, consistent with clinical AF trials. There was a greater than 2-fold higher risk of major bleeding among patients 75 years and older in the ARISTOTLE trial (HR, 2.18; 95% CI, 1.69-2.81) and the ENGAGE TIMI-AF 48 trial (HR, 2.68; 95% CI, 2.04-3.52) compared with younger patients.[15,16] Although research on postbleed prognosis is needed, our results suggest that these predictors (NSAIDs, age, cancer) may inform individualized antithrombotic treatment decisions in patients with SCAF including discontinuation of NSAIDs to mitigate bleeding risk.

Strengths and Limitations

One study strength was that it provided the first, to our knowledge, detailed characterization of major bleeding events among patients treated with apixaban or aspirin for SCAF, including blinded adjudication of major bleeding criteria, bleed severity, and clinical course, which are important for understanding the impact of major bleeding events on patients.

This study also has some limitations. Although we identified NSAID use, increasing age, and cancer as predictors of major bleeding, limited information was available about the type, intensity, and duration of NSAID exposure, and details about cancer diagnosis including site, stage, and treatment, which may modify risk. Because concomitant medication data were collected every 6 months and dates of initiation/cessation were not recorded, due to the nature of the data collection, NSAID exposure may have been underestimated.

Conclusions

Results of this subanalysis of the ARTESiA randomized clinical trial reveal that although apixaban increased the risk of major gastrointestinal bleeding compared with aspirin among patients with SCAF, rates of intracranial and fatal bleeding were similar. Most major bleeding events were characterized by hemoglobin decrease and not adjudicated as clinical emergencies. Bleeding that occurred in patients while taking apixaban were less likely to be at a critical site (including intracranial) compared with those taking aspirin. NSAID use, cancer, and increasing age increased the risk of major bleeding. Knowledge about the type and severity of major bleeding events may help physicians and patients understand the spectrum and consequences of potential bleeding complications to inform decision-making; although further data regarding prognosis are needed.

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