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Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation

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ABSTRACT

BACKGROUND

Subclinical atrial fibrillation is short-lasting and asymptomatic and can usually be detected only by long-term continuous monitoring with pacemakers or defibrillators. Subclinical atrial fibrillation is associated with an increased risk of stroke by a factor of 2.5; however, treatment with oral anticoagulation is of uncertain benefit.

METHODS

We conducted a trial involving patients with subclinical atrial fibrillation lasting 6 minutes to 24 hours. Patients were randomly assigned in a double-blind, double-dummy design to receive apixaban at a dose of 5 mg twice daily (2.5 mg twice daily when indicated) or aspirin at a dose of 81 mg daily. The trial medication was discontinued and anticoagulation started if subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation developed. The primary efficacy outcome, stroke or systemic embolism, was assessed in the intention-to-treat population (all the patients who had undergone randomization); the primary safety outcome, major bleeding, was assessed in the on-treatment population (all the patients who had undergone randomization and received at least one dose of the assigned trial drug, with follow-up censored 5 days after permanent discontinuation of trial medication for any reason).

RESULTS

We included 4012 patients with a mean (±SD) age of 76.8±7.6 years and a mean CHA_2DS_2-VASc score of 3.9±1.1 (scores range from 0 to 9, with higher scores indicating a higher risk of stroke); 36.1% of the patients were women. After a mean follow-up of 3.5±1.8 years, stroke or systemic embolism occurred in 55 patients in the apixaban group (0.78% per patient-year) and in 86 patients in the aspirin group (1.24% per patient-year) (hazard ratio, 0.63; 95% confidence interval [CI], 0.45 to 0.88; P=0.007). In the on-treatment population, the rate of major bleeding was 1.71% per patient-year in the apixaban group and 0.94% per patient-year in the aspirin group (hazard ratio, 1.80; 95% CI, 1.26 to 2.57; P=0.001). Fatal bleeding occurred in 5 patients in the apixaban group and 8 patients in the aspirin group.

CONCLUSIONS

Among patients with subclinical atrial fibrillation, apixaban resulted in a lower risk of stroke or systemic embolism than aspirin but a higher risk of major bleeding. (Funded by the Canadian Institutes of Health Research and others; ARTESIA ClinicalTrials.gov number, NCT01938248.)

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*A full list of the ARTESIA investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Atrial fibrillation is typically diagnosed by means of electrocardiography in patients with symptoms. Clinical atrial fibrillation is a leading cause of stroke, particularly among older persons.[1,2] Vitamin K antagonists and direct-acting oral anticoagulants reduce the risk of stroke among patients with clinical atrial fibrillation while increasing the risk of bleeding.[3-5] Approximately 20 years ago, pacemakers and implantable cardioverter–defibrillators that could continuously detect and characterize atrial arrhythmias were widely introduced.[6] It was quickly observed that short episodes of asymptomatic atrial fibrillation were common, even in patients with no other evidence of clinical atrial fibrillation.[7] Even though these episodes of atrial fibrillation lasted minutes to hours, most were not symptomatic.[7-9]

We proposed the term subclinical atrial fibrillation to describe atrial fibrillation that is asymptomatic or that produces such short-lasting, nonspecific symptoms that it is not readily diagnosed by standard clinical means but is uncovered only with the use of long-term, continuous cardiac rhythm monitoring by an implanted cardiac pacemaker or defibrillator.[9] We reported that subclinical atrial fibrillation was present in more than one third of older patients with hypertension who had received a pacemaker[9] and was associated with an increased risk of ischemic stroke or systemic embolism by a factor of 2.5. However, the absolute increase in stroke risk with subclinical atrial fibrillation was 1 percentage point per year, approximately half the risk increase observed among patients with clinically detected atrial fibrillation.[1,2,10] Given the bleeding risk associated with oral anticoagulants, particularly among older persons,[11] the role of oral anticoagulation in the management of subclinical atrial fibrillation is uncertain.[12-15] Clinical practice guidelines and consensus statements have called for randomized trials to resolve this clinical question.[12-15]

Apixaban is a direct-acting oral anticoagulant that has an excellent risk–benefit profile for stroke prevention among patients with clinical atrial fibrillation.[3,5] The Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-Detected Subclinical Atrial Fibrillation (ARTESIA) trial was designed to determine whether apixaban would result in a lower risk of stroke or systemic embolism than aspirin, with an acceptably low risk of major bleeding, among patients with risk factors for stroke who also had subclinical atrial fibrillation detected by a pacemaker, defibrillator, or implantable cardiac monitor (ICM).

METHODS

TRIAL OVERSIGHT AND CONDUCT

We conducted the trial at 247 clinical sites in 16 European and North American countries. The trial protocol was approved by the ethics committee at each site and has been published previously[16]; it is also available with the full text of this article at NEJM.org. The trial was managed by the Population Health Research Institute (PHRI) under the supervision of the first author and last author, who vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. All the patients provided written informed consent.

The trial was designed by the first four authors and last author. The data were gathered by the trial investigators, and the analyses were performed by the two senior statisticians. The first author drafted the first version of the manuscript. All the authors made the decision to submit the manuscript for publication. No writing assistance was provided by any of the trial funders. The legal sponsor of the trial, PHRI, had confidentiality agreements with all the authors not to disclose the trial results before presentation and publication of the data in November 2023. The Canadian Institutes of Health Research, a national peer-reviewed granting agency, was a primary funder of the trial. The Bristol-Myers Squibb–Pfizer Alliance provided the apixaban, aspirin, and matching placebos and funding for the trial but did not have any role in data analysis or interpretation.

TRIAL POPULATION

Eligible patients had subclinical atrial fibrillation that was detected by an implanted pacemaker, defibrillator, or cardiac monitor, with at least one episode lasting 6 minutes or longer but no episodes lasting longer than 24 hours. Eligible patients also had a CHA_2DS_2-VASc score of 3 or higher (scores range from 0 to 9, with higher scores indicating a higher risk of stroke). Protocol amendments raised the minimum age of participants to 55 years and allowed for the enrollment of patients who were 75 years of age or older or who had a history of stroke without other risk

factors. A total of seven patients younger than 55 years of age were enrolled under earlier versions of the protocol and were included in the final analysis. Patients were excluded if they had a history of clinical atrial fibrillation, an ongoing indication for oral anticoagulation, a history of uncorrected major bleeding in the previous 6 months, or a creatinine clearance of less than 25 ml per minute. The concurrent use of open-label aspirin was allowed but discouraged, whereas the use of open-label dual-antiplatelet therapy was prohibited.

TRIAL INTERVENTIONS

Patients underwent randomization in a double-blind, double-dummy fashion to receive either apixaban at a dose of 5 mg twice daily (reduced to 2.5 twice daily as indicated by product labeling[3,13,14]) or aspirin at a dose of 81 mg daily. If subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation developed, the apixaban or aspirin was stopped, follow-up was continued, and treatment with an open-label anticoagulant was initiated. The trial drug was also stopped as specified in the protocol if the creatinine clearance fell below 25 ml per minute, if the patient began taking a prohibited concomitant medication, or if another indication for long-term oral anticoagulant therapy developed.

OUTCOMES

The primary efficacy outcome, a composite of stroke and systemic embolism, was assessed in the intention-to-treat population (all the patients who had undergone randomization), with censoring of follow-up once subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation developed. The development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation makes patients ineligible for the trial and can be viewed as a competing event. Censoring data from such patients in a Cox model is essentially equivalent to performing a cause-specific competing-risks analysis for our primary outcome of stroke or systemic embolism. Sensitivity analyses were performed in the on-treatment population (all the patients who had undergone randomization and received at least one dose of the assigned trial drug), with follow-up censored 5 days after permanent discontinuation of trial medication for any reason. Stroke severity was assessed with the use of the score on the modified Rankin scale at the next scheduled follow-up visit occurring after a stroke.

The primary safety outcome was major bleeding, according to the definition of the International Society on Thrombosis and Haemostasis. In addition, the severity and clinical course of major bleeding were categorized according to methods described previously.[17,18] The primary analysis of major bleeding involved the on-treatment population.

Additional outcomes included cause-specific mortality, stroke subtype, and transient ischemic attack (TIA) with motor deficit, aphasia, or a duration of more than 5 minutes.[19] Stroke, systemic embolism, and major bleeding events were adjudicated by a committee of experts who were unaware of the trial-group assignments, using a streamlined process in which an event was confirmed if the initial adjudicator agreed with the assessment of the site investigator.

STATISTICAL ANALYSIS

We calculated that the enrollment of 4000 patients would provide the trial with a power of 80% to detect a relative reduction of 35% in the risk of stroke or systemic embolism in the apixaban group. These calculations assumed a risk of 2.75% per patient-year in the control group, a crossover frequency of 8.5%, and the occurrence of 248 primary-outcome events in the two groups.

Formal interim analyses were completed after one third and two thirds of planned primary-outcome events had occurred, and the data and safety monitoring committee recommended that the trial continue to completion. However, owing to slow enrollment and a lower-than-expected event rate, this goal was not achieved. Eventually, we could no longer resupply trial medication; therefore, without any knowledge of treatment effects, a decision was made to perform final trial follow-up visits, which were completed between May and August 2023.

We performed Kaplan-Meier analysis to compare the rate of primary-outcome events in the two groups and used a Cox proportional-hazards model to investigate variable effects, with the trial group as a covariate and with stratification according to the presence or absence of two or more criteria for the lower dose of apixaban. All the analyses were conducted with the use of SAS software, version 9.4 or later. Additional details on the statistical methods are provided

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Apixaban (N=2015)	Aspirin (N=1997)	Total (N=4012)
Age — yr	76.9±7.6	76.7±7.7	76.8±7.6
Female sex — no. (%)	719 (35.7)	728 (36.5)	1447 (36.1)
CHA_2DS_2-VASc score†			
Mean	3.9±1.1	3.9±1.1	3.9±1.1
Score ≥4 — no. (%)	1220 (60.5)	1214 (60.8)	2434 (60.7)
History of hypertension — no. (%)	1643 (81.5)	1626 (81.4)	3269 (81.5)
History of coronary artery disease — no. (%)	731 (36.3)	754 (37.8)	1485 (37.0)
Peripheral arterial disease — no. (%)	168 (8.3)	166 (8.3)	334 (8.3)
Diabetes mellitus — no. (%)	583 (28.9)	584 (29.2)	1167 (29.1)
History of heart failure — no. (%)	550 (27.3)	587 (29.4)	1137 (28.3)
History of stroke, systemic embolism, or TIA — no. (%)	180 (8.9)	181 (9.1)	361 (9.0)
Race or ethnic group — no. (%)‡			
White European	1897 (94.1)	1881 (94.2)	3778 (94.2)
Black African	42 (2.1)	46 (2.3)	88 (2.2)
Native Latin	8 (0.4)	12 (0.6)	20 (0.5)
South Asian	7 (0.3)	10 (0.5)	17 (0.4)
Native North American or Pacific Islander	10 (0.5)	4 (0.2)	14 (0.3)
Other	51 (2.5)	44 (2.2)	95 (2.4)
Baseline antiplatelet use — no. (%)			
Aspirin	1165 (57.8)	1137 (56.9)	2302 (57.4)
Other single antiplatelet agent	77 (3.8)	81 (4.1)	158 (3.9)
Dual antiplatelet therapy	67 (3.3)	70 (3.5)	137 (3.4)
Creatinine clearance — ml/min	70.8±26.7	72.1±30.6	71.4±28.7
Weight — kg	82.5±18.3	82.9±18.1	82.7±18.2
History of major bleeding >6 mo before enrollment — no. (%)	50 (2.5)	47 (2.4)	97 (2.4)
Blood pressure — mm Hg			
Systolic	135.0±18.9	135.0±18.7	135.0±18.8
Diastolic	75.4±10.4	75.5±10.4	75.5±10.4
Device type — no. (%)			
Pacemaker	1414 (70.2)	1370 (68.6)	2784 (69.4)
ICD	270 (13.4)	284 (14.2)	554 (13.8)
CRT-ICD or CRT pacemaker	228 (11.3)	237 (11.9)	465 (11.6)
ICM	103 (5.1)	106 (5.3)	209 (5.2)
No. of episodes of SCAF lasting ≥6 min during the 6 mo before randomization — no./total no. (%)			
0	354/2014 (17.6)	356/1997 (17.8)	710/4011 (17.7)
1 to 5	1283/2014 (63.7)	1274/1997 (63.8)	2557/4011 (63.7)
6 to 50	334/2014 (16.6)	328/1997 (16.4)	662/4011 (16.5)
>50	43/2014 (2.1)	39/2014 (2.0)	82/2011 (4.1)

Table 1. (Continued.)

Characteristic	Apixaban (N=2015)	Aspirin (N=1997)	Total (N=4012)
Longest episode of SCAF in past 6 mo — no./total no. (%)			
No episodes	317/2012 (15.8)	315/1995 (15.8)	632/4007 (15.8)
<6 Min	42/2012 (2.1)	43/1995 (2.2)	85/4007 (2.1)
6 Min to <1 hr	535/2012 (26.6)	497/1995 (24.9)	1032/4007 (25.8)
1 to <6 Hr	681/2012 (33.8)	743/1995 (37.2)	1424/4007 (35.5)
6 to <12 Hr	287/2012 (14.3)	264/1995 (13.2)	551/4007 (13.8)
12 to 24 Hr	150/2012 (7.5)	133/1995 (6.7)	283/4007 (7.1)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. CRT denotes cardiac resynchronization therapy, ICD implantable cardioverter–defibrillator, ICM insertable cardiac monitor, SCAF subclinical atrial fibrillation, and TIA transient ischemic attack.

† CHA_2DS_2-VASc scores (an assessment of the risk of stroke among patients with atrial fibrillation) range from 0 to 9, with higher scores indicating a higher risk of stroke.

‡ Race and ethnic group were reported by the patient.

in the statistical analysis plan (available with the protocol).

RESULTS

TRIAL PATIENTS

Between May 7, 2015, and July 30, 2021, a total of 4012 patients underwent randomization, 2015 to the apixaban group and 1997 to the aspirin group (Fig. S1 in the Supplementary Appendix, available at NEJM.org). A total of 51 patients (26 in the apixaban group and 25 in the aspirin group) did not receive at least one dose of a trial medication. Apixaban or aspirin was permanently discontinued during follow-up owing to the development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation in 490 patients (24.3%) in the apixaban group and 476 patients (23.8%) in the aspirin group. The median time from randomization to discontinuation of a trial medication owing to the development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation was 18.3 months (interquartile range, 8.5 to 34.0). Trial medication was discontinued for other reasons in 687 patients (34.1%) in the apixaban group and 697 patients (34.9%) in the aspirin group.

During follow-up, death occurred in 457 patients (22.7%) in the apixaban group and in 438 patients (21.9%) in the aspirin group. A total of 61 patients in the apixaban group and 57 patients in the aspirin group were withdrawn or were lost to follow-up without a final visit. The remaining patients had a final visit. The mean (±SD) duration of follow-up was 3.5±1.8 years for the intention-to-treat analysis and 2.5±1.8 years for the on-treatment analysis.

The baseline characteristics of the patients are shown in Table 1. The mean age was 76.8±7.6 years, and 36.1% were women. The characteristics of the patients enrolled in this trial are generally representative of patients with subclinical atrial fibrillation, except that the patients in this trial were slightly less likely to have a history of stroke or transient ischemic attack and there was a lower proportion of women (Table S1).[9] The mean CHA_2DS_2-VASc score was 3.9±1.1, and the median duration of the longest episode of subclinical atrial fibrillation in the 6 months before trial enrollment was 1.47 hours (interquartile range, 0.20 to 4.95). Open-label aspirin was used by 57.4% of the patients before randomization, and other single antiplatelet agents were used by 3.9%. Among the patients who had undergone randomization, 9.4% had indications for the lower dose of apixaban.

INTENTION-TO-TREAT ANALYSIS

Stroke or systemic embolism (primary efficacy outcome) occurred in 55 patients assigned to receive apixaban (0.78% per patient-year) and 86

patients assigned to receive aspirin (1.24% per patient-year) (hazard ratio, 0.63; 95% confidence interval [CI], 0.45 to 0.88; P=0.007). Similar between-group differences were observed in ischemic stroke (including stroke of unknown cause) (hazard ratio, 0.62; 95% CI, 0.43 to 0.91) and in stroke from any cause (hazard ratio, 0.64; 95% CI, 0.46 to 0.90) (Fig. 1 and Table 2). The median time to assessment on the modified Rankin scale was 92 days (interquartile range, 17 to 184) for apixaban and 45.5 days (interquartile range, 12 to 139) for aspirin. Stroke severity was assessed as being disabling or fatal (score on the modified Rankin scale, 3 to 6) in 18 of 55 strokes (33%) in the apixaban group and in 36 of 84 strokes (43%) in the aspirin group. The risk of disabling or fatal stroke was lower by 49% with apixaban than with aspirin (hazard ratio, 0.51; 95% CI, 0.29 to 0.88). Deaths were similar in number between the two groups. Major bleeding in the intention-to-treat population occurred more often with apixaban than with aspirin (Table 2).

The risk of the composite of stroke, systemic embolism, or death from cardiovascular causes was similar for patients assigned to receive apixaban and those assigned to receive aspirin. An intention-to-treat analysis that did not censor data for patients after the development of subclinical atrial fibrillation lasting longer than 24 hours or clinical atrial fibrillation showed results similar to those of the primary analysis (Table S2). No significant subgroup interactions were seen for any of the prespecified subgroups of interest.[16]

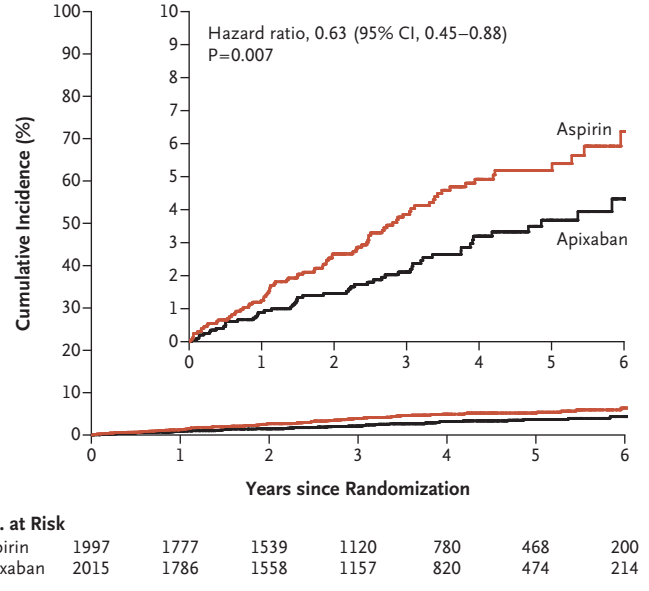

Figure 1. Stroke or Systemic Embolism (Primary Efficacy Outcome).

ON-TREATMENT ANALYSIS

The risk of major bleeding was 1.71% per patient-year with apixaban and 0.94% per patient-year with aspirin (hazard ratio, 1.80; 95% CI, 1.26 to 2.57; P=0.001) (Table 3). Table 4 shows classification of major bleeding according to severity of clinical presentation and clinical course with the use of previously reported criteria.[17,18] Clinical presentation with hemodynamic instability was uncommon, and most bleeding events responded to supportive care, which could include red-cell transfusion. Fatal bleeding occurred in 5 patients with apixaban and 8 patients with aspirin. Symptomatic intracranial hemorrhage occurred in 12 patients with apixaban and 15 patients with aspirin. In the on-treatment analysis, the risk of stroke or systemic embolism was 0.71% per patient-year with apixaban and 1.29% per patient-year with aspirin (hazard ratio, 0.55; 95% CI, 0.37 to 0.83; P=0.004). Additional on-treatment analyses were performed, with adjustment for baseline between-group differences among the patients who did receive at least one dose of a trial drug, and the findings did not affect the overall results.

DISCUSSION

The ARTESIA trial showed that among patients with episodes of subclinical atrial fibrillation and risk factors for stroke, the risk of stroke or systemic embolism was lower by 37% (95% CI, 12 to 55) with apixaban than with aspirin, and the risk of disabling or fatal stroke was lower by 49% (95% CI, 12 to 71). These findings are supported by the intention-to-treat analysis, in which data were not censored after the development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation, and by the on-treatment analysis. The data make a strong case that apixaban prevents stroke in this population, given the high rate of trial-drug discontinuation in this trial. The risk of major bleeding in the on-treatment analysis was increased by a factor of 1.8 (range, 1.3 to 2.6) in the apixaban group as compared with the aspirin group.

Table 2. Clinical Outcomes (Intention-to-Treat Population).*

Outcome	Apixaban (N=2015)		Aspirin (N=1997)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*		
Stroke or systemic embolism	55	0.78	86	1.24	0.63 (0.45–0.88)	0.007
Stroke	55	0.78	84	1.21	0.64 (0.46–0.90)	
Ischemic or unknown type†	45	0.64	71	1.02	0.62 (0.43–0.91)	
Hemorrhagic	10	0.14	13	0.18	0.76 (0.33–1.73)	
Severity according to score on modified Rankin scale‡						
0–2	31	0.44	45	0.65	0.68 (0.43–1.07)	
3–6	19	0.27	37	0.53	0.51 (0.29–0.88)	
Missing data	5	0.07	2	0.03	2.48 (0.48–12.80)	
Systemic embolism	0		2	0.03	NA	
Stroke, TIA, or systemic embolism§	82	1.17	107	1.56	0.75 (0.56–1.00)	
Stroke, systemic embolism, or death from cardiovascular causes	148	2.10	171	2.47	0.85 (0.68–1.06)	
Stroke, myocardial infarction, systemic embolism, or death	419	6.01	418	6.10	0.98 (0.86–1.12)	
Myocardial infarction	37	0.52	41	0.59	0.89 (0.57–1.40)	
Death	362	5.06	341	4.82	1.04 (0.90–1.21)	
Death from cardiovascular causes	105	1.47	108	1.53	0.96 (0.73–1.25)	
Major bleeding¶	106	1.53	78	1.12	1.36 (1.01–1.82)	0.04
Fatal bleeding	10	0.14	14	0.20	0.70 (0.31–1.57)	
Symptomatic intracranial hemorrhage	17	0.24	23	0.33	0.73 (0.39–1.36)	
Gastrointestinal bleeding	55	0.78	31	0.44	1.76 (1.13–2.74)	
Transfusion performed	35	0.49	31	0.44	1.11 (0.68–1.80)	

* Shown are data for the intention-to-treat population (all the patients who had undergone randomization), with censoring for the development of subclinical atrial fibrillation lasting more than 24 hours or clinical atrial fibrillation.
† Data include TIA with positive imaging.
‡ Scores on the modified Rankin scale range from 0 to 6, with higher scores indicating greater disability.
§ Data include TIA with motor deficit, aphasia, or a duration of more than 5 minutes.
¶ Major bleeding was assessed according to the definition of the International Society on Thrombosis and Haemostasis (ISTH).

We previously reported that among older patients with pacemakers, hypertension, and a mean $CHADS_2$ score of 2, the presence of subclinical atrial fibrillation increased the risk of ischemic stroke or systemic embolism by a factor of 2.49 (95% CI, 1.28 to 4.85).[9] In that study, the risk of ischemic stroke or systemic embolism increased from 0.69% per patient-year among patients without subclinical atrial fibrillation to 1.69% per patient-year among those with subclinical atrial fibrillation. In the AVERROES trial, which involved patients with clinical atrial fibrillation and a mean $CHADS_2$ score of 2 who were receiving aspirin, we reported that the rate of stroke or systemic embolism was 3.7% per patient-year.[3] Thus, subclinical atrial fibrillation does not appear to increase the risk of stroke or systemic embolism to the same extent as clinical atrial fibrillation. The risk of stroke or systemic embolism in the aspirin group of the present trial was 1.24% per patient-year, which is substantially less than the expected risk with clinical atrial fibrillation. However, this finding should not lead to complacency, because 37 of the 82 strokes (45%) with available data for scores on the modified Rankin scale in the aspirin group resulted in permanent disability or death.

In considering the clinical benefit of apixaban

Table 3. Clinical Outcomes (On-Treatment Population).*

Outcome	Apixaban (N=1989)		Aspirin (N=1972)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*		
Stroke or systemic embolism	36	0.71	65	1.29	0.55 (0.37–0.83)	0.004
Stroke	36†	0.71	63	1.25	0.57 (0.38–0.85)	
Ischemic or unknown type	29	0.57	53	1.05	0.54 (0.35–0.86)	
Hemorrhagic	8	0.16	10	0.20	0.78 (0.31–1.98)	
Severity according to score on modified Rankin scale						
0–2	22	0.43	32	0.64	0.69 (0.40–1.18)	
3–6	11	0.22	29	0.58	0.37 (0.19–0.75)	
Missing data	3	0.06	2	0.04	1.43 (0.24–8.58)	
Systemic embolism	0		2	0.04	NA	
Stroke, TIA, or systemic embolism‡	53	1.04	86	1.71	0.61 (0.43–0.86)	
Stroke, systemic embolism, or death from cardiovascular causes	76	1.50	94	1.87	0.80 (0.59–1.09)	
Stroke, myocardial infarction, systemic embolism, or death	193	3.81	206	4.11	0.92 (0.75–1.12)	
Myocardial infarction	27	0.53	33	0.66	0.81 (0.49–1.35)	
Death	139	2.73	122	2.42	1.11 (0.87–1.42)	
Death from cardiovascular causes	42	0.83	37	0.73	1.13 (0.72–1.75)	
Major bleeding§	86	1.71	47	0.94	1.80 (1.26–2.57)	0.001
Fatal bleeding	5	0.10	8	0.16	0.63 (0.20–1.91)	
Symptomatic intracranial hemorrhage	12	0.24	15	0.30	0.77 (0.36–1.64)	
Gastrointestinal bleeding	45	0.89	20	0.40	2.23 (1.32–3.78)	
Transfusion performed	26	0.51	18	0.36	1.43 (0.78–2.61)	

* Shown are data for the on-treatment population (all the patients who had undergone randomization and received at least one dose of the assigned trial drug), with follow-up censored 5 days after permanent discontinuation of trial medication for any reason.
† One patient in the apixaban group had both an ischemic stroke and a hemorrhagic stroke. This patient was counted once for the overall category of stroke.
‡ Data include TIA with motor deficit, aphasia, or a duration of more than 5 minutes.
§ Major bleeding was assessed according to the definition of the ISTH.

therapy in patients with subclinical atrial fibrillation, one needs to assess both the benefits and risks. Simply counting strokes as compared with bleeding events might suggest a neutral overall effect. With apixaban as compared with aspirin, 31 fewer cases of stroke or systemic embolism were seen in the intention-to-treat analysis, as compared with 39 more major bleeding events in the on-treatment analysis. However, strokes involve permanent loss of brain tissue, whereas major bleeding is usually reversible, with most patients having complete recovery.[17,18] In the ARTESIA trial, apixaban did not results in substantially higher rates of transfusion, fatal bleeding, hemorrhagic stroke, or other intracranial hemorrhage than aspirin. In addition, although 45% of strokes among patients assigned to receive aspirin resulted in death or clinically significant long-term disability, nearly 90% of all major bleeding events in patients who received apixaban were managed with nonprocedural measures only (including blood transfusion). Only 17 of 93 episodes of major bleeding (18%) in patients assigned to receive apixaban had clinical presentation with hemodynamic instability or neurologic symptoms (13 such episodes were noted with aspirin).

Similarly, only 9 of 93 patients (10%) with bleeding during apixaban therapy required immediate measures to avoid death or died from bleeding (4 such patients were receiving aspirin). Thus, on the basis of the considerably greater severity of the stroke events prevented than the bleeding events caused, we believe that these findings favor consideration of the use of oral anticoagulation for patients with risk factors for stroke in whom subclinical atrial fibrillation develops.

The results of the ARTESIA trial need to be placed in the context of the NOAH-AFNET 6 (Non–Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes) trial, which was prematurely terminated for futility. This trial enrolled 2538 patients whose baseline characteristics were similar to those of patients enrolled in the ARTESIA trial, with atrial high-rate episodes (another term for subclinical atrial fibrillation) lasting 6 minutes or more and at least one additional CHA_2DS_2-VASc risk factor for stroke.[20] Patients were randomly assigned to receive edoxaban or placebo, and many patients in the control group received aspirin. The investigators found no significant between-group difference in the incidence of a composite of stroke, systemic embolism, or death from cardiovascular causes (primary efficacy outcome) or in the incidence of stroke. The analysis of stroke was underpowered because there were only 49 ischemic strokes in total in the two groups, less than half the number in the ARTESIA trial. The investigators reported a possible benefit with respect to a composite of ischemic stroke or systemic embolism, but this finding was difficult to interpret because reported systemic embolism events included myocardial infarction and pulmonary embolism. The conclusions of the NOAH-AFNET 6 trial were that edoxaban, as compared with placebo, did not provide a benefit with respect to the primary efficacy outcome and was associated with a higher incidence of a composite of death or major bleeding.

The difference in the conclusions of the two trials can be explained as follows. First, the NOAH-AFNET 6 trial was stopped early, had relatively few stroke events, and was thus underpowered. Second, the primary efficacy outcome of the NOAH-AFNET 6 trial included death from cardiovascular causes. Because deaths in this population of patients are rarely due to stroke and are commonly due to underlying cardiovascular disease and old age,[3,9] adding death from cardiovascular causes to the primary outcome dilutes any potential signal related to stroke reduction. Third, the control group in the NOAH-AFNET 6 trial was assigned to received placebo (and many received aspirin), whereas all the patients in the control group in the ARTESIA trial were assigned to receive aspirin. Aspirin is effective for stroke prevention in patients with previous stroke, but whether it reduces the risk of stroke among patients with atrial fibrillation is controversial.[4] The use of aspirin in the control group in the ARTESIA trial probably had little effect on the signal for reduction in stroke but almost certainly mitigated the signal for harm, because aspirin is known to increase bleeding. However, the difference in the control groups of the two trials does not explain the fact that the ARTESIA trial showed a significant reduction in stroke and the NOAH-AFNET 6 trial did not.

Although the results of the ARTESIA trial are directly relevant to patients with implanted cardiac electronic devices, one might consider broader implications given the proliferation of implanted and wearable cardiac monitors as well as direct-to-consumer devices used to screen for atrial fibrillation.[21-23] Although it was initially contemplated that the high prevalence of subclinical atrial fibrillation was confined to patients with

Table 4. Clinical Presentation and Management of Major Bleeding.*

Variable	Apixaban	Aspirin
No. of major bleeding events	93	49
Clinical presentation — no. (%)		
1: Without emergency	11 (12)	6 (12)
2: Need for some measures	57 (61)	27 (55)
3: Hemodynamic instability or neurologic symptoms	17 (18)	13 (27)
4: Fatal	2 (2)	2 (4)
Missing data	6 (6)	1 (2)
Clinical course — no. (%)		
1: Conservative measures	21 (23)	16 (33)
2: Supportive care, transfusion	54 (58)	22 (45)
3: Immediate measures needed to avoid death	9 (10)	4 (8)
4: Death unavoidable	3 (3)	6 (12)
Missing data	6 (6)	1 (2)

* Categorization is based on classification of bleeding used in previous publications.[17,18] Percentages may not total 100 because of rounding.

pacemakers, subsequent studies involving ICMs showed subclinical atrial fibrillation in many older patients without pacemakers.[24] Some of these patients may also have risk factors for stroke that are similar to those of the patients in the ARTESIA trial.[24-28] However, the results of the ARTESIA trial apply directly only to patients who are already at increased risk for stroke in whom subclinical atrial fibrillation is detected by an implanted device.

In this trial involving patients with risk factors for stroke who were found to have subclinical atrial fibrillation, apixaban resulted in a lower risk of stroke or systemic embolism than aspirin. This effect included a substantial between-group difference in disabling or fatal stroke. The risk of major bleeding was higher with apixaban than with aspirin; most cases responded readily to supportive care.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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