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Risk of Stroke or Systemic Embolism According to Baseline Frequency and Duration of Subclinical Atrial Fibrillation: Insights From the ARTESiA Trial

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BACKGROUND: In the ARTESiA trial (Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation), apixaban, compared with aspirin, reduced stroke or systemic embolism in patients with device-detected subclinical atrial fibrillation (SCAF). Clinical guidelines recommend considering SCAF episode duration when deciding whether to prescribe oral anticoagulation for this population.

METHODS: We performed a retrospective cohort study in ARTESiA. Using Cox regression adjusted for CHA_2DS_2-VASc score and treatment allocation (apixaban or aspirin), we assessed frequency of SCAF episodes and duration of the longest SCAF episode in the 6 months before randomization as predictors of stroke risk and of apixaban treatment effect.

RESULTS: Among 3986 patients with complete baseline SCAF data, 703 (17.6%) had no SCAF episode ≥6 minutes in the 6 months before enrollment. Among 3283 patients (82.4%) with ≥1 episode of SCAF ≥6 minutes in the 6 months before enrollment, 2542 (77.4%) had up to 5 episodes, and 741 (22.6%) had ≥6 episodes. The longest episode lasted <1 hour in 1030 patients (31.4%), 1 to <6 hours in 1421 patients (43.3%), and >6 hours in 832 patients (25.3%). Higher baseline SCAF frequency was not associated with increased risk of stroke or systemic embolism: 1.1% for 1 to 5 episodes versus 1.2%/patient-year for ≥6 episodes (adjusted hazard ratio, 0.89 [95% CI, 0.59–1.34]). In an exploratory analysis, patients with previous SCAF but no episode ≥6 minutes in the 6 months before enrollment had a lower risk of stroke or systemic embolism than patients with at least one episode during that period (0.5% versus 1.1%/patient-year; adjusted hazard ratio, 0.48 [95% CI, 0.27–0.85]). The frequency of SCAF did not modify the reduction in stroke or systemic embolism with apixaban ($P_{interaction}$=0.1). The duration of the longest SCAF episode in the 6 months before enrollment was not associated with the risk of stroke or systemic embolism during follow-up (<1 hour: 1.0%/patient-year [reference]; 1–6 hours: 1.2%/patient-year [adjusted hazard ratio, 1.27 (95% CI, 0.85–1.90)]; >6 hours: 1.0%/patient-year [adjusted hazard ratio, 1.02 (95% CI, 0.63–1.66)]). SCAF duration did not modify the reduction in stroke or systemic embolism with apixaban (P_{trend}=0.1).

CONCLUSIONS: In ARTESiA, baseline SCAF frequency and longest episode duration were not associated with risk of stroke or systemic embolism and did not modify the effect of apixaban on reduction of stroke or systemic embolism.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01938248.

Key Words: anticoagulants ■ atrial fibrillation ■ defibrillators ■ pacemaker ■ stroke

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Clinical Perspective

What Is New?

- Using data from the randomized ARTESiA trial (Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation), we evaluated whether the frequency or duration of device-detected subclinical atrial fibrillation (SCAF) were associated with the risk of stroke or systemic embolism, and the effect of apixaban in reducing these events.
- Frequency of SCAF and duration of the longest SCAF episode in the 6 months before trial enrollment were not associated with the risk of stroke or systemic embolism.
- These factors also did not affect the observed reduction in thrombotic events with apixaban.

What Are the Clinical Implications?

- For patients with device-detected SCAF whose longest episode lasts <24 hours, baseline SCAF frequency and duration do not provide information that is helpful for risk stratification.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
aHR	adjusted hazard ratio
ARTESiA	Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation
ASSERT	Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial
HR	hazard ratio
NOAH AFNET 6	Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes
REACT-AF	Rhythm Evaluation for Anticoagulation With Continuous Monitoring of Atrial Fibrillation
SCAF	subclinical atrial fibrillation

Patients with subclinical atrial fibrillation (SCAF) captured by an implanted rhythm device (pacemaker, implantable cardioverter defibrillator, or implanted cardiac monitor) are at increased risk of stroke or systemic embolism.[1–7] The ARTESiA trial (Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation) found that compared with aspirin, apixaban reduced the risk of stroke in patients with SCAF (0.8% versus 1.2% per patient-year in the intention-to-treat population; hazard ratio [HR], 0.63 [95% CI, 0.45–0.88]).[2] Given the relatively low risk of stroke or systemic embolism in ARTESiA, there is an impetus to identify high-risk subgroups of patients with SCAF who may derive greater benefit from oral anticoagulation. Clinical practice guidelines recommend using SCAF episode duration and burden for risk stratification in this patient population.[8,9]

Observational studies of patients with clinical atrial fibrillation (AF; detected by surface ECG) suggest that stroke risk may increase with increasing time spent in AF (often called "AF burden").[8–11] We previously reported a similar finding from ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial) on patients with SCAF, suggesting that stroke risk increases markedly to >3% per year among patients with episodes of SCAF lasting >24 hours.[12] Given this risk, which approximates that of clinical AF, the ARTESiA trial excluded patients with SCAF >24 hours in duration.[7,13] The effects of SCAF pattern and duration on stroke and on the treatment effect of apixaban for shorter episodes, lasting between 6 minutes and 24 hours, remain unknown.

The objectives of this prespecified, secondary analysis of the ARTESiA trial were to determine whether the risk of stroke or systemic embolism varied with the baseline pattern of SCAF. We evaluated whether the risk of stroke or systemic embolism correlated with the frequency of episodes of SCAF in the 6 months before enrollment in the ARTESiA trial. We also assessed whether the risk of stroke or systemic embolism changed along with the duration of the longest single episode of SCAF in the 6 months before enrollment. We explored whether the treatment effect of apixaban versus aspirin was modified by the frequency or duration of SCAF. We hypothesized that the risk of stroke or systemic embolism would increase with higher frequency of SCAF episodes and with longer SCAF episodes.

METHODS

Study Design and Population

ARTESiA randomly assigned patients with risk factors for stroke and with at least one episode of SCAF at any time lasting between 6 minutes and 24 hours to receive 5 mg of apixaban twice daily (2.5 mg twice daily for patients with prespecified dose reduction criteria) or 81 mg of aspirin daily.[2] If participants developed SCAF lasting >24 hours or clinical AF, study medication was discontinued, open-label oral anticoagulation was recommended, and participants were censored for the remainder of follow-up. ARTESiA is registered at ClinicalTrials.gov (URL: https://www.clinicaltrials.gov; Unique identifier: NCT01938248). The local ethics committee approved the trial

protocol at each study site, and all participants gave written informed consent.

Baseline Assessment of Frequency and Duration of SCAF

ARTESiA enrolled patients with SCAF at any time in the past, but not necessarily in the 6 months immediately before enrollment. During the enrollment visit, study site researchers reviewed device interrogation logs for the presence of SCAF in the 6 months before enrollment. If there were SCAF episodes in the 6 months before enrollment, researchers recorded the number of episodes of SCAF lasting ≥6 minutes in the 6 months before enrollment, categorizing them as 0, 1 to 5, 6 to 50, or >50. They also recorded the duration of the longest episode of SCAF. The 6-month time frame was chosen a priori to ensure an equal baseline period for all study participants and one that approximates a normal clinical follow-up interval. A blinded arrhythmia physician confirmed qualifying SCAF episodes <6 hours.[14]

Study Outcomes

This secondary analysis used the same primary outcomes as the main ARTESiA trial. For efficacy, the outcome was a composite of stroke and systemic embolism. For safety, we assessed major bleeding according to the International Society on Thrombosis and Haemostasis definition.[15] A committee of blinded experts adjudicated primary outcome events.

Statistical Analyses

The analyses in the current report include all patients in the intention-to-treat population who had complete baseline data on SCAF. We included all events from the time of randomization until the end of follow-up, censoring patients at the time of development of SCAF >24 hours or clinical AF, consistent with the primary analysis of ARTESiA. We performed sensitivity analyses using the on-treatment population, defined as all patients who underwent randomization and received ≥1 dose of the assigned trial drug, with follow-up censored 5 days after permanent discontinuation of trial medication for any reason.

We calculated incidence rates for our primary outcomes, expressed as percent per person-year. We evaluated the risk of stroke or systemic embolism by categories of the frequency of SCAF episodes (1–5 episodes versus ≥6 episodes) in the 6 months before enrollment. In an exploratory analysis, we compared 0 episodes with ≥1 episode. We also assessed the risk of stroke or systemic embolism by duration of the longest SCAF episode (<1 hour versus 1–6 hours versus >6 hours); we selected these categories on the basis of their approximate tertile distribution, practicality, and predominance in the guidelines and literature.[8,9,12,16,17] We used a global Schoenfeld test to verify the Cox proportional hazards assumption.

We used Cox proportional hazards models, adjusted for CHA_2DS_2-VASc score and treatment allocation, to compute adjusted HRs (aHR) and accompanying 95% CIs.[13] We assessed whether the reduction in the unadjusted hazards for stroke or systemic embolism with apixaban compared with aspirin was modified by the baseline frequency of SCAF using interaction terms. We assessed whether the reduction in the unadjusted hazards for treatment effect on stroke or systemic embolism with apixaban compared with aspirin was modified by the baseline duration of SCAF using tests for trend. We performed an exploratory analysis assessing the risk of major bleeding according to the frequency and duration of the longest episode of SCAF in the 6 months before trial.

We performed Cox analyses using restricted cubic splines to visually explore the relationship between the duration of the longest episode of SCAF as a continuous variable and the outcome of stroke or systemic embolism, adjusting for CHA_2DS_2-VASc score and treatment allocation. In the descriptive statistics, we present categorical variables as number and percentage and continuous variables as median and interquartile range. We used SAS software, version 9.4 (SAS Institute), for all statistical analyses.

RESULTS

Study Participants and Pattern of SCAF

ARTESiA enrolled patients with a mean age of 76.8±7.6 years; 36.1% were women. The mean follow-up was 3.5±1.8 years. The median duration of the longest episode of SCAF in the 6 months before trial enrollment was 1.47 hours (interquartile range, 0.20–4.95 hours). Of 4012 patients enrolled in ARTESiA, 3986 had complete data on baseline SCAF frequency and duration. A total of 703 (17.6%) patients had no SCAF episode ≥6 minutes in the 6 months before enrollment, even though they had SCAF that was detected before that. Among 3283 patients (82.4%) with ≥1 episode of SCAF ≥6 minutes in the 6 months before enrollment, 2542 (77.4%) had up to 5 episodes, and 741 (22.6%) had ≥6 episodes (Table 1). The longest episode lasted <1 hour in 1030 patients (31.4%), 1 to <6 hours in 1421 patients (43.3%), and >6 hours in 832 patients (25.3%; Table 2). The derivation of the study population is detailed in Figure S1, and the number of participants whose longest SCAF episode met any given duration is shown in Figure S2.

Study Outcomes According to Baseline Frequency of SCAF

Among patients with ≥1 episode of SCAF ≥6 minutes in the 6 months before enrollment, increasing frequency of SCAF was not associated with stroke or systemic embolism: 1.1%/patient-year for 1 to 5 episodes versus 1.2%/patient-year for ≥6 episodes (aHR, 0.89 [95% CI, 0.59–1.34]). These results were consistent when analyses were performed using the on-treatment population (Table S1). In an exploratory analysis, patients with SCAF at some time in the past but no episodes ≥6 minutes in the 6 months before enrollment had a lower risk of stroke than patients with ≥1 episode in the previous 6 months (0.5%/patient-year versus 1.1%/patient-year; aHR, 0.48 [95% CI, 0.27–0.85]; Table 3). The reduction in stroke with apixaban compared with aspirin was not modified by the presence of SCAF ($P_{interaction}$=0.1; (Figure 1A; Table 4).

Table 1. Baseline Characteristics According to Number of SCAF Episodes in the 6 Months Before Enrollment in ARTESiA

Characteristics	Overall	None	1–5 Episodes	≥6 Episodes
No.	3986	703	2542	741
Age, y	76.8±7.6	76.7±7.7	76.8±7.7	76.8±7.7
Female sex, n (%)	1438 (36.1)	245 (34.9)	920 (36.2)	273 (36.8)
CHA_2DS_2-VASc score, mean±SD	4.0 (1.1)	3.9 (1.1)	4.0 (1.2)	4.0 (1.2)
Hypertension	3249 (81.5)	570 (81.1)	2082 (81.9)	597 (80.6)
Coronary artery disease	1479 (37.1)	263 (37.4)	963 (37.9)	253 (34.1)
Peripheral arterial disease	332 (8.3)	68 (9.7)	205 (8.1)	59 (8.0)
Diabetes	1160 (29.1)	208 (29.6)	745 (29.3)	207 (27.9)
Heart failure	1132 (28.4)	191 (27.2)	729 (28.7)	212 (28.6)
Previous stroke	357 (9.0)	56 (8.8)	226 (8.9)	75 (10.1)
Race and ethnicity				
White European	3752 (94.1)	673 (95.7)	2380 (93.6)	699 (94.3)
Black African	88 (2.2)	8 (1.1)	61 (2.4)	19 (2.6)
South Asian	17 (0.4)	4 (0.6)	13 (0.5)	0
Native North American or Pacific Islander	14 (0.4)	1 (0.1)	10 (0.4)	3 (0.4)
Other	95 (2.4)	13 (1.9)	66 (2.6)	16 (2.2)
Creatinine clearance, mL/min	71.4±28.6	70.0±27.5	72.1±29.8	72.1±29.8
Weight, kg	82.7±18.2	82.8±18.4	83.0±18.6	83.0±18.6
History of major bleeding*	97 (2.4)	21 (3.0)	59 (2.3)	17 (2.3)
Systolic blood pressure, mm Hg	135±19	134±19	135±19	135±19
Diastolic blood pressure, mm Hg	75±10	75±10	75±11	75±10
Device type				
Pacemaker	2765 (69.4)	530 (75.4)	1693 (66.6)	542 (73.1)
ICD	552 (13.9)	84 (11.9)	386 (15.2)	82 (11.1)
CRT	462 (11.6)	70 (10.0)	307 (12.1)	85 (11.5)
ICM	207 (5.2)	19 (2.7)	156 (6.1)	32 (4.3)

Values are mean±SD or n (%). ARTESiA indicates the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation trial; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; ICM, implanted cardiac monitor; and SCAF, subclinical atrial fibrillation.

*>6 months before trial enrollment.

We did not find any evidence of difference in the risk of major bleeding according to the baseline frequency of SCAF (Table S2).

Study Outcomes According to Baseline Duration of SCAF

The duration of the longest SCAF episode in the 6 months before enrollment was not associated with stroke or systemic embolism during follow-up (<1 hour: 1.0%/patient-year [reference]; 1–6 hours: 1.2%/patient-year [aHR, 1.27 (95% CI, 0.85–1.90)]; >6 hours: 1.0%/patient-year [aHR, 1.02 (95% CI, 0.63–1.66)]; Table 3; Figure 2). The reduction in stroke with apixaban compared with aspirin was not modified by the duration of the longest SCAF episode (P_{trend}=0.1; Figure 1B; Table 4). These results were consistent when analyses were performed using the on-treatment population (Figure S3; Table S2). We did not find any evidence of difference in the risk of major bleeding according to the baseline frequency of SCAF (Table S2).

Data Availability Statement

The data that support the findings of this study are available upon reasonable written request to be reviewed by the ARTESiA publication committee. Requests can be made to the corresponding author of this article.

DISCUSSION

The key finding is that among patients with ≥1 episode of SCAF in the 6 months before enrollment in the ARTESiA trial, neither the frequency of SCAF episodes nor the duration of the longest SCAF episode was associated with increased risk of stroke. In addition, the reduction in stroke with apixaban compared with aspirin was not modified by the frequency of SCAF or by the duration

Table 2. Baseline Characteristics According to the Duration of the Longest SCAF Episode in the 6 Months Before Enrollment in ARTESiA

Characteristics	Overall	<1 h	1–6 h	>6 h
No.	3283	1030	1421	832
Age, y	76.8±7.6	76.9±7.6	76.7±7.6	76.7±7.6
Female sex	1193 (36.3)	400 (38.8)	525 (37.0)	268 (32.2)
CHA_2DS_2-VASc score	4.0±1.1	4.0±1.1	4.0±1.2	3.4±1.2
Hypertension	2679 (81.6)	842 (81.8)	1160 (81.6)	677 (81.4)
Coronary artery disease	1216 (37.0)	358 (34.8)	546 (38.4)	312 (37.5)
Peripheral arterial disease	264 (8.0)	80 (7.8)	115 (8.1)	69 (8.3)
Diabetes	952 (29.0)	315 (30.6)	416 (29.3)	221 (26.6)
Heart failure	941 (28.7)	263 (25.5)	415 (29.2)	263 (31.6)
Previous stroke	301 (9.2)	102 (9.9)	130 (9.2)	69 (8.3)
Race and ethnicity				
White European	3079 (93.8)	966 (93.8)	1333 (93.8)	780 (93.8)
Black African	80 (2.4)	27 (2.6)	34 (2.4)	19 (2.3)
South Asian	13 (0.4)	6 (0.6)	6 (0.4)	1 (0.1)
Native North American or Pacific Islander	13 (0.4)	2 (0.2)	5 (0.4)	6 (0.7)
Other	82 (2.5)	24 (2.3)	37 (2.6)	21 (2.5)
Creatinine clearance, mL/min	71.7±28.9	70.4±30.7	72.8±29.0	72.8±29.0
Weight, kg	82.7±18.2	81.0±18.0	83.4±18.6	83.36±18.6
History of major bleeding*	76 (2.3)	20 (1.9)	40 (2.8)	16 (1.9)
Systolic blood pressure, mm Hg	135±19	135±19	135±19	135±19
Diastolic blood pressure, mm Hg	75±10	76±10	75±11	76±11
Device type				
Pacemaker	2235 (68.1)	704 (68.4)	958 (67.4)	573 (68.9)
ICD	468 (14.3)	143 (13.9)	198 (13.9)	127 (15.3)
CRT	392 (11.9)	95 (9.2)	193 (13.6)	104 (12.5)
ICM	188 (5.7)	88 (8.5)	72 (5.1)	28 (3.4)

Values are mean±SD or n (%). ARTESiA indicates the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation trial; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; ICM, implanted cardiac monitor; and SCAF, subclinical atrial fibrillation.

*>6 months before trial enrollment.

of the longest SCAF episode. We also observed that patients without any SCAF in the 6 months before enrollment in the trial had a low risk of stroke or systemic embolism.

Studies of patients with clinical AF have suggested that the risk of stroke increases with increasing AF duration. In a pooled analysis of 6563 aspirin-treated patients from 2 large clinical trials, patients with paroxysmal AF had a lower CHA_2DS_2-VASc–adjusted hazard of ischemic stroke (2.1%/year) than patients with persistent AF (3.0%/year; aHR, 1.83 [95% CI, 1.43–2.35]) or permanent AF (4.2%/year; aHR, 1.44 [95% CI, 1.05–1.98]).[18] In a cohort study of 1965 patients with paroxysmal AF who were not taking anticoagulants, the highest tertile of AF burden (>11% of monitoring time in AF on a continuous 14-day ambulatory ECG monitor) was associated with a >3-fold increase in CHA_2DS_2-VASc–adjusted hazard of stroke (aHR, 3.16 [95% CI, 1.51–6.62]) compared with the combined 2 lower tertiles of AF burden.[10] In an observational study of 2481 patients with AF who underwent cardioversion without anticoagulation, AF durations of <12 hours were associated with a significantly lower risk of stroke compared with durations 12 to 24 hours (odds ratio, 4.0 [95% CI, 1.7–9.1]) or 24 to 48 hours (odds ratio, 3.3 [95% CI, 1.3–8.9]). Several pathophysiological mechanisms have been proposed to explain these observations of higher stroke risk with increasing clinical AF duration, including AF triggering a prothrombotic state and promotion of negative atrial remodeling.[19–24] This relationship may also be influenced by confounding: AF and stroke have shared risk factors, and patients with more comorbidities may be at higher risk for both AF and stroke.[18,20,22,25] To date, SCAF has been believed to follow a similar pattern as clinical AF, with the associated risk of stroke increasing with episode duration.[8,9]

The lack of a relationship between increasing SCAF frequency or duration with stroke risk seen in this analysis of the ARTESiA trial contrasts with patterns observed in patients with clinical AF. However, the observed absolute differences in AF burden in this study are small: 24

Table 3. Risk of Stroke or Systemic Embolism According to Frequency and Duration of the Longest Episode of SCAF in the 6 Months Before Enrollment in ARTESiA (Pooled Apixaban and Aspirin Cohort: Intention-to-Treat Population)

SCAF frequency	Events/N (% per person-year)	aHR* (95%CI)	*P* value
SCAF episodes			
None	13/703 (0.5)	0.48 (0.27–0.85)	0.01
≥1	127/3283 (1.1)	Reference	
No. of SCAF episodes			
1–5	97/2542 (1.1)	0.89 (0.59–1.34)	0.6
6+	30/741 (1.2)	Reference	
Duration of longest SCAF episode, h			
<1	39/1030 (1.0)	Reference	
1–6	61/1421 (1.2)	1.27 (0.85–1.90)	0.2
>6	27/832 (1.0)	1.02 (0.63–1.66)	0.9

aHR indicates adjusted hazard ratio; ARTESiA, the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation trial; and SCAF, subclinical atrial fibrillation.

*Adjusted for CHA_2DS_2-VASc score and treatment allocation (apixaban or aspirin).

hours of SCAF in 6 months of monitoring corresponds to an AF burden of 0.6%, and a 6-minute episode represents a 0.01% burden over the same period. This analysis is consistent with several other studies of patients with SCAF. A systematic review and meta-analysis published in 2021 included 23 observational studies that reported the risk of stroke and systemic embolism according to the duration of longest recorded episode of SCAF, ranging from ≤30 seconds to 24 hours.[26] The authors performed linear metaregression and found no statistical evidence of an association between increasing duration of the longest duration of SCAF and the risk of stroke or systemic embolism (HR, 1.08 per 1 log minute increase [95% CI, 0.93–1.26]). A secondary analysis of ASSERT examined SCAF duration as a time-varying covariate in the 893 participants with SCAF during trial follow-up.[12] This analysis compared SCAF durations of >6 minutes to 6 hours, >6 hours to 24 hours, and >24 hours categorically, finding that only episode durations >24 hours were associated with an increased risk of stroke (3.1%/year; aHR, 3.24 [95% CI, 1.51–6.95]). In the randomized NOAH AFNET 6 trial (Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes), there was no evidence of interaction between baseline SCAF episode duration and the treatment effect of edoxaban for the triprimary outcome (a composite of cardiovascular death, stroke, or systemic embolism).[3]

The current study provides evidence that baseline differences in the duration of SCAF up to 24 hours in the 6 months before enrollment in the ARTESiA trial did not modify the associated risk of stroke or systemic embolism. Moreover, we found no evidence that the treatment effect of apixaban compared with aspirin is different with increasing episode duration. The 2020 European Society of Cardiology AF guidelines counsel clinicians to expect higher stroke rates with increasing SCAF duration.[8] The 2023 American Atrial Fibrillation Guideline recommends considering episode duration when deciding whether to prescribe oral anticoagulation to patients with SCAF.[9] This analysis strongly suggests that for patients with SCAF and no single episode lasting >24 hours at enrollment, baseline episode duration does not provide information that is helpful in further risk-stratifying patients with device-detected AF.

The exploratory portion of our analysis found that patients who had ≥1 episode of SCAF ≥6 minutes at any time in the past but without SCAF in the 6 months before enrollment carried a lower risk of stroke or systemic embolism on apixaban or aspirin compared with those who had ≥1 SCAF episode ≥6 minutes in the same period. The number of patients without SCAF in the 6 months before enrollment is small, and information about their previous SCAF history was not collected. Thus, this observation should be considered hypothesis-generating. The randomized REACT-AF trial (Rhythm Evaluation for Anticoagulation With Continuous Monitoring of Atrial Fibrillation) is testing a strategy of stopping or starting a direct oral anticoagulant according to the presence or absence of AF as detected by an ECG monitor embedded in a wristwatch.[27] The REACT-AF trial may inform a surveillance strategy for patients with device-detected SCAF.

This prespecified analysis of the randomized ARTESiA trial offers a novel perspective of the associations of baseline SCAF frequency and duration with the occurrence of stroke or systemic embolism. Analysis of outcomes based on SCAF patterns over the previous 6 months mirrors the data that are available for decision-making in real-world clinical practice. The randomized design refutes any evidence that the treatment effect of apixaban varies with changes in frequency and duration; however, this analysis has important limitations. The associations of duration and frequency with stroke outcomes are observational and therefore subject to residual confounding. The subgroups are underpowered compared with the overall trial. Patients with SCAF >24 hours were not eligible for the ARTESiA trial, and those who developed SCAF >24 hours during follow-up were directed to switch to open-label oral anticoagulation, which prevented us from analyzing durations >24 hours. Episode frequency was collected at baseline as a categorical variable, which prevents analysis of this measure as a continuous outcome. We analyzed episode duration and frequency but not total time spent in AF (also known as burden), which also may be an important factor.[11] We analyzed frequency and duration as baseline covariates; these measures are known to change over time.[12,28] ARTESiA participants were predominantly

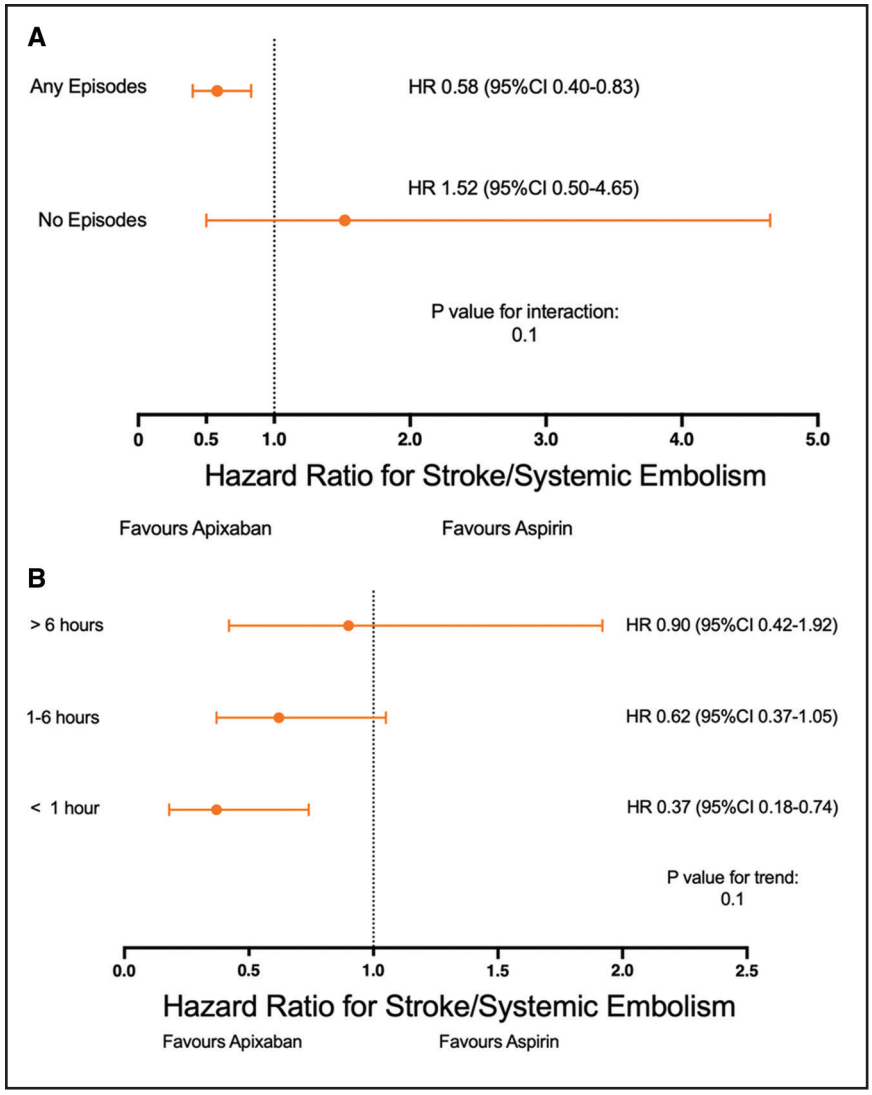

Figure 1. Differences in treatment effect of apixaban for reduction in stroke or systemic embolism compared with aspirin according to frequency and duration of subclinical atrial fibrillation.
A, According to the presence or absence of device-detected subclinical atrial fibrillation in the 6 months before enrollment in the ARTESiA trial (Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation). **B**, According to the duration of the longest episode of device-detected subclinical atrial fibrillation in the 6 months before enrollment in ARTESiA. HR indicates hazard ratio.

European and White, and the results may not be generalizable to other groups. The median baseline episode duration in ARTESiA was 1.5 hours (interquartile range, 0.2 to 5.0 hours)[29]; thus, there were few patients and few events with episodes lasting >12 hours. However, this distribution of episode duration is comparable to the episode durations seen over follow-up in ASSERT, in which fewer than half of patients with SCAF had an episode lasting >6 hours over a mean follow up of 2.5 years.[12]

Table 4. Modification of Treatment Effect of Apixaban Compared With Aspirin on Stroke or Systemic Embolism by Frequency and Duration of SCAF in the 6 Months Before Enrollment in ARTESiA (Intention-to-Treat Population)

Model type	Overall events/n (% per person-year)	Apixaban events/n (% per person-year)	Aspirin events/n (% per person-year)	Apixaban vs aspirin		$P_{interaction}$	P_{trend}
				HR (95% CI)	*P* value		
SCAF episodes	140/3986 (1.0)	55/2001 (0.8)	85/1985 (1.2)	0.63 (0.45– 0.89)	0.008		
None	13/703 (0.5)	8/351 (0.6)	5/352 (0.4)	1.52 (0.50– 4.65)	0.463	0.1	0.1
≥1	127/3283 (1.1)	47/1650 (0.8)	80/1633 (1.4)	0.58 (0.40– 0.83)	0.003		
Duration of longest SCAF episode, h							
<1	39/1030 (1.0)	11/534 (0.6)	28/496 (1.5)	0.37 (0.18– 0.74)	0.005	0.2	
1–6	61/1421 (1.2)	23/679 (1.0)	38/742 (1.5)	0.62 (0.37– 1.05)	0.075		0.1
>6	27/832 (1.0)	13/437 (0.9)	14/395 (1.1)	0.90 (0.42– 1.92)	0.786		

The treatment effect estimates by subgroup were derived from the full model, which included the interaction terms, and were extracted from the contrast statements. ARTESiA indicates the Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation trial; HR, hazard ratio; and SCAF, subclinical atrial fibrillation.

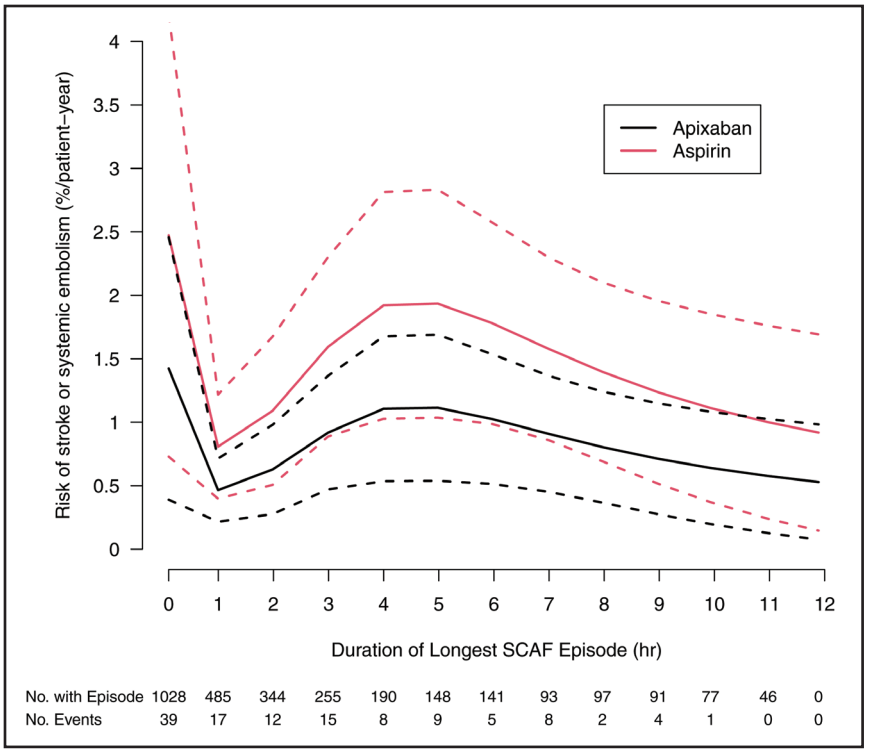

Figure 2. Restricted cubic spline curve exploring the association of stroke or systemic embolism with the duration of the longest subclinical atrial fibrillation episode in the 6 months before enrollment in the ARTESiA trial (intention-to-treat population). The *x* axis is derived on the log scale and converted back to linear hours. This graphic does not consider those with no episodes in the 6 months before enrollment. This graphic excludes participants whose longest episode of subclinical atrial fibrillation (SCAF) was >12 hours because of small numbers. A total of 280 participants had SCAF >12 hours, and among them, 6 experienced a stroke or systemic embolism, corresponding to a risk of 0.74%/patient-years (95% CI, 0.15–3.68). ARTESiA indicates Apixaban for the Reduction of Thromboembolism in Patients With Device-Detected Subclinical Atrial Fibrillation.

Conclusions

In the ARTESiA trial, neither the frequency nor the duration of the longest episode of subclinical AF in the 6 months before trial enrollment modified the risk of stroke or embolism or the treatment benefit of apixaban in reducing stroke or systemic embolism. Patients who had no SCAF in the 6 months before trial enrollment had a lower stroke rate than those with more recent SCAF episodes.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S3

Figures S1–S3

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