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Apixaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

RESULTS

The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P=0.42).

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

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*The members of the steering committee, as well as other committee members and investigators in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, are listed in the Supplementary Appendix, available at NEJM.org.

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Patients with atrial fibrillation are at increased risk for stroke. Warfarin and other vitamin K antagonists are highly effective treatments, reducing the risk of stroke by about two thirds, but their use is limited by a narrow therapeutic range, drug and food interactions, required monitoring, and risk of bleeding.[1] A randomized trial has confirmed the effectiveness of warfarin in the current era.[2] Two new oral anticoagulants have recently been shown to be equivalent or superior to warfarin in preventing stroke or systemic embolism.[3,4] Apixaban is a direct oral factor Xa inhibitor with rapid absorption, a 12-hour half-life, and 25% renal excretion.[5] In patients with atrial fibrillation who were not candidates for vitamin K antagonists, apixaban, as compared with aspirin, reduced the rate of stroke or systemic embolism by 55% without increasing the risk of major bleeding.[6] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial,[7] we compared apixaban with warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.

Methods

Study Oversight

The trial was designed and led by a steering committee that included academic investigators and representatives of the sponsors (Bristol-Myers Squibb and Pfizer). Approval by the appropriate ethics committees was obtained at all sites. All patients provided written informed consent. The primary analyses were performed both at Bristol-Myers Squibb and at the Duke Clinical Research Institute. All the authors participated in the design of the trial and the planning of the analyses. The first author wrote the first draft of the manuscript, and all the authors participated in subsequent revisions (with no writing assistance other than copy editing) and approved the final version of the manuscript. The trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. All the authors assume responsibility for the accuracy and completeness of the data and the analyses and for the fidelity of the study to the protocol.

Trial Design

The trial design has been reported previously.[7] With the use of a double-blind, double-dummy design, we randomly assigned patients to treatment with apixaban or dose-adjusted warfarin. The primary objective was to determine whether apixaban was noninferior to warfarin in reducing the rate of stroke (ischemic or hemorrhagic) or systemic embolism among patients with atrial fibrillation and at least one other risk factor for stroke. The primary safety outcome was major bleeding, according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH). Key secondary objectives were to determine whether apixaban was superior to warfarin with respect to the primary outcome and to the rates of major bleeding and death from any cause. To control the overall type I error, prespecified hierarchical sequential testing was performed first on the primary outcome for noninferiority, then on the primary outcome for superiority, then on major bleeding, and finally on death from any cause.

Study Population

Eligible patients had atrial fibrillation or flutter at enrollment or two or more episodes of atrial fibrillation or flutter, as documented by electrocardiography, at least 2 weeks apart in the 12 months before enrollment. In addition, at least one of the following risk factors for stroke was required: an age of at least 75 years; previous stroke, transient ischemic attack, or systemic embolism; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction of no more than 40%; diabetes mellitus; or hypertension requiring pharmacologic treatment. Key exclusion criteria were atrial fibrillation due to a reversible cause, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation (e.g., a prosthetic heart valve), stroke within the previous 7 days, a need for aspirin at a dose of >165 mg a day or for both aspirin and clopidogrel, and severe renal insufficiency (serum creatinine level of >2.5 mg per deciliter [221 μmol per liter] or calculated creatinine clearance of <25 ml per minute).[7] Patients were classified as not having received warfarin previously if they had used warfarin or another vitamin K antagonist for no more than 30 consecutive days. Investigators at

all study centers were encouraged to enroll a sizable proportion of patients (≥40%) who had not previously received warfarin.

RANDOMIZATION AND STUDY DRUGS

Randomization was stratified according to whether patients had received warfarin previously and according to clinical site. Apixaban or matching placebo was administered twice daily, with apixaban given in 5-mg doses; 2.5-mg doses were used in a subset of patients with two or more of the following criteria: an age of at least 80 years, a body weight of no more than 60 kg, or a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter) or more. Warfarin (or matching placebo) was provided as 2-mg tablets and was adjusted to achieve a target international normalized ratio (INR) of 2.0 to 3.0. Patients who were receiving a vitamin K antagonist before randomization were instructed to discontinue the drug 3 days before randomization, and the study drug was initiated when the INR was less than 2.0. INRs were monitored with the use of a blinded, encrypted, point-of-care INR device. An algorithm was provided to guide the adjustment of the warfarin dose. The time that patients' INRs were within the therapeutic range was calculated by the Rosendaal method.[8] A program was implemented to improve the quality of INR control through education and feedback at the site and country levels.

An algorithm was provided to manage temporary discontinuations of the study drug around the time of interventional procedures while maintaining concealment of the group assignments. At the end of the trial, when patients discontinued the study drug, guidance was provided in making the transition to open-label warfarin while maintaining concealment of the treatment assignments and ensuring appropriate anticoagulation. In addition to monthly study visits focusing on control of the INR, visits every 3 months included an assessment of clinical outcomes and adverse events. For each patient who was lost to follow-up or who withdrew consent, attempts were made to determine vital status at the end of the trial.

STUDY OUTCOMES

The primary efficacy outcome was stroke or systemic embolism. Stroke was defined as a focal neurologic deficit, from a nontraumatic cause, lasting at least 24 hours and was categorized as ischemic (with or without hemorrhagic transformation), hemorrhagic, or of uncertain type (in the case of patients who did not undergo brain imaging or in whom an autopsy was not performed). The key secondary efficacy outcome was death from any cause. The rate of myocardial infarction was also assessed as a secondary efficacy outcome.

The primary safety outcome was major bleeding, which was defined, according to the ISTH criteria,[9] as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g per deciliter or transfusion of at least 2 units of packed red cells, occurring at a critical site, or resulting in death. The secondary safety outcome was a composite of major bleeding and clinically relevant nonmajor bleeding, which was defined as clinically overt bleeding that did not satisfy the criteria for major bleeding and that led to hospital admission, physician-guided medical or surgical treatment, or a change in antithrombotic therapy. Other safety outcomes included any bleeding, other adverse events, and liver-function abnormalities.

The primary and secondary efficacy and safety outcomes were adjudicated on the basis of prespecified criteria by a clinical-events committee whose members were not aware of study-group assignments. For details, see the Supplementary Appendix, available at NEJM.org.

STATISTICAL ANALYSIS

The primary noninferiority hypothesis required that apixaban preserve at least 50% of the relative reduction in the risk of stroke or systemic embolism associated with warfarin (62%) in six previous, major randomized, controlled trials.[10] This hypothesis provided a lower 95% confidence interval of 1.88 for the relative risk with placebo as compared with warfarin, and one half of this value was 1.44 (or 1.38 on a log scale). We estimated that with the occurrence of the primary outcome in 448 patients, the study would have 90% power to ensure that the upper boundary of the 99% confidence interval for the relative risk would be less than 1.44 and that the upper boundary of the 95% confidence interval for the relative risk would be less than 1.38, on the assumption that apixaban and warfarin had identical effects. On the basis of the overall event rate during the trial, we planned to recruit 18,000 pa-

tients in order to reach this number of events with approximately 2 years of follow-up. An independent data and safety monitoring committee reviewed the accumulating trial data, with one prespecified interim analysis for efficacy.

The primary and key secondary analyses were performed with the use of the Cox proportional-hazards model, with previous warfarin status and geographic region (North America, South America, Europe, or Asian Pacific) used as strata in the model. The primary and secondary efficacy analyses included all patients who underwent randomization (intention-to-treat population) and included all events from the time of randomization until the cutoff date for efficacy outcomes (predefined as January 30, 2011). The analyses of bleeding events included all patients who received at least one dose of a study drug and included all events from the time the first dose of a study drug was received until 2 days after the last dose was received. In a modified intention-to-treat sensitivity analysis, we analyzed bleeding events that occurred in patients who received at least one dose of a study drug and included all

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Apixaban (N=9120)	Warfarin (N=9081)
Age — yr		
Median	70	70
Interquartile range	63–76	63–76
Female sex — no. (%)	3234 (35.5)	3182 (35.0)
Region — no. (%)		
North America	2249 (24.7)	2225 (24.5)
Latin America	1743 (19.1)	1725 (19.0)
Europe	3672 (40.3)	3671 (40.4)
Asian Pacific	1456 (16.0)	1460 (16.1)
Systolic blood pressure — mm Hg		
Median	130	130
Interquartile range	120–140	120–140
Weight — kg		
Median	82	82
Interquartile range	70–96	70–95
Prior myocardial infarction — no. (%)	1319 (14.5)	1266 (13.9)
Prior clinically relevant or spontaneous bleeding — no. (%)	1525 (16.7)	1515 (16.7)
History of fall within previous year — no. (%)	386 (4.2)	367 (4.0)
Type of atrial fibrillation — no. (%)		
Paroxysmal	1374 (15.1)	1412 (15.5)
Persistent or permanent	7744 (84.9)	7668 (84.4)
Prior use of vitamin K antagonist for >30 consecutive days — no. (%)	5208 (57.1)	5193 (57.2)
Qualifying risk factors		
Age ≥75 yr — no. (%)	2850 (31.2)	2828 (31.1)
Prior stroke, TIA, or systemic embolism — no. (%)	1748 (19.2)	1790 (19.7)
Heart failure or reduced left ventricular ejection fraction — no. (%)	3235 (35.5)	3216 (35.4)
Diabetes — no. (%)	2284 (25.0)	2263 (24.9)
Hypertension requiring treatment — no. (%)	7962 (87.3)	7954 (87.6)
$CHADS_2$ score		
Mean	2.1±1.1	2.1±1.1
Distribution — no. (%)		
1	3100 (34.0)	3083 (34.0)
2	3262 (35.8)	3254 (35.8)
≥3	2758 (30.2)	2744 (30.2)

Table 1. (Continued.)

Characteristic	Apixaban (N=9120)	Warfarin (N=9081)
Medications at time of randomization — no. (%)		
ACE inhibitor or ARB	6464 (70.9)	6368 (70.1)
Amiodarone	1009 (11.1)	1042 (11.5)
Beta-blocker	5797 (63.6)	5685 (62.6)
Aspirin	2859 (31.3)	2773 (30.5)
Clopidogrel	170 (1.9)	168 (1.9)
Digoxin	2916 (32.0)	2912 (32.1)
Calcium blocker	2744 (30.1)	2823 (31.1)
Statin	4104 (45.0)	4095 (45.1)
Nonsteroidal antiinflammatory agent	752 (8.2)	768 (8.5)
Gastric antacid drugs	1683 (18.5)	1667 (18.4)
Renal function, creatinine clearance — no. (%)		
Normal, >80 ml/min	3761 (41.2)	3757 (41.4)
Mild impairment, >50 to 80 ml/min	3817 (41.9)	3770 (41.5)
Moderate impairment (>30 to 50 ml/min)	1365 (15.0)	1382 (15.2)
Severe impairment (≤30 ml/min)	137 (1.5)	133 (1.5)
Not reported	40 (0.4)	39 (0.4)

* Plus–minus values are means ±SD. None of the characteristics differed significantly between the groups (P>0.05 for all comparisons). ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and TIA transient ischemic attack.

Table 2. Efficacy Outcomes.*

Outcome	Apixaban Group (N=9120)		Warfarin Group (N=9081)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary outcome: stroke or systemic embolism	212	1.27	265	1.60	0.79 (0.66–0.95)	0.01
Stroke	199	1.19	250	1.51	0.79 (0.65–0.95)	0.01
Ischemic or uncertain type of stroke	162	0.97	175	1.05	0.92 (0.74–1.13)	0.42
Hemorrhagic stroke	40	0.24	78	0.47	0.51 (0.35–0.75)	<0.001
Systemic embolism	15	0.09	17	0.10	0.87 (0.44–1.75)	0.70
Key secondary efficacy outcome: death from any cause	603	3.52	669	3.94	0.89 (0.80–0.998)	0.047
Other secondary outcomes						
Stroke, systemic embolism, or death from any cause	752	4.49	837	5.04	0.89 (0.81–0.98)	0.02
Myocardial infarction	90	0.53	102	0.61	0.88 (0.66–1.17)	0.37
Stroke, systemic embolism, myocardial infarction, or death from any cause	810	4.85	906	5.49	0.88 (0.80–0.97)	0.01
Pulmonary embolism or deep-vein thrombosis	7	0.04	9	0.05	0.78 (0.29–2.10)	0.63

* Analyses were performed on data from the intention-to-treat population and included all events through the cutoff date for efficacy outcomes of January 30, 2011; comparisons of the primary outcome and of death from any cause were analyzed as part of hierarchical sequence testing (starting with testing the primary outcome for noninferiority, then the primary outcome for superiority, then major bleeding, and finally death from any cause), to control the type I error.

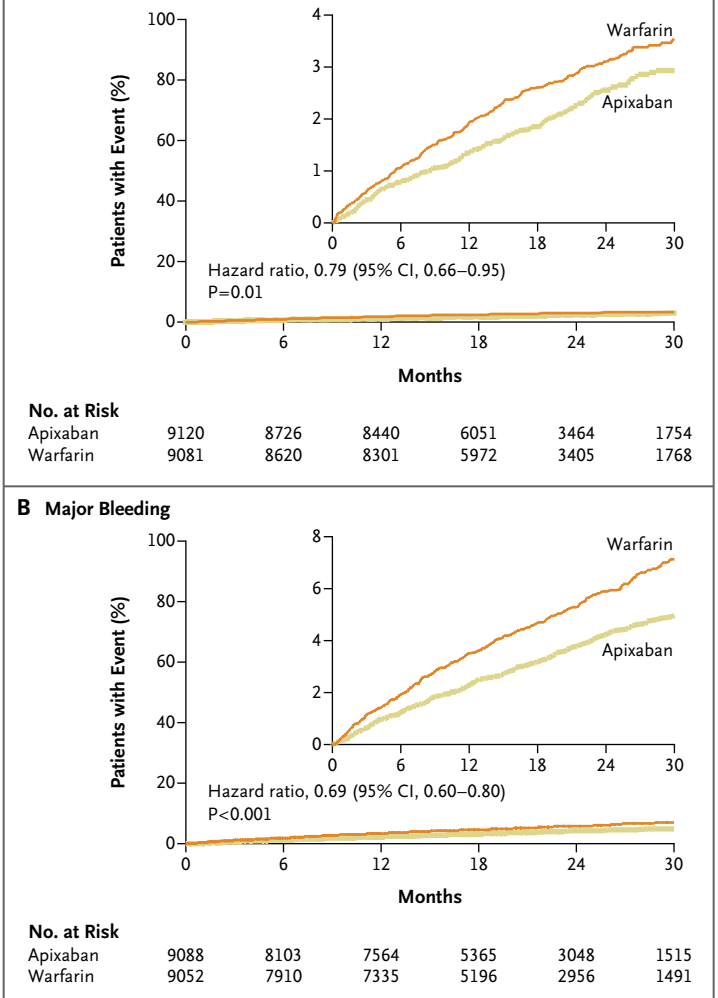


Figure 1. Kaplan–Meier Curves for the Primary Efficacy and Safety Outcomes.
The primary efficacy outcome (Panel A) was stroke or systemic embolism. The primary safety outcome (Panel B) was major bleeding, as defined according to the criteria of the International Society on Thrombosis and Haemostasis. The inset in each panel shows the same data on an enlarged segment of the y axis.

events from the time of randomization until January 30, 2011. All reported P values for noninferiority are one-sided, and all reported P values for superiority are two-sided. All statistical analyses were performed with the use of SAS software, version 9.0 (SAS Institute).

RESULTS

PATIENTS AND FOLLOW-UP

From December 19, 2006, through April 2, 2010, we recruited 18,201 patients at 1034 clinical sites in 39 countries. A total of 9120 were assigned to the apixaban group and 9081 to the warfarin group. The two groups were well balanced with respect to baseline characteristics (Table 1). The median age was 70 years; 35.3% of the patients were women, and the mean $CHADS_2$ score was 2.1. (The $CHADS_2$ score, an index of the risk of stroke in patients with atrial fibrillation, ranges from 1 to 6, with higher scores indicating a greater risk of stroke.) Approximately 57% of the patients had previously received a vitamin K antagonist, and 19% had had a previous stroke, transient ischemic attack, or systemic embolism.

Data on vital status at the end of the trial were missing for 380 patients (2.1%). The absence of data on vital status was due to withdrawal of consent in the case of 92 patients in the apixaban group (1.0%) and 107 patients in the warfarin group (1.2%) and was due to loss to follow-up in the case of 35 patients in the apixaban group (0.4%) and 34 in the warfarin group (0.4%).

STUDY DRUGS

A reduced dose of apixaban (2.5 mg twice daily) or placebo was administered in 428 patients in the apixaban group (4.7%) and 403 in the warfarin group (4.4%). Fewer patients in the apixaban group than in the warfarin group discontinued a study drug before the end of the study: 25.3% of the patients in the apixaban group, with 3.6% of the discontinuations due to death, versus 27.5% of patients in the warfarin group, with 3.8% due to death (P=0.001). Patients in the warfarin group had an INR in the therapeutic range (2.0 to 3.0) for a median of 66.0% of the time and a mean of 62.2% of the time, after the exclusion of INR values during the first 7 days after randomization and during study-drug interruptions.

PRIMARY OUTCOME

The primary outcome of stroke or systemic embolism occurred in 212 patients in the apixaban group (1.27% per year) as compared with 265 patients in the warfarin group (1.60% per year) (hazard ratio in the apixaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority and P=0.01 for superiority) (Table 2 and Fig. 1A). The rate of hemorrhagic stroke was 49% lower in the apixaban group than in the warfarin group, and the rate of ischemic or uncertain type of stroke was 8% lower in the apixaban group than in the warfarin group (Table 2). Fatal or disabling stroke occurred in 84 patients in the apixaban group (0.50% per year) as com-

Table 3. Bleeding Outcomes and Net Clinical Outcomes.*

Outcome	Apixaban Group (N=9088)		Warfarin Group (N=9052)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate	Patients with Event	Event Rate		
	no.	*%/yr*	*no.*	*%/yr*		
Primary safety outcome: ISTH major bleeding†	327	2.13	462	3.09	0.69 (0.60–0.80)	<0.001
Intracranial	52	0.33	122	0.80	0.42 (0.30–0.58)	<0.001
Other location	275	1.79	340	2.27	0.79 (0.68–0.93)	0.004
Gastrointestinal	105	0.76	119	0.86	0.89 (0.70–1.15)	0.37
Major or clinically relevant nonmajor bleeding	613	4.07	877	6.01	0.68 (0.61–0.75)	<0.001
GUSTO severe bleeding	80	0.52	172	1.13	0.46 (0.35–0.60)	<0.001
GUSTO moderate or severe bleeding	199	1.29	328	2.18	0.60 (0.50–0.71)	<0.001
TIMI major bleeding	148	0.96	256	1.69	0.57 (0.46–0.70)	<0.001
TIMI major or minor bleeding	239	1.55	370	2.46	0.63 (0.54–0.75)	<0.001
Any bleeding	2356	18.1	3060	25.8	0.71 (0.68–0.75)	<0.001
Net clinical outcomes						
Stroke, systemic embolism, or major bleeding	521	3.17	666	4.11	0.77 (0.69–0.86)	<0.001
Stroke, systemic embolism, major bleeding, or death from any cause	1009	6.13	1168	7.20	0.85 (0.78–0.92)	<0.001

* The bleeding outcomes were assessed in patients who received at least one dose of a study drug and events that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. The net clinical outcome includes all efficacy outcomes through the cutoff date for the efficacy analysis and bleeding outcomes that occurred from the time the patients received the first dose of the study drug through 2 days after they received the last dose. GUSTO denotes Global Use of Strategies to Open Occluded Coronary Arteries, and TIMI Thrombolysis in Myocardial Infarction.

† The comparison of the primary safety outcome of bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria is in the hierarchical sequence preserving a type I error.

pared with 117 patients in the warfarin group (0.71% per year) (hazard ratio, 0.71; 95% CI, 0.54 to 0.94). Ischemic stroke occurred in 149 patients in the apixaban group and in 155 patients in the warfarin group, and an unknown type of stroke occurred in 14 patients in the apixaban group and 21 patients in the warfarin group. Among the patients with ischemic strokes, hemorrhagic transformation occurred in 12 patients in the apixaban group and 20 patients in the warfarin group. Fatal stroke occurred in 42 patients in the apixaban group and 67 patients in the warfarin group.

KEY SECONDARY AND OTHER EFFICACY OUTCOMES

The rate of death from any cause was lower in the apixaban group than in the warfarin group (3.52% per year vs. 3.94% per year; hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of death from cardiovascular causes (including death from hemorrhagic stroke) was 1.80% per year in the apixaban group and 2.02% per year in the warfarin group (hazard ratio, 0.89; 95% CI, 0.76 to 1.04), and the rate of death from noncardiovascular causes (including fatal bleeding other than that from hemorrhagic stroke) was 1.14% per year in the apixaban group and 1.22% per year in the warfarin group (hazard ratio, 0.93; 95% CI, 0.77 to 1.13). The rate of myocardial infarction was lower in the apixaban group than in the warfarin group, but the difference was not significant (Table 2).

BLEEDING

Major bleeding, as defined according to ISTH criteria, occurred in 327 patients in the apixaban group (2.13% per year), as compared with 462 patients in the warfarin group (3.09% per year) (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001) (Table 3 and Fig. 1B). There appeared to be an even greater reduction in the rate of serious bleeding as defined according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria for severe bleeding and according to the Thrombolysis in Myocardial Infarction (TIMI) criteria for major bleeding (Table 3). The

A Primary Efficacy Outcome: Stroke and Systemic Embolism

Subgroup	No. of Patients	Apixaban	Warfarin	P Value for Interaction
		no. of events (%/yr)		
All patients	18,201	212 (1.27)	265 (1.60)	
Prior use of warfarin or other vitamin K antagonist				0.39
Yes	10,401	102 (1.1)	138 (1.5)	
No	7,800	110 (1.5)	127 (1.8)	
Age				0.12
<65 yr	5,471	51 (1.0)	44 (0.9)	
65 to <75 yr	7,052	82 (1.3)	112 (1.7)	
≥75 yr	5,678	79 (1.6)	109 (2.2)	
Sex				0.60
Male	11,785	132 (1.2)	160 (1.5)	
Female	6,416	80 (1.4)	105 (1.8)	
Weight				0.26
≤60 kg	1,985	34 (2.0)	52 (3.2)	
>60 kg	16,154	177 (1.2)	212 (1.4)	
Type of atrial fibrillation				0.70
Permanent or persistent	15,412	191 (1.4)	235 (1.7)	
Paroxysmal	2,786	21 (0.8)	30 (1.1)	
Prior stroke or TIA				0.71
Yes	3,436	73 (2.5)	98 (3.2)	
No	14,765	139 (1.0)	167 (1.2)	
Diabetes mellitus				0.71
Yes	4,547	57 (1.4)	75 (1.9)	
No	13,654	155 (1.2)	190 (1.5)	
Heart failure				0.50
Yes	5,541	70 (1.4)	79 (1.6)	
No	12,660	142 (1.2)	186 (1.6)	
$CHADS_2$ score				0.45
1	6,183	44 (0.7)	51 (0.9)	
2	6,516	74 (1.2)	82 (1.4)	
≥3	5,502	94 (1.9)	132 (2.8)	
Level of renal impairment				0.72
Severe or moderate	3,017	54 (2.1)	69 (2.7)	
Mild	7,587	87 (1.2)	116 (1.7)	
No impairment	7,518	70 (1.0)	79 (1.1)	
Apixaban dose				0.22
2.5 mg twice daily or placebo	831	12 (1.7)	22 (3.3)	
5 mg twice daily or placebo	17,370	200 (1.3)	243 (1.5)	
Geographic region				0.44
North America	4,474	42 (1.0)	56 (1.3)	
Latin America	3,468	43 (1.4)	52 (1.8)	
Europe	7,343	75 (1.1)	77 (1.1)	
Asian Pacific	2,916	52 (2.0)	80 (3.1)	
Aspirin use at randomization				0.44
Yes	5,632	70 (1.3)	94 (1.9)	
No	12,569	142 (1.2)	171 (1.5)	

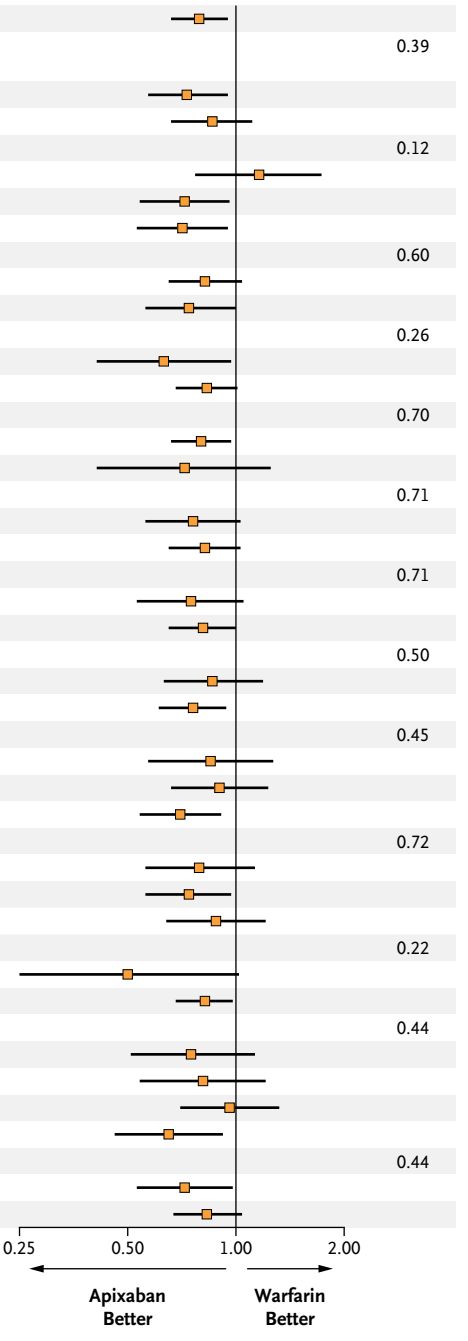
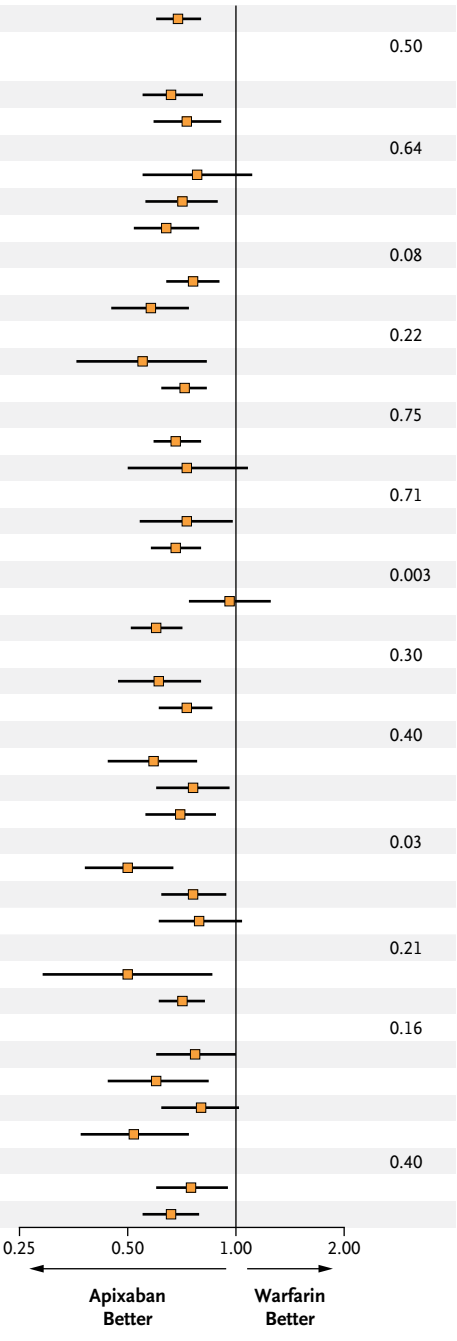


Figure 2. Relative Risks of the Primary Efficacy and Safety Outcomes, According to Major Prespecified Subgroups.

Prespecified subgroups not included in the figure were subgroups according to race, ethnic group, body-mass index, number of risk factors, age of 75 years or more, and use or nonuse of clopidogrel at the time of randomization, as well as subgroups of women according to age group. Heart failure was defined as symptomatic heart failure or a left ventricular ejection fraction of 40% or less. The $CHADS_2$ score, an index of the risk of stroke in patients with atrial fibrillation, ranges from 1 to 6, with higher scores indicating a greater risk of stroke. TIA denotes transient ischemic attack.

B Major Bleeding

Subgroup	No. of Patients	Apixaban	Warfarin	P Value for Interaction
		no. of events (%/yr)		
All patients	18,140	327 (2.13)	462 (3.09)	
Prior use of warfarin or other vitamin K antagonist				0.50
Yes	10,376	185 (2.1)	274 (3.2)	
No	7,764	142 (2.2)	188 (3.0)	
Age				0.64
<65 yr	5,455	56 (1.2)	72 (1.5)	
65 to <75 yr	7,030	120 (2.0)	166 (2.8)	
≥75 yr	5,655	151 (3.3)	224 (5.2)	
Sex				0.08
Male	11,747	225 (2.3)	294 (3.0)	
Female	6,393	102 (1.9)	168 (3.3)	
Weight				0.22
≤60 kg	1,978	36 (2.3)	62 (4.3)	
>60 kg	16,102	290 (2.1)	398 (3.0)	
Type of atrial fibrillation				0.75
Permanent or persistent	15,361	283 (2.2)	402 (3.2)	
Paroxysmal	2,776	44 (1.9)	60 (2.6)	
Prior stroke or TIA				0.71
Yes	3,422	77 (2.8)	106 (3.9)	
No	14,718	250 (2.0)	356 (2.9)	
Diabetes mellitus				0.003
Yes	4,526	112 (3.0)	114 (3.1)	
No	13,614	215 (1.9)	348 (3.1)	
Heart failure				0.30
Yes	5,527	87 (1.9)	137 (3.1)	
No	12,613	240 (2.2)	325 (3.1)	
$CHADS_2$ score				0.40
1	6,169	76 (1.4)	126 (2.3)	
2	6,492	125 (2.3)	163 (3.0)	
≥3	5,479	126 (2.9)	173 (4.2)	
Level of renal impairment				0.03
Severe or moderate	3,005	73 (3.2)	142 (6.4)	
Mild	7,565	157 (2.5)	199 (3.2)	
No impairment	7,496	96 (1.5)	119 (1.8)	
Apixaban dose				0.21
2.5 mg twice daily or placebo	826	20 (3.3)	37 (6.7)	
5 mg twice daily or placebo	17,314	307 (2.1)	425 (3.0)	
Geographic region				0.16
North America	4,463	106 (2.8)	137 (3.6)	
Latin America	3,460	60 (2.1)	94 (3.5)	
Europe	7,313	110 (1.7)	135 (2.2)	
Asian Pacific	2,904	51 (2.1)	96 (4.1)	
Aspirin use at randomization				0.40
Yes	5,608	129 (2.7)	164 (3.7)	
No	12,532	198 (1.9)	298 (2.8)	



rate of intracranial hemorrhage was 0.33% per year in the apixaban group and 0.80% per year in the warfarin group (hazard ratio, 0.42; 95% CI, 0.30 to 0.58; P<0.001), and the rate of any bleeding was 25.8% per year in the warfarin group and 18.1% per year in the apixaban group, an absolute reduction of 7.7 percentage points (P<0.001). In a modified intention-to-treat sensitivity analysis that included the entire treatment period, there was a consistent 27% relative reduction in

the rate of major bleeding in the apixaban group, as compared with the warfarin group (P<0.001). Fatal bleeding (including fatal hemorrhagic stroke), as evaluated in the intention-to-treat analysis, occurred in 34 patients in the apixaban group and 55 patients in the warfarin group.

SUBGROUPS

The reduction in the primary outcome with apixaban was consistent across all major subgroups (Fig. 2), and statistical tests for interaction were not significant (P>0.10) for all of the 21 predefined subgroups. With respect to the outcome of major bleeding, the only baseline characteristics for which the interaction was significant were diabetes status and renal function, with a greater reduction in bleeding among patients who did not have diabetes (P=0.003 for interaction) and among patients with moderate or severe renal impairment (P=0.03 for interaction).

OVERALL SAFETY OUTCOMES

Adverse events occurred in almost equal proportions of patients in the apixaban group and in the warfarin group (81.5% of the patients in the apixaban group and 83.1% of patients in the warfarin group), as did serious adverse events (35.0% and 36.5% in the two groups, respectively) (for details, see the Supplementary Appendix). The rates of abnormalities on liver-function testing and liver-related serious adverse events were similar in the two groups.

DISCUSSION

In patients with atrial fibrillation and at least one additional risk factor for stroke, the use of apixaban, as compared with warfarin, significantly reduced the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11%. For every 1000 patients treated for 1.8 years, apixaban, as compared with warfarin, prevented a stroke in 6 patients, major bleeding in 15 patients, and death in 8 patients. The predominant effect on stroke prevention was on hemorrhagic stroke, with prevention of a hemorrhagic stroke in 4 patients per 1000 and prevention of an ischemic or unknown type of stroke in 2 patients per 1000.

The results were consistent in subgroups according to geographic region, status with respect to previous warfarin exposure, age, sex, level of renal impairment, and risk factors for stroke, as well as in other predefined subgroups. Apixaban had an acceptable side-effect profile, with no unexpected side effects, and the rate of discontinuation of the study drug was lower in the apixaban group than in the warfarin group.

Warfarin is highly effective in preventing stroke in patients with atrial fibrillation but is associated with a variable response, has drug and food interactions, requires regular monitoring for dose adjustment, and carries a risk of bleeding (including intracranial hemorrhage). In part because of these limitations, only about half of patients who would benefit from warfarin therapy actually receive the drug.[11] The alternative treatment regimen with apixaban (at a dose of 5 mg twice daily), which does not require anticoagulation monitoring, not only is more effective than warfarin for stroke prevention but also accomplishes this goal at a substantially lower risk of bleeding and with lower rates of discontinuation. These findings are supported by the results of the Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment trial (AVERROES; ClinicalTrials.gov number, NCT00496769),[6] in which the same apixaban regimen, as compared with low-dose aspirin, was shown to substantially reduce the risk of stroke without any difference in the rates of major bleeding and with lower rates of discontinuation. Although major bleeding was less common with apixaban, at a dose of 5 mg twice daily, than with warfarin in patients with atrial fibrillation, the use of the same dose of apixaban, as compared with placebo, resulted in more bleeding in patients with acute coronary syndromes who were receiving both aspirin and clopidogrel.[12] The significant reduction in mortality observed in our study was consistent with trends toward lower rates of death among patients receiving apixaban than among those receiving aspirin in the AVERROES trial.

Two alternative oral anticoagulants, the direct thrombin inhibitor dabigatran[3] and the factor Xa inhibitor rivaroxaban,[4] have recently been shown in randomized clinical trials to be at least as effective as warfarin in preventing stroke. Each of these agents, like apixaban, has the major advantage of convenience, since there is no need for anticoagulation monitoring. In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY, NCT00262600) the oral di-

rect thrombin inhibitor dabigatran administered in two doses per day was compared with open-label warfarin. The 150-mg dose of dabigatran administered twice daily, as compared with warfarin, was shown to reduce the rate of stroke, including ischemic or unspecified stroke, with a similar overall rate of bleeding, although the rate of gastrointestinal bleeding was increased. The 110-mg dose administered twice daily was associated with a rate of stroke that was similar to that with warfarin but with a lower rate of major bleeding. Both doses resulted in lower rates of intracranial hemorrhage. In our study, apixaban at a dose of 5 mg twice daily (with the recommendation to use a reduced dose in patients with a predicted higher drug exposure) appears to combine the advantages of each of the two doses of dabigatran, with both a greater overall reduction in the rate of stroke and a lower rate of bleeding than the rates with warfarin. As compared with warfarin, apixaban is also associated with a reduction in the rate of gastrointestinal bleeding and with consistently lower bleeding rates across age groups[13] and all other major subgroups. Fewer patients receiving apixaban had a myocardial infarction than those receiving either warfarin (in our study) or aspirin (in the AVERROES trial).

Rivaroxaban, the second new alternative, was shown to be noninferior to warfarin for the prevention of stroke and systemic embolism in the intention-to-treat analysis 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, NCT00403767).[4] The rates of intracranial hemorrhage and fatal bleeding were lower with rivaroxaban than with warfarin, but there was no advantage with respect to other major bleeding. The differences between our findings and those of other trials comparing novel anticoagulants with warfarin may be related to differences in the doses of drugs, the pharmacokinetic and pharmacodynamic properties of the drugs,[14] patient populations, or other features of the clinical-trial design. The lower risk of hemorrhagic stroke associated with all three novel anticoagulants suggests that there is a specific risk associated with warfarin, possibly related to its inhibition of multiple coagulation factors or interaction between warfarin and tissue factor VIIa complexes in the brain.[15]

In conclusion, in patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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