ORIGINAL ARTICLE

Apixaban in Patients with Atrial Fibrillation

Stuart J. Connolly, M.D., John Eikelboom, M.B., B.S., Campbell Joyner, M.D., Hans-Christoph Diener, M.D., Ph.D., Robert Hart, M.D., Sergey Golitsyn, M.D., Ph.D., Greg Flaker, M.D., Alvaro Avezum, M.D., Ph.D., Stefan H. Hohnloser, M.D., Rafael Diaz, M.D., Mario Talajic, M.D., Jun Zhu, M.D., Prem Pais, M.B., B.S., M.D., Andrzej Budaj, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Petr Jansky, M.D., Patrick Commerford, M.B., Ch.B., Ru San Tan, M.B., B.S., Kui-Hian Sim, M.B., B.S., Basil S. Lewis, M.D., Walter Van Mieghem, M.D., Gregory Y.H. Lip, M.D., Jae Hyung Kim, M.D., Ph.D., Fernando Lanas-Zanetti, M.D., Antonio Gonzalez-Hermosillo, M.D., Antonio L. Dans, M.D., Muhammad Munawar, M.D., Ph.D., Martin O'Donnell, M.B., Ph.D., John Lawrence, M.D., Gayle Lewis, Rizwan Afzal, M.Sc., and Salim Yusuf, M.B., B.S., D.Phil., for the AVERROES Steering Committee and Investigators*

ABSTRACT

BACKGROUND

Vitamin K antagonists have been shown to prevent stroke in patients with atrial fibrillation. However, many patients are not suitable candidates for or are unwilling to receive vitamin K antagonist therapy, and these patients have a high risk of stroke. Apixaban, a novel factor Xa inhibitor, may be an alternative treatment for such patients.

METHODS

In a double-blind study, we randomly assigned 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable to receive apixaban (at a dose of 5 mg twice daily) or aspirin (81 to 324 mg per day), to determine whether apixaban was superior. The mean follow up period was 1.1 years. The primary outcome was the occurrence of stroke or systemic embolism.

RESULTS

Before enrollment, 40% of the patients had used a vitamin K antagonist. The data and safety monitoring board recommended early termination of the study because of a clear benefit in favor of apixaban. There were 51 primary outcome events (1.6% per year) among patients assigned to apixaban and 113 (3.7% per year) among those assigned to aspirin (hazard ratio with apixaban, 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001). The rates of death were 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (hazard ratio, 0.79; 95% CI, 0.62 to 1.02; P=0.07). There were 44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (hazard ratio with apixaban, 1.13; 95% CI, 0.74 to 1.75; P=0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin. The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, P<0.001). The treatment effects were consistent among important subgroups.

CONCLUSIONS

In patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. (Funded by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number, NCT00496769.)

The affiliations of the authors are listed in the Appendix. Address reprint requests to Dr. Connolly at Population Health Research Institute, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at stuart.connolly@phri.ca.

*A complete list of the AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) Steering Committee members and site investigators is available in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1007432) was published on February 10, 2011, at NEJM.org.

N Engl J Med 2011;364:806-17.

Atrial fibrillation is a common arrhythmia that increases the risk of stroke.[1] Vitamin K antagonist therapy is more effective than aspirin for the prevention of stroke in patients with atrial fibrillation, but its use is limited by a narrow window for a therapeutic benefit and by the need for lifelong coagulation monitoring owing to a marked variation in its effect both from one patient to another and within the individual patient.[2] Maintaining the international normalized ratio (INR) in the therapeutic range is challenging and for many patients is achieved less than 60% of the time — a finding that counteracts the potential benefit of vitamin K antagonist therapy and increases its risks.[3] Consequently, at least a third of patients with atrial fibrillation who are at risk for stroke are either not started on vitamin K antagonist therapy or discontinue the therapy once it is started.[3-5]

Aspirin reduces the risk of stroke in patients with atrial fibrillation by about 20% and is used in treating patients with atrial fibrillation for whom vitamin K antagonist therapy is unsuitable.[6] The addition of clopidogrel to aspirin in patients for whom vitamin K antagonist therapy is unsuitable further reduces the risk of stroke by 28%, but the combination increases the risk of major hemorrhage.[7] There is a need for better antithrombotic agents.

Apixaban is a direct and competitive inhibitor of factor Xa.[8] It has about 50% bioavailability, and approximately 25% is excreted by the kidney. Apixaban, at a dose of 2.5 mg twice daily, has been shown to be effective and safe for the prevention of venous thromboembolism after elective orthopedic surgery.[9,10] The AVERROES (Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) study was therefore designed to determine the efficacy and safety of apixaban, at a dose of 5 mg twice daily, as compared with aspirin, at a dose of 81 to 324 mg daily, for the treatment of patients with atrial fibrillation for whom vitamin K antagonist therapy was considered unsuitable.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted the study at 522 centers in 36 countries. Enrollment began on September 10, 2007, and was completed on December 23, 2009. The study was designed by the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org), together with the sponsors, Bristol-Myers Squibb and Pfizer. The data were collected, validated, and analyzed at the Population Health Research Institute at Hamilton Health Sciences and McMaster University, Hamilton, Canada, with on-site monitoring by the sponsors. All drafts of the manuscript were written by the first author, with the sponsors and all the other authors providing comments. All the authors vouch for the findings. There were no agreements between the authors and the sponsors that limited the authors' ability to publish the overall study results. The protocol was approved by the ethics committee at each participating site, and all patients provided written informed consent before enrollment.

The study protocol, which is available at NEJM.org, has been described in detail previously.[11] Patients were eligible if they were 50 years of age or older and had atrial fibrillation documented in the 6 months before enrollment or by 12-lead electrocardiography on the day of screening. Patients also had to have at least one of the following risk factors for stroke: prior stroke or transient ischemic attack, an age of 75 years or older, arterial hypertension (receiving treatment), diabetes mellitus (receiving treatment), heart failure (New York Heart Association class 2 or higher at the time of enrollment), a left ventricular ejection fraction of 35% or less, or documented peripheral-artery disease. In addition, patients could not be receiving vitamin K antagonist therapy, either because it had already been demonstrated to be unsuitable for them or because it was expected to be unsuitable. The reasons that vitamin K antagonist therapy was unsuitable for the patient had to be documented on the study case-report forms.

The key exclusion criteria were the presence of conditions other than atrial fibrillation for which the patient required long-term anticoagulation, valvular disease requiring surgery, a serious bleeding event in the previous 6 months or a high risk of bleeding (e.g., active peptic ulcer disease, a platelet count of <100,000 per cubic millimeter or hemoglobin level of <10 g per deciliter, stroke within the previous 10 days, documented hemorrhagic tendencies, or blood dyscrasias), current alcohol or drug abuse or psychosocial issues, life expectancy of less than 1 year, severe renal insufficiency (a serum creatinine level of

>2.5 mg per deciliter [221 μmol per liter] or a calculated creatinine clearance of <25 ml per minute), an alanine aminotransferase or aspartate aminotransferase level greater than 2 times the upper limit of the normal range or a total bilirubin more than 1.5 times the upper limit of the normal range, and allergy to aspirin.

Patients were randomly assigned to receive apixaban at a dose of 5 mg twice daily or aspirin at a dose of 81 to 324 mg per day. Randomization was performed with the use of a 24-hour central, computerized, automated voice-response system. In keeping with the double-dummy design, patients who were assigned to receive apixaban also received an aspirin placebo, and those assigned to receive aspirin also received an apixaban placebo. A reduced dose of apixaban (2.5 mg twice daily) was used throughout the study for patients who met two of the following criteria: an age of 80 years or older, a body weight of 60 kg or less, or a serum creatinine level of 1.5 mg per deciliter (133 μmol per liter) or higher. The dose of aspirin was one to four 81-mg tablets daily, with the dose selected at the discretion of the local investigator. Investigators were encouraged to discontinue any nonstudy aspirin at the time of randomization. Patients taking a thienopyridine at baseline were not eligible for inclusion in the study, although these drugs could be prescribed during the study if an indication emerged.

OUTCOMES

The primary efficacy outcome was the occurrence of stroke (ischemic or hemorrhagic) or systemic embolism. Stroke was a clinical diagnosis that was made on the basis of typical symptoms lasting at least 24 hours. Brain imaging, which was available in the vast majority of patients, was not required but was recommended for the general diagnosis of stroke; however, it was required to differentiate ischemic from hemorrhagic events. The primary safety outcome was the occurrence of major bleeding, defined as clinically overt bleeding accompanied by one or more of the following: a decrease in the hemoglobin level of 2 g per deciliter or more over a 24-hour period, transfusion of 2 or more units of packed red cells, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding. Other outcomes of interest included the rates of myocardial infarction, death from vascular causes, and death from any cause, as well as of composites of major vascular events. All outcomes were adjudicated by a committee whose members were unaware of the treatment assignments. Cases of stroke and intracranial hemorrhage were adjudicated by neurologists.

STATISTICAL ANALYSIS

We estimated that with a total of 5600 patients enrolled and 226 primary outcome events, the study would have at least 90% power to detect a 35% relative reduction in events with apixaban as compared with aspirin, at a one-side alpha level of 0.025, assuming a rate of the primary outcome of 3.3% per year (i.e., 3.3 events per 100 person-years) among patients taking aspirin. An independent data and safety monitoring board monitored the study for safety. Formal interim analyses were planned when 50% and 75% of the primary efficacy events had accrued. Stopping rules were based on an analysis of the primary outcome for which modified Haybittle–Peto boundaries of 4 SD (log hazard ratio) were used in the first half of the study and 3 SD in the second half. If either of these thresholds was crossed, a confirmatory analysis was to be performed 3 months later, and if that analysis also crossed the specified boundary, the data and safety monitoring board could recommend that the trial be terminated. The $CHADS_2$ scale was used to assess a patient's risk of stroke. The $CHADS_2$ scale is a measure of the risk of stroke in patients with atrial fibrillation. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient, with a higher score indicating a greater risk of stroke. All primary efficacy and safety analyses were based on the intention-to-treat principle. Cox proportional-hazards modeling and log-rank testing were used for efficacy and safety analyses. Baseline data are reported as means ±SD for quantitative data and as percentages for proportions. Data on adverse events were compared with the use of chi-square tests.

RESULTS

PATIENTS

The baseline clinical characteristics were well balanced between the two study groups (Table 1). A total of 37% of the patients were from North

America or Western Europe. In the 30 days before screening, three quarters of the patients had been taking aspirin and 15% had been taking a vitamin K antagonist. Of the 5599 patients enrolled, 2216 (40%) had previously received but discontinued vitamin K antagonist therapy; for 932 of these patients (42%), it was determined that the INR could not be maintained in the therapeutic range (Table 2). In the case of 2387 of the 5599 patients enrolled in the study (43%), the physician had determined that INR measurements could not be obtained or were unlikely to be obtained at the requested intervals. Vitamin K antagonist therapy was considered to be unsuitable for 1195 patients (21%) because the risk of stroke was only moderate, as assessed by a score of 1 on the $CHADS_2$ scale. There were 2092 patients (37%) who did not want to take vitamin K antagonists; in the case of 815 patients (15%), this was the only reason that vitamin K antagonist therapy was unsuitable.

EARLY TERMINATION OF STUDY

The data and safety monitoring committee reviewed the results of the first planned interim analysis of efficacy on February 19, 2010, at which time 104 events had occurred, and observed a treatment benefit in favor of apixaban for the primary outcome that exceeded 4 SD. The results of a confirmatory analysis were reviewed on May 28, 2010, at which time the P value was 0.000002 (z=4.76), and study termination was recommended. Events that occurred through May 28, 2010, were included in the primary analyses. The patients' final study visits were scheduled to occur between July 1 and August 15, 2010. The mean duration of follow-up through May 28, 2010, was 1.1 years.

STUDY TREATMENT

Most patients received apixaban or an apixaban placebo at a dose of 5 mg twice a day. A total of 6% of the patients in the apixaban group and 7% in the aspirin group received 2.5 mg twice a day, according to protocol. A daily dose of 81 mg of aspirin or aspirin placebo was used in the case of 65% of the patients in the apixaban group and 64% in the aspirin group. A total of 264 of the 2808 patients in the apixaban group (9%) and 246 of the 2791 in the aspirin group (9%) took nonstudy aspirin more than 50% of the time during the study. Clopidogrel was used at least once during the study in combination with aspirin or aspirin placebo by 38 patients in the apixaban group (1%) and 46 in the aspirin group (2%) and was used more than 50% of the time by 13 patients and 18 patients in the two groups, respectively.

OUTCOME EVENTS

There were 51 primary outcome events (a rate of 1.6% per year) among patients assigned to apixaban and 113 (3.7% per year) among patients assigned to aspirin (hazard ratio with apixaban, 0.45, 95% confidence interval [CI], 0.32 to 0.62; P<0.001; z=4.76) (Table 3 and Fig. 1). The corresponding rates of ischemic stroke were 1.1% per year and 3.0% per year (hazard ratio with apixaban, 0.37; 95% CI, 0.25 to 0.55; P<0.001). There were six cases of hemorrhagic stroke (intracerebral hemorrhage) among patients receiving apixaban and nine among those receiving aspirin. The rate of death was 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (hazard ratio with apixaban, 0.79; 95% CI, 0.62 to 1.02; P=0.07). The rate of hospitalization for cardiovascular causes was lower in the apixaban group than in the aspirin group (12.6% per year vs. 15.9% per year; hazard ratio with apixaban, 0.79; 95% CI 0.69 to 0.91; P<0.001). In an analysis that included all events up to the final study visits, there were 56 primary outcome events (a rate of 1.6% per year) in the apixaban group and 126 (3.6% per year) in the aspirin group (hazard ratio with apixaban, 0.44; 95% CI, 0.32 to 0.60; P<0.001; z=5.12).

ADVERSE EVENTS

There were 44 major bleeding events (a rate of 1.4% per year) among patients taking apixaban and 39 (1.2% per year) among those taking aspirin (hazard ratio with apixaban,1.13; 95% CI, 0.74 to 1.75; P=0.57) (Fig. 1B). There were 188 and 153 minor bleeding events in the apixaban and aspirin groups, respectively (hazard ratio with apixaban, 1.24; 95% CI, 1.00 to 1.53; P=0.05). In an on-treatment analysis, which included only events that occurred in patients while they were receiving the study treatment (i.e., ≤2 days after permanent discontinuation of the study medication), there were 45 major bleeding events (1.4% per year) among patients in the apixaban group, as compared with 29 (0.9% per year) among patients in the aspirin group (hazard ratio, 1.54; 95% CI, 0.96 to 2.45; P=0.07). The composite rate of stroke, systemic embolism, myocardial

infarction, death from vascular causes, or major bleeding was reduced with apixaban, as compared with aspirin (intention-to-treat analysis, 5.3% per year vs. 7.2% per year; hazard ratio 0.74; 95% CI, 0.60 to 0.90; P=0.003; on-treatment analysis, 4.0% per year vs. 6.3% per year; hazard ratio, 0.64; 95% CI, 0.51 to 0.80; P<0.001).

At 2 years, the rates of permanent discontinuation of the study medication were 17.9% per year in the apixaban group and 20.5% per year in the aspirin group; the risk of permanent discontinuation was 12% lower in the apixaban group than in the aspirin group (hazard ratio with apixaban, 0.88; 95% CI, 0.78 to 0.99; P=0.03). Significantly fewer patients in the apixaban group than in the aspirin group had a serious adverse event (22%

Table 1. Baseline Characteristics of the Patients and Doses of Study Medication.*

Variable	Apixaban (N=2808)	Aspirin (N=2791)
Age — yr	70±9	70±10
Heart rate — beats/min	74±14	74±14
Systolic blood pressure — mm Hg	132±16	132±16
Body-mass index†	28±5	28±5
Male sex — no. (%)	1660 (59)	1617 (58)
Baseline electrocardiographic findings — no. (%)		
Atrial fibrillation	1923 (68)	1894 (68)
Atrial flutter	19 (1)	20 (1)
Sinus rhythm	707 (25)	730 (26)
Paced or other rhythm	147 (5)	139 (5)
Left ventricular hypertrophy	490 (17)	498 (18)
Risk factors for stroke — no. (%)		
Prior stroke or transient ischemic attack	390 (14)	374 (13)
Hypertension, receiving treatment	2408 (86)	2429 (87)
Heart failure	1118 (40)	1053 (38)
NYHA class 1 or 2	932 (33)	878 (31)
NYHA class 3 or 4	186 (7)	175 (6)
Left ventricular ejection fraction ≤35%	144 (5)	144 (5)
Peripheral-artery disease	66 (2)	87 (3)
Diabetes, receiving treatment	537 (19)	559 (20)
Mitral stenosis	64 (2)	50 (2)
Classification of atrial fibrillation — no. (%)		
Paroxysmal	760 (27)	752 (27)
Persistent	587 (21)	590 (21)
Permanent	1460 (52)	1448 (52)
$CHADS_2$‡		
Mean score	2.0±1.1	2.1±1.1
Score — no. (%)		
0 or 1	1004 (36)	1022 (37)
2	1045 (37)	954 (34)
≥3	758 (27)	812 (29)
High-school education or more — no. (%)	1635 (58)	1635 (59)
Use of vitamin K antagonist within 30 days before screening — no. (%)	401 (14)	426 (15)
Use of aspirin within 30 days before screening — no. (%)	2137 (76)	2081 (75)

Table 1. (Continued.)

Variable	Apixaban (N=2808)	Aspirin (N=2791)
Medication use at baseline — no. (%)		
ACE inhibitor or ARB	1790 (64)	1786 (64)
Verapamil or diltiazem	251 (9)	248 (9)
Beta-blocker	1563 (56)	1534 (55)
Digoxin	821 (29)	754 (27)
Amiodarone	298 (11)	328 (12)
Statin	883 (31)	879 (31)
Region — no. (%)		
North America	408 (15)	396 (14)
Latin America	589 (21)	596 (21)
Western Europe	625 (22)	633 (23)
Eastern Europe	639 (23)	611 (22)
Asia and South Africa	547 (19)	555 (20)
Study dose of aspirin or aspirin-placebo — no. (%)		
81 mg	1816 (65)	1786 (64)
162 mg	718 (26)	750 (27)
243 mg	73 (3)	60 (2)
324 mg	193 (7)	184 (7)
Data not available	7 (<1)	11 (<1)
Study dose of 2.5 mg twice daily of apixaban or apixaban-placebo — no. (%)	179 (6)	182 (7)

* Plus–minus values are means ±SD. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, and NYHA New York Heart Association.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ $CHADS_2$ is a measure of the risk of stroke in patients with atrial fibrillation. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient, with a higher score indicating a greater risk of stroke. There were 15 patients with a $CHADS_2$ score of 0, 11 of whom had either peripheral-artery disease or a left ventricular ejection fraction of 35% or less.

vs. 27%, P<0.001), mostly owing to a reduced number of events related to vascular disorders of the central nervous system among patients taking apixaban. Liver-function tests were performed at every visit during the study. A total of 38 patients in the apixaban group (1%) and 44 in the aspirin group (2%) had aspartate aminotransferase or alanine aminotransferase levels that were 3 or more times the upper limit of the normal range; 6 patients in the apixaban group and 10 in the aspirin group had aspartate aminotransferase or alanine aminotransferase levels that were 3 or more times the upper limit of the normal range along with total bilirubin levels that were 2 or more times the upper limit of the normal range. For a list of serious adverse events and abnormal liver-function tests, see Table 1 in the Supplementary Appendix.

SUBGROUP ANALYSES

There were no significant interactions between the treatment effects and various characteristics of the patients (Fig. 2). The benefit of apixaban was consistent in subgroups according to prior receipt or no prior receipt of vitamin K antagonists and in subgroups according to $CHADS_2$ score. Among 764 patients who were at high risk because of a prior stroke or transient ischemic attack, there was a reduction in the rate of stroke or systemic embolism with apixaban as compared with aspirin (2.5% per year vs. 8.3% per year; absolute rate reduction, 5.8 percentage points per year).

Table 2. Reasons for Unsuitability of Vitamin K Antagonist (VKA) Therapy.*

Reason for Unsuitability of Therapy	Apixaban (N=2808)	Aspirin (N=2791)	Previous Use of Vitamin K Antagonist (N=2216)	No Previous Use of Vitamin K Antagonist (N=3383)
			number (percent)	
Assessment that INR could not be maintained in therapeutic range	465 (17)	468 (17)	932 (42)	—
Adverse event not related to bleeding during VKA therapy	86 (3)	94 (3)	180 (8)	—
Serious bleeding event during VKA therapy	92 (3)	82 (3)	173 (8)	—
Assessment that INR could not or was unlikely to be measured at requested intervals	1196 (43)	1191 (43)	827 (37)	1560 (46)
Expected difficulty in contacting patient for urgent change in dose of VKA	322 (11)	331 (12)	167 (8)	486 (14)
Uncertainty about patient's ability to adhere to instructions regarding VKA therapy	437 (16)	405 (15)	262 (12)	580 (17)
Concurrent medications that could alter activity of VKA	50 (2)	53 (2)	33 (1)	70 (2)
Concurrent medications whose metabolism could be affected by VKA	35 (1)	46 (2)	19 (1)	62 (2)
Assessment that patient would be unable or unlikely to adhere to restrictions on factors such as alcohol and diet	134 (5)	141 (5)	127 (6)	148 (4)
Hepatic disease	13 (<1)	9 (<1)	4 (<1)	18 (1)
Mild cognitive impairment	85 (3)	86 (3)	56 (3)	115 (3)
Heart failure or cardiomyopathy	179 (6)	188 (7)	95 (4)	272 (8)
Other factors that could be associated with increased risk of VKA use	96 (3)	123 (4)	121 (5)	98 (3)
$CHADS_2$ score of 1 and VKA therapy not recommended by physician†	590 (21)	605 (22)	458 (21)	737 (22)
Other characteristics indicating risk of stroke too low to warrant treatment with VKA	55 (2)	40 (1)	32 (1)	63 (2)
Patient's refusal to take VKA	1053 (38)	1039 (37)	819 (37)	1273 (38)
Other reasons	184 (7)	189 (7)	249 (11)	124 (4)
$CHADS_2$ score of 1 as only reason for unsuitability of VKA therapy	313 (11)	336 (12)	216 (10)	433 (13)
Patient's refusal to take VKA as only reason for unsuitability	421 (15)	394 (14)	199 (9)	616 (18)
Multiple reasons for unsuitability of VKA therapy	1444 (51)	1440 (52)	1436 (65)	1448 (43)

* The reason for the unsuitability of VKA therapy was missing for one patient in the apixaban group. INR denotes international normalized ratio.

† $CHADS_2$ is a measure of the risk of stroke in patients with atrial fibrillation. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient, with a higher score indicating a greater risk of stroke.

DISCUSSION

In patients for whom vitamin K antagonist therapy was considered unsuitable, apixaban, as compared with aspirin, reduced the risk of stroke or systemic embolism by more than 50%, without a significant increase in the risk of major bleeding. Although the early termination of the trial is a

Table 3. Rates of Study Outcomes in the Two Treatment Groups.*

Outcome	Apixaban (N=2808)		Aspirin (N=2791)		Hazard Ratio with Apixaban (95% CI)	P Value
	no. of patients with first event	%/yr	*no. of patients with first event*	%/yr		
Stroke or systemic embolism	51	1.6	113	3.7	0.45 (0.32–0.62)	<0.001
Stroke, systemic embolism, or death	143	4.6	223	7.2	0.64 (0.51–0.78)	<0.001
Stroke, systemic embolism, myocardial infarction or death from vascular cause	132	4.2	197	6.4	0.66 (0.53–0.83)	<0.001
Stroke, systemic embolism, myocardial infarction, death from vascular cause, or major bleeding event	163	5.3	220	7.2	0.74 (0.60–0.90)	0.003
Stroke†	49	1.6	105	3.4	0.46 (0.33–0.65)	<0.001
Ischemic	35	1.1	93	3.0	0.37 (0.25–0.55)	<0.001
Hemorrhagic	6	0.2	9	0.3	0.67 (0.24–1.88)	0.45
Unspecified	9	0.3	4	0.1	2.24 (0.69–7.27)	0.18
Disabling or fatal	31	1.0	72	2.3	0.43 (0.28–0.65)	<0.001
Systemic embolism	2	0.1	13	0.4	0.15 (0.03–0.68)	0.01
Myocardial infarction	24	0.8	28	0.9	0.86 (0.50–1.48)	0.59
Death						
From any cause	111	3.5	140	4.4	0.79 (0.62–1.02)	0.07
From vascular cause	84	2.7	96	3.1	0.87 (0.65–1.17)	0.37
Hospitalization for cardiovascular cause	367	12.6	455	15.9	0.79 (0.69–0.91)	<0.001
Bleeding event						
Major	44	1.4	39	1.2	1.13 (0.74–1.75)	0.57
Intracranial	11	0.4	13	0.4	0.85 (0.38–1.90)	0.69
Subdural‡	4	0.1	2	0.1	—	—
Other intracranial, excluding hemorrhagic stroke and subdural‡	1	<0.1	2	0.1	—	—
Extracranial or unclassified	33	1.1	27	0.9	1.23 (0.74–2.05)	0.42
Gastrointestinal	12	0.4	14	0.4	0.86 (0.40–1.86)	0.71
Non-gastrointestinal	20	0.6	13	0.4	1.55 (0.77–3.12)	0.22
Fatal§	4	0.1	6	0.2	0.67 (0.19–2.37)	0.53
Clinically relevant nonmajor	96	3.1	84	2.7	1.15 (0.86–1.54)	0.35
Minor	188	6.3	153	5.0	1.24 (1.00–1.53)	0.05

* The percent per year is the rate per 100 patient-years of follow-up. All analyses were based on the time to a first event; patients could have more than one event.

† Stroke included ischemic and hemorrhagic (i.e., primary intracerebral bleeding) types; some strokes could not be classified (unspecified). Hemorrhagic stroke is also included in the categories of major bleeding and intracranial bleeding. Disabling or fatal stroke was defined by a modified Rankin score of 3 to 6. The modified Rankin score is a measure of the severity of stroke on a scale from 0 (no symptoms or disability) to 6 (death).

‡ Hazard ratios and P values were not calculated for these events because there were so few events.

§ Bleeding events were reported as fatal by the investigator and were confirmed at adjudication.

potential limitation and could theoretically have inflated the estimate of benefit, the statistical threshold for stopping the trial was very high, and the boundary had to be exceeded on two consecutive formal reviews, thereby ensuring the robustness of the findings.

Patients were eligible for this study if their physicians considered vitamin K antagonist ther-

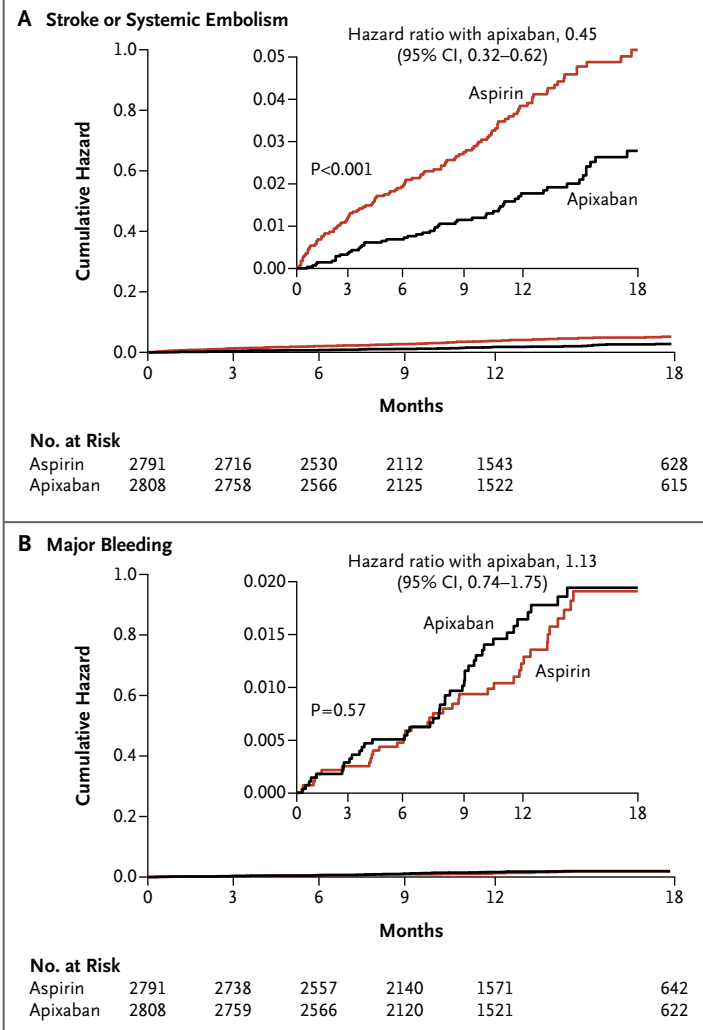


Figure 1. Cumulative Hazard Rates for the Primary Efficacy and Safety Outcomes, According to Treatment Group.

Panel A shows the cumulative hazard rates for the primary efficacy outcome (stroke or systemic embolism), and Panel B the rates for the primary safety outcome (major bleeding) in the apixaban and aspirin groups.

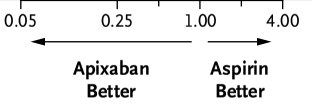
apy to be unsuitable for them. Large administrative database surveys indicate that at least one third of patients who are considered to be ideal candidates for anticoagulation therapy are not receiving it.[12-14] The difficulties of monitoring the INR in patients who are receiving vitamin K antagonist therapy are well documented and contribute to its underuse. The difficulty or anticipated difficulty of maintaining the INR in the therapeutic range was a major reason for the unsuitability of vitamin K antagonist therapy in this study. In a meta-analysis of surveys of warfarin use in the United States, the mean time that the INR was in the therapeutic range was 55%.[3] More than one third of the patients in our study refused to take a vitamin K antagonist. A similar rate of refusal of vitamin K antagonist therapy was reported in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) A (ClinicalTrials.gov number, NCT00249873).[7] The reluctance of patients to use a vitamin K antagonist is not surprising, given the inconvenience of INR monitoring, the lifestyle changes required, and the real and perceived difficulties associated with warfarin therapy. The 2006 American College of Cardiology–American Heart Association–European Society of Cardiology guidelines for the management of atrial fibrillation recommend that for patients with a $CHADS_2$ score of 1, physicians choose either a vitamin K antagonist or aspirin.[15] In the current study, apixaban was much more effective than aspirin for the prevention of stroke, with a risk of bleeding that was similar to that of aspirin, indicating that its ratio of benefit to risk may be better than that of vitamin K antagonists and that it could be useful in these moderate-risk patients.

Other antithrombotic agents have been compared with aspirin for the treatment of patients with atrial fibrillation. In ACTIVE A, the addition of clopidogrel to aspirin reduced the risk of stroke by 28%,[7] and in meta-analyses of randomized trials of vitamin K antagonist therapy as compared with aspirin, vitamin K antagonist therapy reduced the risk of stroke by 39%.[6,16] These indirect comparisons suggest that apixaban is more effective than clopidogrel plus aspirin and at least as effective as warfarin. The latter hypothesis is being tested in the ongoing Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation randomized study (ARISTOTLE; NCT00412984).[17]

Neither the intention-to-treat analysis nor the on-treatment analysis showed a significant increase in the risk of major bleeding with apixaban as compared with aspirin, although the point estimate of the hazard ratio was higher in the on-treatment analysis. The on-treatment analysis may provide a more specific measure of the effect of therapy but does so at the risk of introducing potential bias. Hemorrhagic strokes and other intracranial bleeding (e.g., subdural bleeding) are perhaps the most feared and serious adverse effects of antithrombotic therapy in patients with

A Stroke or Systemic Embolism

Characteristic	No. of Patients	Aspirin	Apixaban	Hazard Ratio with Apixaban (95% CI)	P Value for Interaction
		no. of events (%/yr)			
Overall	5599	113 (3.7)	51 (1.6)		
Age					0.08
<65 yr	1714	19 (2.0)	7 (0.7)		
65 to <75 yr	1987	28 (2.7)	24 (2.0)		
≥75 yr	1897	66 (6.1)	20 (2.0)		
Sex					0.42
Female	2321	64 (4.9)	25 (1.9)		
Male	3277	49 (2.7)	26 (1.4)		
Estimated GFR					0.36
<50 ml/min	1198	36 (5.8)	16 (2.5)		
50 to <80 ml/min	2374	59 (4.5)	22 (1.7)		
≥80 ml/min	2021	18 (1.6)	13 (1.1)		
$CHADS_2$ score					0.23
0–1	2026	18 (1.6)	10 (0.9)		
2	1999	40 (3.7)	25 (2.1)		
≥3	1570	55 (6.3)	16 (1.9)		
Prior stroke or TIA					0.18
No	4835	80 (3.0)	41 (1.5)		
Yes	764	33 (8.3)	10 (2.5)		
Study aspirin dose					0.99
<162 mg daily	3602	85 (4.3)	39 (1.9)		
≥162 mg daily	1978	27 (2.4)	12 (1.1)		
Previous VKA use					0.13
Yes	2216	52 (4.2)	17 (1.4)		
No	3383	61 (3.3)	34 (1.8)		
Patient refused VKA					0.61
No	3506	73 (3.8)	35 (1.8)		
Yes	2092	40 (3.4)	16 (1.4)		
Heart failure					0.74
No	3428	66 (3.6)	28 (1.5)		
Yes	2171	45 (3.8)	23 (1.8)		



B Major Bleeding

Characteristic	No. of Patients	Aspirin	Apixaban	Hazard Ratio with Apixaban (95% CI)	P Value for Interaction
		no. of events (%/yr)			
Overall	5599	39 (1.2)	44 (1.4)		
Age					0.85
<65 yr	1714	5 (0.5)	7 (0.7)		
65 to <75 yr	1987	10 (1.0)	11 (0.9)		
≥75 yr	1897	24 (2.2)	26 (2.6)		
Sex					0.97
Female	2321	17 (1.3)	19 (1.5)		
Male	3277	22 (1.2)	25 (1.4)		
Estimated GFR					0.92
<50 ml/min	1198	16 (2.5)	20 (3.2)		
50 to <80 ml/min	2374	17 (1.3)	17 (1.3)		
≥80 ml/min	2021	6 (0.5)	7 (0.6)		
$CHADS_2$ score					0.70
0–1	2026	6 (0.5)	6 (0.5)		
2	1999	14 (1.3)	14 (1.2)		
≥3	1570	19 (2.1)	24 (2.9)		
Prior stroke or TIA					0.73
No	4835	28 (1.0)	30 (1.1)		
Yes	764	11 (2.7)	14 (3.5)		
Study aspirin dose					0.14
<162 mg daily	3602	22 (1.1)	32 (1.6)		
≥162 mg daily	1978	17 (1.5)	12 (1.1)		
Previous VKA use					0.74
Yes	2216	21 (1.7)	22 (1.8)		
No	3383	18 (1.0)	22 (1.2)		
Patient refused VKA					0.84
No	3506	24 (1.2)	28 (1.4)		
Yes	2092	15 (1.3)	16 (1.4)		
Heart failure					0.36
No	3428	22 (1.1)	28 (1.5)		
Yes	2171	17 (1.4)	16 (1.3)		

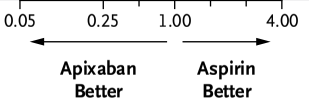


Figure 2. Relative Risks of the Primary Efficacy and Safety Outcomes, According to Subgroup.

Panel A shows the relative risk of the primary efficacy outcome (stroke or systemic embolism) with apixaban as compared with aspirin, according to subgroup; Panel B shows the relative risks of the primary safety outcome (major bleeding) in the same subgroups. The squares and horizontal lines indicate hazard ratios and corresponding 95% confidence intervals; the sizes of the squares are proportional to the sizes of the subgroups. Dashed vertical lines represent the point estimates of the overall hazard ratio. $CHADS_2$ is a measure of the risk of stroke in patients with atrial fibrillation. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient, with a higher score indicating a greater risk of stroke. GFR denotes glomerular filtration rate, TIA transient ischemic attack, and VKA vitamin K antagonist.

atrial fibrillation.[18] A meta-analysis showed that vitamin K antagonist therapy as compared with aspirin more than doubled the risk of intracranial bleeding,[6] and in ACTIVE W (NCT00243178), vitamin K antagonist therapy as compared with clopidogrel plus aspirin more than doubled the risk of hemorrhagic stroke.[19] In the current study, apixaban as compared with aspirin reduced the risk of ischemic stroke by more than 60% but did not appear to increase the risk of hemorrhagic stroke. This finding, together with the report of a much lower risk of hemorrhagic stroke with dabigatran as compared with warfarin,[20] indicates that reduction of intracranial bleeding will be one of the most important benefits of the newer oral antithrombotic drugs over vitamin K antagonist therapy.

To evaluate the net benefit of apixaban, we used a composite outcome that included ischemic events and major bleeding. The rate of this outcome was significantly reduced with apixaban as compared with aspirin (5.3% per year vs. 7.2% per year, P=0.003). Both major ischemic and bleeding events increase the risk of death. In this study, the rate of death with apixaban as compared with aspirin was reduced by 1 percentage point per year (P=0.07). Among patients with atrial fibrillation, hospitalization for cardiovascular causes is strongly associated with increased mortality,[21] directly reflects the well-being of patients, and has a major impact on health care costs. In our study, the rate of hospitalization for cardiovascular causes was significantly reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, P<0.001). Apixaban was also associated with fewer serious adverse events and lower rates of discontinuation of medication, indicating that it had an acceptable side-effect profile as compared with aspirin. On the basis of the results of the intention-to-treat analysis, treating 1000 patients for 1 year with apixaban rather than with aspirin would prevent 21 strokes or systemic emboli, 9 deaths, and 33 hospitalizations for cardiovascular causes, at the cost of 2 major bleeding events.

In summary, among patients with atrial fibrillation who are at high risk for stroke and for whom vitamin K antagonist therapy is unsuitable, apixaban, as compared with aspirin, substantially reduced the risk of stroke, with no significant increase in the risk of major bleeding or intracranial bleeding. The net clinical benefit of apixaban in these patients was therefore substantial.

Dr. Connolly reports receiving payment for serving on the boards of Boehringer Ingelheim, Sanofi-Aventis, Portola, and Merck, consulting fees from Boehringer Ingelheim, Sanofi-Aventis, Portola, and Merck, grant support on behalf of his institution, McMaster University, from Boehringer Ingelheim, Sanofi-Aventis, Portola, and Bristol-Myers Squibb, and lecture fees from Boehringer Ingelheim, Sanofi-Aventis, and Portola; Dr. Eikelboom, receiving consulting fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, AstraZeneca, and Novartis and lecture fees from Bristol-Myers Squibb, Sanofi-Aventis, Eli Lilly, and AstraZeneca; Dr. Joyner, receiving honoraria from Hamilton Health Sciences as the cochair of the RELY adjudication committee; Dr. Diener, receiving payment for serving on the boards of Abbott, AstraZeneca, Boehringer Ingelheim, CoAxia, D-Pharm, GlaxoSmithKline, Janssen-Cilag, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Sanofi-Aventis, Servier, and Solvay, consulting fees from Abbott, AstraZeneca, Bayer Vital, Bristol-Myers Squibb, Boehringer Ingelheim, CoAxia, D-Pharm, Fresenius, GlaxoSmithKline, Janssen-Cilag, Knoll, Merck Sharpe and Dohme, Medtronic, MindFrame, Neurobiological Technologies, Novartis, Novo-Nordisk, Paion, Parke-Davis, Pfizer, Sanofi-Aventis, Sankyo, Schering-Plough, Servier, Solvay, Thrombogenics, Wyeth, and Yamaguchi, grant support on behalf of his institution, University Duisburg-Essen, from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Janssen-Cilag, and Sanofi-Aventis, lecture fees from Abbott, AstraZeneca, Bristol-Myers Squibb, Bayer Vital, Boehringer Ingelheim, CoAxia, D-Pharm, GlaxoSmithKline, Merck Sharpe and Dohme, MindFrame, Neurobiological Technologies, Novartis, Sanofi-Aventis, Servier, Solvay, and Thrombogenics, payment from Boehringer Ingelheim and Sanofi-Aventis for manuscript preparation, and payment from Boehringer Ingelheim for developing educational presentations; Dr. Flaker, receiving payment for serving as a consultant on Bristol-Myers Squibb's advisory board; Dr. Avezum, receiving payment from Boehringer Ingelheim for giving lectures in the Satellite Symposium; Dr. Hohnloser, receiving consulting fees from Boehringer Ingelheim, St. Jude Medical, Sanofi-Aventis, and Cardiome, and lecture fees from Boehringer Ingelheim, St. Jude Medical, Sanofi-Aventis, and Cardiome; Dr. Talajic, receiving consulting fees from Boehringer Ingelheim and Bristol-Myers Squibb, grant support on behalf of his institution, the Montreal Heart Institute, from Boehringer Ingelheim, and lecture fees from Boehringer Ingelheim and Bristol-Myers Squibb; Dr. Budaj, receiving consulting fees from Sanofi-Aventis, Eli Lilly, Novartis, and AstraZeneca, grant support both for himself and on behalf of his institution, Grochowski Hospital, from Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, Bristol-Myers Squibb, and AstraZeneca, lecture fees from Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca, and reimbursement for travel, accommodations, or meeting expenses from Sanofi-Aventis, Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca; Dr. Parkhomenko, receiving consulting fees from AstraZeneca, Merck Sharpe and Dohme, Bayer, Takeda, GlaxoSmithKline, Borschagovskiy, Servier, Sanofi-Aventis, Astellas, and Boehringer Ingelheim, lecture fees from Servier, Orion, GlaxoSmithKline, and Pfizer, and payment from Servier and Pfizer for developing educational presentations; Dr. Commerford, having testified as an expert witness on the importance of anticoagulation in atrial fibrillation, receiving consulting fees from UpToDate and reimbursement for committee meeting expenses on behalf of his institution, the Cardiac Clinic, from Boehringer Ingelheim, Sanofi-Aventis, and Bristol-Myers Squibb; Dr. Tan, receiving payment for serving on a regional advisory board for Bayer; Dr. Lewis, receiving consulting fees from Bristol-Myers Squibb; Dr. Lip, receiving consulting fees from Astellas, Boehringer Ingelheim, Bayer, Daiichi, Merck, Portola, Biotronic,

Sanofi-Aventis, and AstraZeneca, grant support on behalf of his institution, City Hospital, from Bayer, lecture fees from Boehringer Ingelheim, Bayer, Merck, and Sanofi-Aventis, and payment from Boehringer Ingelheim for developing educational presentations; Dr. Lawrence, being an employee of Bristol-Myers Squibb; and Dr. Yusuf, receiving consulting fees from Boehringer Ingelheim, Sanofi-Aventis, Novartis, AstraZeneca, Bristol-Myers Squibb, and Glaxo-SmithKline, and grant support from Boehringer Ingelheim, Sanofi-Aventis, Novartis, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb. No other potential conflict of interest relevant to this article was reported.

Supported by Bristol-Myers Squibb and Pfizer.

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

APPENDIX

The authors' affiliations are as follows: Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, ON, Canada (S.J.C., J.E., G.L., R.A., S.Y.); University of Toronto, Toronto (C.J.); University Duisburg–Essen, Essen, Germany (H.-C.D.); University of Texas, San Antonio (R.H.); Russian Cardiology Research and Production Center, Moscow (S.G.); University of Missouri, Columbia (G.F.); Instituto Dante Pazzanese de Cardiologia, São Paulo (A.A.); Johann-Wolfgang-Goethe-Universität, Frankfurt, Germany (S.H.H.); Estudios Clinícos Latinoamérica, Rosario, Argentina (R.D.); Montreal Heart Institute, Université de Montréal, Montreal (M.T.); FuWai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing (J.Z.); St. John's Medical College and Research Institute, Bangalore, India (P.P.); Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland (A.B.); Institute of Cardiology, Kiev, Ukraine (A.P.); University Hospital Motol, Prague, Czech Republic (P.J.); Department of Medicine, University of Cape Town, Cape Town, South Africa (P.C.); National Heart Center, Singapore, Singapore (R.S.T.); Clinical Research Centre, Sarawak, Malaysia (K.-H.S.); Lady Davis Carmel Medical Center, Haifa, Israel (B.S.L.); Ziekenhuis Oost-Limburg Campus St.-Jan, Genk, Belgium (W.V.M.); City Hospital, Birmingham, United Kingdom (G.Y.H.L.); St. Paul's Hospital, Catholic University of Korea, Seoul (J.H.K.); Universidad de La Frontera, Temuco, Chile (F.L.-Z.); Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City (A.G.-H.); University of the Philippines College of Medicine, Manila (A.L.D.); Harapan Kita Hospital, Jakarta, Indonesia (M.M.); HRB Clinical Research Facility, Galway, Ireland (M.O.); and Bristol-Myers Squibb, Princeton, NJ (J.L.).

REFERENCES

1. Lip GY, Tse HF. Management of atrial fibrillation. Lancet 2007;370:604-18.

2. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:Suppl:160S-198S.

3. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. J Manag Care Pharm 2009;15:244-52.

4. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke 2010;41:397-401.

5. Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation. Circ Cardiovasc Qual Outcomes 2010;3:624-31.

6. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.

7. The ACTIVE Investigators. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. N Engl J Med 2009;360:2066-78.

8. Eikelboom JW, Weitz JI. New anticoagulants. Circulation 2010;121:1523-32.

9. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Portman RJ. Apixaban or enoxaparin for thromboprophylaxis after knee replacement. N Engl J Med 2009;361:594-604. [Erratum, N Engl J Med 2009;361:1814.]

10. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet 2010;375:807-15.

11. Eikelboom JW, O'Donnell M, Yusuf S, et al. Rationale and design of AVERROES: apixaban versus acetylsalicylic acid to prevent stroke in atrial fibrillation patients who have failed or are unsuitable for vitamin K antagonist treatment. Am Heart J 2010;159:348-53.

12. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290:2685-92.

13. Nieuwlaat R, Capucci A, Camm AJ, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26:2422-34.

14. Birman-Deych E, Radford MJ, Nilasena DS, Gage BF. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37:1070-4.

15. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 2006;114(7):e257-e354. [Erratum, Circulation 2007;116(6):e138.]

16. Hart RG, Pearce LA, Aguilar MI. Adjusted-dose warfarin versus aspirin for preventing stroke in patients with atrial fibrillation. Ann Intern Med 2007;147:590-2.

17. Lopes RD, Alexander JH, Al-Khatib SM, et al. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010;159:331-9. [Erratum, Am Heart J 2010;159:1162.]

18. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. Stroke 2005;36:1588-93.

19. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006;367:1903-12.

20. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51. [Erratum, N Engl J Med 2010;363:1877.]

21. Wyse DG, Slee A, Epstein AE, et al. Alternative endpoints for mortality in studies of patients with atrial fibrillation: the AFFIRM study experience. Heart Rhythm 2004;1:531-7.