ORIGINAL ARTICLE

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE Investigators*

ABSTRACT

BACKGROUND

Vitamin K antagonists reduce the risk of stroke in patients with atrial fibrillation but are considered unsuitable in many patients, who usually receive aspirin instead. We investigated the hypothesis that the addition of clopidogrel to aspirin would reduce the risk of vascular events in patients with atrial fibrillation.

METHODS

A total of 7554 patients with atrial fibrillation who had an increased risk of stroke and for whom vitamin K–antagonist therapy was unsuitable were randomly assigned to receive clopidogrel (75 mg) or placebo, once daily, in addition to aspirin. The primary outcome was the composite of stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes.

RESULTS

At a median of 3.6 years of follow-up, major vascular events had occurred in 832 patients receiving clopidogrel (6.8% per year) and in 924 patients receiving placebo (7.6% per year) (relative risk with clopidogrel, 0.89; 95% confidence interval [CI], 0.81 to 0.98; P=0.01). The difference was primarily due to a reduction in the rate of stroke with clopidogrel. Stroke occurred in 296 patients receiving clopidogrel (2.4% per year) and 408 patients receiving placebo (3.3% per year) (relative risk, 0.72; 95% CI, 0.62 to 0.83; P<0.001). Myocardial infarction occurred in 90 patients receiving clopidogrel (0.7% per year) and in 115 receiving placebo (0.9% per year) (relative risk, 0.78; 95% CI, 0.59 to 1.03; P=0.08). Major bleeding occurred in 251 patients receiving clopidogrel (2.0% per year) and in 162 patients receiving placebo (1.3% per year) (relative risk, 1.57; 95% CI, 1.29 to 1.92; P<0.001).

CONCLUSIONS

In patients with atrial fibrillation for whom vitamin K–antagonist therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage. (ClinicalTrials.gov number, NCT00243178.)

The members of the writing group (Stuart J. Connolly and Janice Pogue, Population Health Research Institute, Hamilton, ON, Canada; Robert G. Hart, University of Texas Health Center, San Antonio; Stefan H. Hohnloser, Goethe University Hospital, Frankfurt, Germany; Marc Pfeffer, Brigham and Women's Hospital, Boston; and Susan Chrolavicius and Salim Yusuf, Population Health Research Institute, Hamilton, ON, Canada) of Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) assume responsibility for the overall content and integrity of the article. Address reprint requests to Dr. Connolly at the Population Health Research Institute, McMaster University, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at stuart.connolly@phri.ca.

*The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) investigators are listed in the Appendix.

This article (10.1056/NEJMoa0901301) was published at NEJM.org on March 31, 2009.

N Engl J Med 2009;360.

Atrial fibrillation is a common cardiac arrhythmia that increases the risk of stroke by a factor of five.[1] Adjusted-dose vitamin K antagonists and antiplatelet agents reduce the risk of stroke by 64% and 22%, respectively.[2] As compared with aspirin, vitamin K antagonists reduce the risk of stroke by 38% but more than double the risk of intracranial hemorrhage and increase the risk of major extracranial hemorrhage by 70%. They do not reduce mortality from any cause or from vascular causes.[2,3] On the basis of these data, vitamin K antagonists are recommended for patients at higher risk for stroke, and aspirin for patients at lower risk.[4,5]

Vitamin K antagonists have a narrow window for a therapeutic benefit and require regular monitoring of the international normalized ratio (INR).[6] Several surveys in North America and Europe indicate that only about 50% of patients with atrial fibrillation who are at increased risk for stroke receive vitamin K antagonists.[7-10] Patients may not be treated with a vitamin K antagonist for any number of reasons, including concern about interactions with other drugs, the increased risk of hemorrhage, inadequate compliance with INR monitoring, and a desire by the patient to avoid vitamin K–antagonist therapy. Most of these patients are treated with aspirin.

The benefit of combining clopidogrel with aspirin has been proven in patients with acute coronary syndromes.[11] The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE) was initiated to evaluate the role of clopidogrel plus aspirin for the prevention of stroke and other vascular events in patients with atrial fibrillation. ACTIVE W, which has previously been reported,[12] compared clopidogrel plus aspirin with a vitamin K antagonist. ACTIVE A, reported here, compared clopidogrel plus aspirin with aspirin alone in patients with atrial fibrillation who were at increased risk for stroke and for whom therapy with a vitamin K antagonist was considered unsuitable.

METHODS

TRIAL DESIGN

The design of ACTIVE A has been described previously.[13] The study was a randomized, double-blind, multicenter trial performed at 580 centers in 33 countries. The sponsors, Sanofi-Aventis and Bristol-Myers Squibb, assisted in protocol development and on-site monitoring but had no role in data collection or analysis or in the writing of the manuscript. A steering committee consisting of national coordinators, the principal investigators, and representatives of the sponsors supervised the trial. The study was coordinated by the Population Health Research Institute at McMaster University, which also managed and analyzed the data. The trial protocol was approved by ethics committees at all participating centers. The academic authors vouch for the accuracy and completeness of the data and the analyses.

STUDY PARTICIPANTS

Patients were eligible for ACTIVE (either ACTIVE A or ACTIVE W) if they had atrial fibrillation at enrollment or had had at least two episodes of intermittent atrial fibrillation in the previous 6 months. In addition, patients were required to have at least one of the following risk factors for stroke: an age of 75 years or more; systemic hypertension during treatment; previous stroke, transient ischemic attack, or non–central nervous system systemic embolism; a left ventricular ejection fraction of less than 45%; peripheral vascular disease; or an age of 55 to 74 years and diabetes mellitus or coronary artery disease. Patients were excluded if they required a vitamin K antagonist or clopidogrel or had any of the following risk factors for hemorrhage: documented peptic ulcer disease within the previous 6 months; a history of intracerebral hemorrhage; significant thrombocytopenia (platelet count $<50\times10^9$ per liter); or ongoing alcohol abuse. All patients provided written informed consent before participating in the study.

TREATMENT ASSIGNMENT AND FOLLOW-UP

Patients who were considered to be candidates for vitamin K–antagonist therapy were enrolled in ACTIVE W, and those for whom such therapy was considered to be unsuitable were enrolled in ACTIVE A. Patients in both ACTIVE W and ACTIVE A could also be enrolled in ACTIVE I, involving factorial randomization to either irbesartan or placebo. The ACTIVE I trial is ongoing.

By means of an interactive telephone system, patients in ACTIVE A were randomly assigned in equal numbers, in blocks of varying sizes, to receive clopidogrel at a dose of 75 mg or matching placebo once daily, in a double-blind fashion. All patients also received aspirin (recommended dose, 75 to 100 mg per day). The protocol specified that patients undergoing cardioversion at any point during the trial were to be treated with an open-

label vitamin K antagonist for 4 weeks before and after cardioversion and were then to resume the assigned study treatment.

Follow-up visits for the assessment of compliance and outcome events were scheduled at 1 month and 3 months, every 3 months thereafter for the first year, and then every 6 months until the end of the trial. Follow-up for all surviving patients was continued until the final visit in November 2008.

TRIAL OUTCOMES

The primary study outcome was any major vascular event (stroke, non–central nervous system systemic embolism, myocardial infarction, or death from vascular causes). The most important secondary outcome was stroke. Other secondary outcomes were the other individual components of the primary outcome (non–central nervous system systemic embolism, myocardial infarction, and death from vascular causes) and the composite of the primary outcome and major hemorrhage.

Stroke was defined as the sudden onset of a focal neurologic deficit lasting more than 24 hours and classified as ischemic (including hemorrhagic transformation), hemorrhagic, or of uncertain type. The severity of stroke was assessed with the use of the modified Rankin scale (on which scores range from 0 to 6, with 0 indicating no symptoms and 6 indicating death) at the time of hospital discharge or within 7 days after the onset of stroke. The risk of stroke was assessed post hoc by means of the $CHADS_2$ score, which reflects the risk of stroke in patients with atrial fibrillation, with values ranging from 0 to 6 and higher scores indicating an increased risk. Myocardial infarction was diagnosed according to standard guidelines.[14] Death from vascular causes was defined as any death not clearly due to a nonvascular cause. Major hemorrhage was defined as any overt bleeding requiring transfusion of at least two units of blood or any overt bleeding meeting the criteria for severe hemorrhage, which included any of the following: fatal hemorrhage, a drop in the hemoglobin level of 5.0 g per deciliter or more, hypotension requiring inotropic agents, intraocular bleeding leading to substantial loss of vision, requirement for surgical intervention, symptomatic intracranial hemorrhage, or requirement for transfusion of four units or more of blood. Minor bleeding was defined as any nonmajor bleeding associated with modification of the study-drug regimen. All major outcomes were adjudicated by an event-adjudication committee, and all strokes by a neurologist; the committee members and the neurologists were unaware of the treatment assignments.

STATISTICAL ANALYSIS

The hypothesis being tested in ACTIVE A was that the use of clopidogrel plus aspirin would reduce the risk of the primary outcome, as compared with the use of aspirin alone. On the basis of an expected annual primary-event rate of 8% among patients treated with aspirin alone, we estimated that enrollment of 7500 patients during a period of 2 years would provide a statistical power of 88% to detect a relative reduction of 15% in the risk of major vascular events with the addition of clopidogrel to aspirin. The study was designed to accrue at least 1600 primary events.

An independent data and safety monitoring board periodically reviewed the efficacy and safety data. Stopping rules were based on modified Haybittle–Peto boundaries of 4 SD in the first half of the study and 3 SD in the second half for efficacy data and 3 SD in the first half of the study and 2 SD in the second half for safety data. Two formal interim analyses of efficacy were performed when 50% and 75% of the expected number of primary events had accrued; no correction of the reported P value for these interim tests was performed.

All analyses were based on the intention-to-treat principle. Data for patients lost to follow-up were censored at the time of the last date of contact. Kaplan–Meier curves were plotted for each of the two treatment groups and were compared by means of a log-rank test. Cox proportional-hazards models stratified by treatment assignment in ACTIVE I were used to calculate relative risks (hazard ratios) and 95% confidence intervals. A test of interaction between the treatment groups of ACTIVE A and those of ACTIVE I was performed by the data and safety monitoring board, which reported no significant interaction for the primary outcome or for major bleeding. Additional Cox models were used to evaluate interactions between treatment assignment and other subgroups of interest.

RESULTS

A total of 7554 patients were enrolled in ACTIVE A between June 2003 and May 2006 and were randomly assigned to receive clopidogrel (3772

Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.*

Characteristic	Clopidogrel plus Aspirin (N=3772)	Aspirin (N=3782)
Age — yr	70.9±10.2	71.1±10.2
Blood pressure — mm Hg		
Systolic	136.3±19.0	136.2±19.1
Diastolic	80.9±11.7	80.9±11.6
Heart rate — beats/min	75.2±14.5	74.8±14.4
Body-mass index†	28.2±4.9	28.2±4.9
$CHADS_2$‡		
Mean score	2.0±1.1	2.0±1.1
Score — no. (%)		
0§	105 (2.8)	101 (2.7)
1	1360 (36.1)	1338 (35.4)
2	1263 (33.5)	1315 (34.8)
3	622 (16.5)	623 (16.5)
4	301 (8.0)	279 (7.4)
5	103 (2.7)	103 (2.7)
6	14 (0.4)	22 (0.6)
Male sex — no. (%)	2212 (58.6)	2185 (57.8)
History of atrial fibrillation, type — no. (%)		
Permanent	2408 (64.0)	2406 (63.7)
Paroxysmal	844 (22.4)	824 (21.8)
Persistent	509 (13.5)	546 (14.5)
Atrial fibrillation, duration — no. (%)		
<6 mo	958 (25.4)	951 (25.2)
6 mo to 2 yr	784 (20.8)	839 (22.2)
>2 yr	2027 (53.8)	1990 (52.6)
History of hypertension — no. (%)	3217 (85.3)	3210 (84.9)
History of stroke or TIA — no. (%)	499 (13.2)	493 (13.0)
History of ischemic heart disease — no. (%)		
Myocardial infarction	525 (13.9)	553 (14.6)
CABG	195 (5.2)	212 (5.6)
CAD	267 (7.1)	316 (8.4)
Diabetes mellitus — no. (%)	734 (19.5)	728 (19.2)
Peripheral artery disease — no. (%)	105 (2.8)	114 (3.0)
Congestive heart failure — no. (%)	1240 (32.9)	1256 (33.2)
Cardiac pacemaker — no. (%)	473 (12.5)	465 (12.3)
ECG findings at baseline — no. (%)		
Atrial fibrillation	2813 (74.6)	2777 (73.4)
Atrial flutter	28 (0.7)	31 (0.8)
Sinus rhythm	763 (20.2)	809 (21.4)
Left ventricular hypertrophy	602 (16.0)	628 (16.6)

Table 1. (Continued.)

Characteristic	Clopidogrel plus Aspirin (N=3772)	Aspirin (N=3782)
Medication use at baseline — no. (%)		
VKA	314 (8.3)	331 (8.8)
Aspirin	3131 (83.0)	3115 (82.4)
Clopidogrel	72 (1.9)	78 (2.1)
Antiarrhythmic agent	847 (22.5)	890 (23.5)
Reason for enrollment in ACTIVE A — no. (%)		
Specific risk of bleeding¶	870 (23.5)	861 (23.0)
Physician's judgment that VKA inappropriate	1871 (50.4)	1886 (50.4)
Patient's preference not to take VKA, only reason	969 (26.1)	995 (26.6)
Region — no. (%)		
North America	375 (9.9)	363 (9.6)
Western Europe and Israel	1150 (30.5)	1181 (31.2)
Eastern Europe	1235 (32.7)	1238 (32.7)
South America	786 (20.8)	776 (20.5)
Asia–Pacific	164 (4.3)	158 (4.2)
South Africa	62 (1.6)	66 (1.7)

* Plus–minus values are means ±SD. There were no significant differences in characteristics between the two groups except for angiographic evidence of coronary artery disease (CAD) (P=0.04). Data were missing for 4 patients in the clopidogrel group and 1 patient in the placebo group for the $CHADS_2$ score; 11 and 6 patients, respectively, for type of atrial fibrillation; 3 and 2 patients, respectively, for duration of atrial fibrillation; and 62 and 40 patients, respectively, for reason for enrollment in ACTIVE A. CABG denotes coronary-artery bypass grafting, ECG electrocardiography, TIA transient ischemic attack, and VKA vitamin K antagonist.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ The $CHADS_2$ score is an algorithm for predicting the risk of stroke in patients with atrial fibrillation. The score assigns points for various risk factors, as follows: congestive heart failure, 1 point; hypertension, 1 point; age greater than 75 years, 1 point; diabetes, 1 point; and previous stroke or transient ischemic attack, 2 points. The score is calculated by summing all the points for a given patient.

§ Patients with a $CHADS_2$ score of 0 who met the inclusion criteria of ACTIVE had peripheral vascular disease or were exactly 75 years of age or were between 55 and 74 years of age and had coronary artery disease.

¶ Specific risks of bleeding included an inability to comply with monitoring of the international normalized ratio (27.5%), a predisposition to falls or head trauma (9.8%), persistent elevation of blood pressure to more than 160/100 (3.2%), previous serious bleeding while the patient was receiving anticoagulant therapy (5.8%), a history of severe alcohol abuse in the previous 2 years (1.1%), documented peptic ulcer disease between 6 months and 1 year before enrollment (0.7%), thrombocytopenia (platelet count, $<150\times10^9$ per liter) (2.2%), and a requirement for long-term therapy with nonsteroidal antiinflammatory drugs (other than a cyclooxygenase-2 inhibitor) (1.6%).

patients) or placebo (3782 patients) in addition to aspirin; all patients received at least one dose of the assigned study medication (clopidogrel or placebo). Forty-three patients (<1%) were lost to follow-up, which ended in November 2008. The median duration of follow-up for both groups was 3.6 years.

STUDY POPULATION

Table 1 lists the baseline characteristics of the patients. The mean age was 71 years; 58.2% of the patients were men. Atrial fibrillation was permanent in 63.7%, persistent in 14.0%, and paroxysmal in 22.1%. The mean $CHADS_2$ score was 2.0. At baseline, 82.7% of patients were receiving aspirin, and 8.5% were taking a vitamin K antagonist. Reasons given for enrollment in ACTIVE A were a specific risk of bleeding (for 22.9% of patients), no such risk but a physician's judgment that a vitamin K antagonist was inappropriate for the patient (49.7%), and the patient's preference not to take a vitamin K antagonist as the sole reason (26.0%) (Table 1).

ADHERENCE TO THE TREATMENT REGIMENS

Rates of discontinuation of the study medication were 16.3% and 15.2% for clopidogrel and placebo, respectively, at 1 year, increasing to 39.4% and

Table 2. Relative Risks of Primary and Secondary Outcomes, According to Treatment Group.*

Outcome	Clopidogrel plus Aspirin (N=3772)		Aspirin (N=3782)		Relative Risk (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome	832	6.8	924	7.6	0.89 (0.81–0.98)	0.01
Stroke						
Any	296	2.4	408	3.3	0.72 (0.62–0.83)	<0.001
Ischemic	235	1.9	343	2.8	0.68 (0.57–0.80)	
Hemorrhagic	30	0.2	22	0.2	1.37 (0.79–2.37)	
Of uncertain type	41	0.3	51	0.4	0.81 (0.54–1.22)	
Fatal	70	0.5	93	0.7	0.75 (0.55–1.03)	
Stroke, according to severity						
Nondisabling	107	0.9	153	1.2	0.70 (0.54–0.89)	0.004
Disabling or fatal	198	1.6	267	2.1	0.74 (0.62–0.89)	0.001
Myocardial infarction	90	0.7	115	0.9	0.78 (0.59–1.03)	0.08
Non–central nervous system systemic embolism	54	0.4	56	0.4	0.96 (0.66–1.40)	0.84
Death from vascular causes	600	4.7	599	4.7	1.00 (0.89–1.12)	0.97
Death from any cause	825	6.4	841	6.6	0.98 (0.89–1.08)	0.69

* The primary outcome was the composite of stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes. Nondisabling strokes were those in patients with modified Rankin scores of 0 to 2. Disabling or fatal strokes were those in patients with modified Rankin scores of 3 to 6. According to the modified Rankin scale, a score of 0 indicates no symptoms; 1, no clinically significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, death.

37.1% at 4 years. All patients were receiving aspirin at the time of randomization, with use decreasing in both groups to 92.9% at 1 year and 81.1% at 4 years. At baseline, the daily dose of aspirin used was 75 to 100 mg in 96.0% of patients and more than 100 mg in 3.5%. The most common antithrombotic medications used by patients who permanently discontinued the study medication were vitamin K antagonists (taken by 29.4% of patients in the clopidogrel group and 31.0% in the placebo group) and aspirin alone (25.1% in the clopidogrel group and 23.6% in the placebo group). A total of 777 patients (10.3%) received a vitamin K antagonist after discontinuation of the trial medication.

OUTCOMES

The primary end point occurred in 832 patients receiving clopidogrel (6.8% per year) as compared with 924 patients receiving placebo (7.6% per year) (relative risk, 0.89; 95% confidence interval [CI], 0.81 to 0.98; P=0.01) (Table 2 and Fig. 1A). The reduction in the risk of major vascular events in the clopidogrel group was primarily due to a reduction in the incidence of stroke. Stroke occurred in 296 patients receiving clopidogrel (2.4% per year) and 408 patients receiving placebo (3.3% per year) (relative risk, 0.72; 95% CI, 0.62 to 0.83; P<0.001) (Table 2 and Fig. 1B). Myocardial infarction occurred in 90 patients receiving clopidogrel (0.7% per year) and in 115 patients receiving placebo (0.9% per year; relative risk, 0.78; 95% CI, 0.59 to 1.03; P=0.08).

Annual rates of non–central nervous system systemic embolism and death from vascular causes were similar between the two groups. A total of 1666 deaths occurred, including 163 fatal strokes, which accounted for 9.8% of all deaths. Other major causes of death included death from nonvascular causes (28.0% of all deaths), arrhythmia (20.9%), and heart failure (18.7%). There were 69 fatal hemorrhages, which accounted for 4.1% of all deaths. The total number of days of hospitalization for cardiovascular causes was 30,276 for clopidogrel plus aspirin and 34,813 for aspirin alone.

TYPES AND SEVERITY OF STROKE

The rate of ischemic stroke was significantly lower in the clopidogrel group than in the placebo group

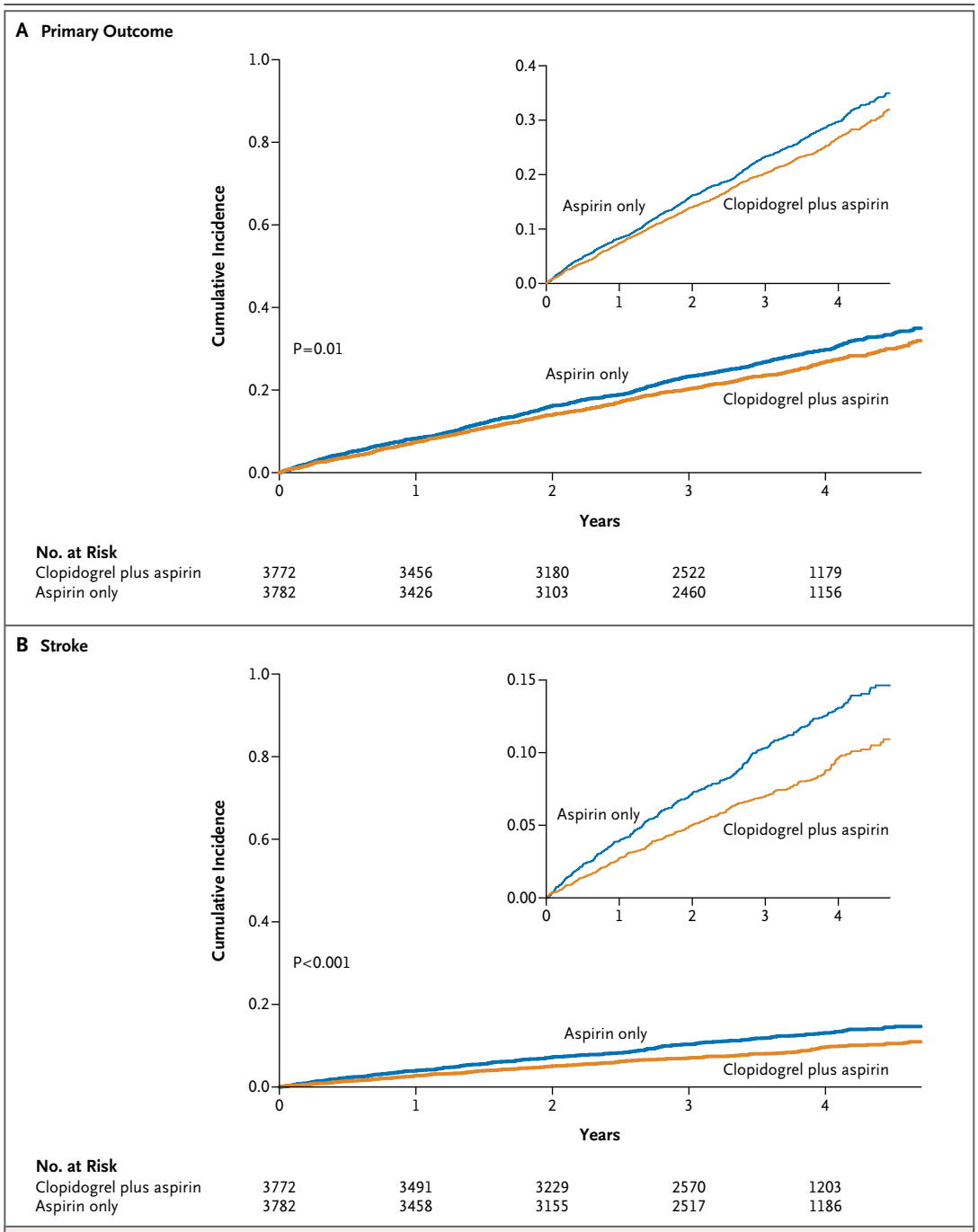


Figure 1. Cumulative Incidence of Trial Outcomes, According to Treatment Group.

Panel A shows the cumulative incidence of the primary end point (stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes). The relative risk for aspirin plus clopidogrel, as compared with aspirin alone, was 0.89 (95% confidence interval [CI], 0.81 to 0.98; P=0.01). Panel B shows the cumulative incidence of stroke. The relative risk for aspirin plus clopidogrel, as compared with aspirin alone, was 0.72 (95% CI, 0.62 to 0.83; P<0.001).

(1.9% per year vs. 2.8% per year, P<0.001) (Table 2). There was a nonsignificant increase in the rate of hemorrhagic stroke in association with the addition of clopidogrel, from 0.17% to 0.23% per year. The risk of stroke of any severity, as measured by means of the modified Rankin score,

was reduced with the use of clopidogrel plus aspirin. The addition of clopidogrel prevented the occurrence of 46 nondisabling strokes (modified Rankin score, 0 to 2) and 69 disabling or fatal strokes (modified Rankin score, 3 to 6). There was a net decrease of 23 fatal strokes with the addition of clopidogrel, as a result of 26 fewer fatal strokes of ischemic or uncertain cause and 3 more fatal hemorrhagic strokes.

HEMORRHAGE

Major bleeding occurred in 251 patients receiving clopidogrel as compared with 162 patients receiving placebo (2.0% per year vs. 1.3% per year; relative risk, 1.57; 95% CI, 1.29 to 1.92; P<0.001) (Table 3). With clopidogrel, there was an excess of 83 episodes of major bleeding not related to stroke (62 of which were severe), including an excess of 13 fatal episodes. The most common site of hemorrhage was the gastrointestinal tract (132 episodes with clopidogrel vs. 68 with placebo, for an excess of 64 episodes with clopidogrel). With the combination of major vascular events (the primary outcome) and major hemorrhage, there was no significant difference between the overall event rate with aspirin plus clopidogrel and the rate with aspirin alone (968 vs. 996 events; relative risk, 0.97; 95% CI, 0.89 to 1.06; P=0.54).

SUBGROUP ANALYSES

Subgroup analyses were performed for major vascular events (the primary outcome) (Fig. 2A) and stroke (Fig. 2B). Although there appeared to be a significant interaction relating both age and the $CHADS_2$ score to the effect of clopidogrel on major vascular events, this interaction was not evident for stroke. In addition, an interaction with baseline use of vitamin K antagonists was found with regard to stroke but not vascular events. The lack of consistency in these interactions indicates that there was only weak evidence of differential treatment effects according to these subgroups.

DISCUSSION

In ACTIVE A, we compared the combination of aspirin plus clopidogrel with aspirin alone for the prevention of major vascular events in patients with atrial fibrillation who had an increased risk of stroke and in whom therapy with a vitamin K antagonist was considered to be unsuitable. The addition of clopidogrel to aspirin reduced the rate of major vascular events from 7.6% per year to 6.8%. This was primarily due to a reduction in the rate of stroke. The rate of major hemorrhage increased with the addition of clopidogrel, from 1.3% to 2.0% per year.

It is useful to compare the risk–benefit ratios for clopidogrel plus aspirin versus aspirin and vitamin K antagonists versus aspirin. In a meta-analysis, as compared with aspirin, warfarin reduced the risk of stroke by 38% and increased the risks of major extracranial hemorrhage by 70% and intracranial hemorrhage by 128%.[2] In ACTIVE A,

Table 3. Relative Risks of Hemorrhage, According to Treatment Group.

Bleeding	Clopidogrel plus Aspirin		Aspirin		Relative Risk (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Major bleeding	251	2.0	162	1.3	1.57 (1.29–1.92)	<0.001
Severe	190	1.5	122	1.0	1.57 (1.25–1.98)	<0.001
Fatal	42	0.3	27	0.2	1.56 (0.96–2.53)	0.07
Minor bleeding	408	3.5	175	1.4	2.42 (2.03–2.89)	<0.001
Any bleeding	1014	9.7	651	5.7	1.68 (1.52–1.85)	<0.001
Site of major bleeding*						
Gastrointestinal	132	1.1	68	0.5	1.96 (1.46–2.63)	<0.001
Gastrointestinal, with transfusion	117	0.9	61	0.5	1.93 (1.42–2.63)	<0.001
Intracranial	54	0.4	29	0.2	1.87 (1.19–2.94)	0.006
Extracranial	200	1.6	134	1.1	1.51 (1.21–1.88)	<0.001

* Four patients had both intracranial and extracranial bleeding.

clopidogrel plus aspirin reduced the risk of stroke by 28% and increased the risk of major extracranial hemorrhage by 51% and major intracranial hemorrhage by 87%. This comparison suggests that therapy with a vitamin K antagonist is more effective than clopidogrel plus aspirin but is associated with a greater risk of hemorrhage, although the patient populations and concomitant therapies in ACTIVE A and the meta-analysis trials are not completely comparable.

Myocardial infarction was not a common outcome in ACTIVE A (115 events in the placebo group and 90 in the clopidogrel group). The difference in the rate of myocardial infarction between the two groups, although not significant (P=0.08), is plausible because it is consistent with the results of previous trials involving patients with acute coronary syndromes.[11,15] It might at first seem surprising that the 28% reduction in stroke found in ACTIVE A did not result in a significant reduction in mortality from vascular causes or from any cause. However, the use of vitamin K antagonists has been shown to reduce the rate of stroke by 38% as compared with the use of aspirin, with no significant effect on mortality.[2] Given that only 10% of the 1666 deaths in ACTIVE A were due to stroke, it is unlikely that any intervention that primarily reduces the risk of stroke will significantly reduce mortality. The majority of deaths were related to arrhythmia (21%), heart failure (19%) and nonvascular causes (28%).

In patients with atrial fibrillation, there is evidence of both a hypercoagulable state and increased platelet activation.[16] Markers of coagulation activation and thrombin generation are elevated in patients with atrial fibrillation and are suppressed with the use of vitamin K antagonists.[17-19] Markers of platelet activation, such as soluble P-selectin, are also elevated in patients with atrial fibrillation.[20-23] In the Rotterdam Study of elderly patients, there was a strong independent association between the soluble P-selectin level and mortality from cardiac causes in patients with atrial fibrillation.[22] The role of platelet activation in stroke in patients with atrial fibrillation has been questioned because of the modest protective effect of aspirin against stroke.[2] However, some patients with atrial fibrillation who are receiving aspirin may have only partial inhibition of platelet aggregation.[24] The addition of clopidogrel to aspirin in patients with atrial fibrillation results in a significantly greater reduction in platelet aggregation than that observed with aspirin alone,[25] suggesting that more effective platelet inhibition could augment the protective effect of aspirin. The results of ACTIVE A confirm this hypothesis and provide strong evidence for an important role of abnormal platelet activation in the pathogenesis of stroke in patients with atrial fibrillation.

It is important to emphasize that oral anticoagulation therapy with a vitamin K antagonist is the preferred and recommended therapy for the prevention of ischemic stroke in patients with atrial fibrillation who are at increased risk for stroke.[4,5] However, current guidelines also note that "the selection of the antithrombotic agent should be based upon the absolute risks of stroke and bleeding and the relative risk and benefit for a given patient,"[5] a specification for which precise guidance is not available. Patients were eligible for ACTIVE A if, in addition to being at increased risk for stroke, they were not considered to be candidates for vitamin K–antagonist therapy. At baseline, only 8.5% of patients in ACTIVE A were receiving a vitamin K antagonist, as compared with 77% in ACTIVE W. Therefore, the decision to enroll a patient in ACTIVE A or ACTIVE W was generally consistent with a preexisting clinical judgment.

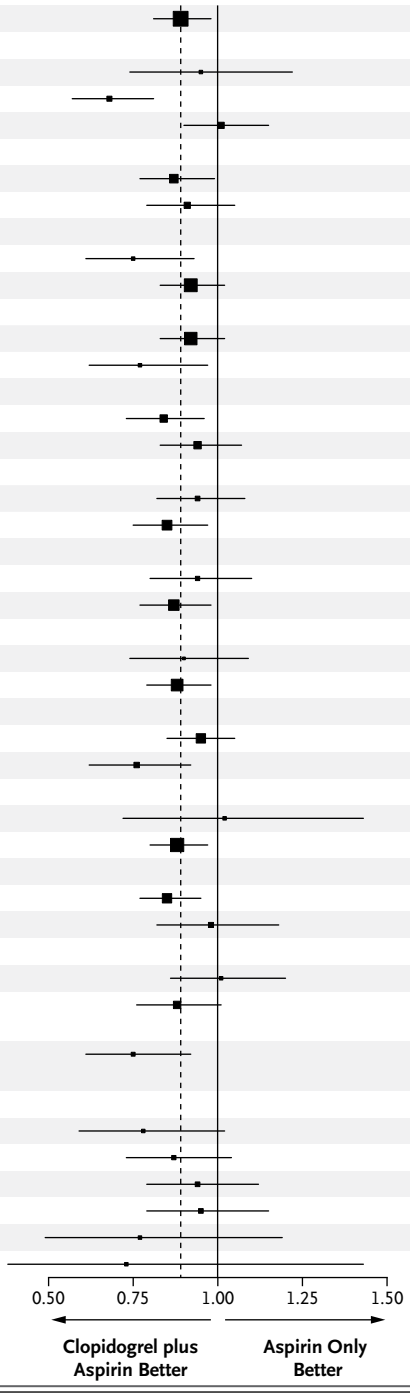
In ACTIVE W, therapy with a vitamin K antago-

Figure 2 (see next page). Relative Risks for Various Subgroups, According to Treatment Group.

Panel A shows the relative risk of the primary outcome (stroke, myocardial infarction, non–central nervous system systemic embolism, or death from vascular causes) with clopidogrel plus aspirin as compared with aspirin alone in prespecified and other subgroups of interest. Panel B shows the relative risk of stroke with clopidogrel plus aspirin as compared with aspirin alone in the same subgroups. In each panel, the size of the square is proportionate to the number of patients in the subgroup who had an occurrence of the end point; the horizontal lines indicate the 95% confidence intervals. The dashed vertical line indicates the overall relative risk reduction for the entire trial cohort. Also shown are P values for the test of an interaction between the outcome and the treatment group within each subgroup. The risk of stroke was assessed by means of the $CHADS_2$ score, which reflects the risk of stroke in patients with atrial fibrillation, with values ranging from 0 to 6 and higher scores indicating an increased risk. Vitamin K antagonist (VKA) therapy was therapy received before, not during or after, trial enrollment. Data were not available for some patients in some subgroups. CAD denotes coronary artery disease, and MI myocardial infarction.

A

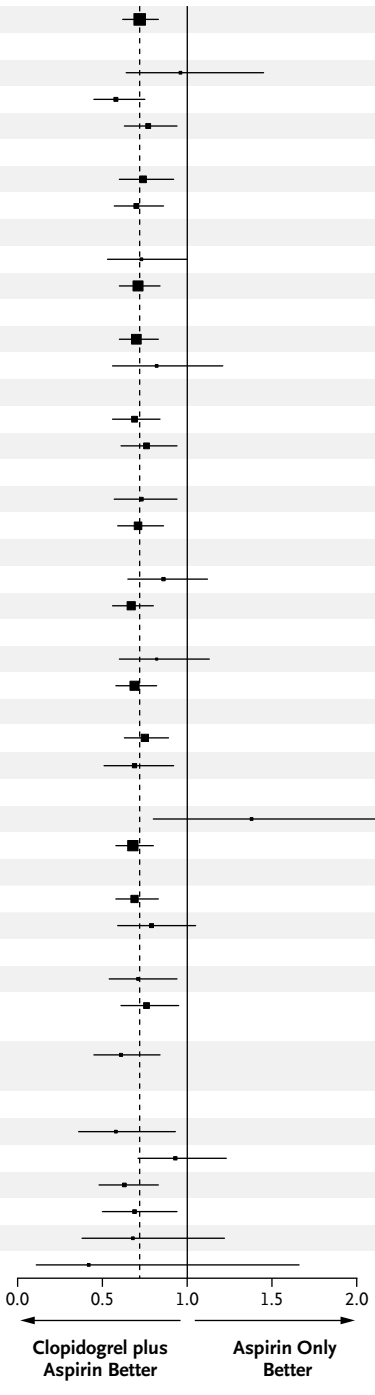
Subgroup	Total No. of Patients	Clopidogrel plus Aspirin %/yr	Aspirin Only %/yr	P Value for Interaction
Overall	7554	6.75	7.60	
Age				0.001
<65 yr	1866	3.70	3.87	
65–74 yr	2549	5.03	7.38	
≥75 yr	3138	10.56	10.41	
Sex				0.71
Male	4397	6.32	7.23	
Female	3157	7.38	8.13	
Stroke or TIA				0.09
Yes	992	9.98	13.42	
No	6561	6.29	6.87	
Hypertension				0.17
Yes	6427	6.62	7.24	
No	1125	7.48	9.77	
Systolic blood pressure				0.22
≥136 mm Hg	3771	6.04	7.24	
<136 mm Hg	3777	7.49	7.99	
Congestive heart failure				0.29
Yes	2496	10.49	11.17	
No	5054	5.11	6.02	
MI or CAD				0.44
Yes	2208	8.77	9.40	
No	5345	5.97	6.88	
Diabetes				0.85
Yes	1462	8.51	9.48	
No	6089	6.34	7.18	
$CHADS_2$ score				0.0499
>1	4645	9.02	9.58	
1	2698	3.64	4.82	
VKA therapy				0.49
Yes	645	5.88	5.88	
No	6906	6.83	7.78	
Atrial fibrillation				0.19
Permanent	4814	7.84	9.20	
Persistent or paroxysmal	2723	4.97	5.07	
Reason for enrollment in ACTIVE A				0.07
Risk of bleeding	1731	10.76	10.62	
Physician's judgment that VKA inappropriate	3757	6.03	6.91	
Patient's preference not to take VKA, only reason	1964	4.90	6.57	
Region				0.75
North America	738	7.57	9.69	
Western Europe and Israel	2331	6.36	7.34	
Eastern Europe	2473	5.70	6.05	
South America	1562	8.76	9.28	
Asia–Pacific	322	6.40	8.29	
South Africa	128	7.21	10.13	



nist reduced the rate of stroke by 42% as compared with therapy with clopidogrel plus aspirin. This reduction is similar to the 38% reduction in the rate of stroke with vitamin K antagonists as compared with aspirin alone, reported in the meta-analysis of warfarin trials.[2] These two findings, taken together, would seem to suggest that there should be little or no difference in efficacy between clopidogrel plus aspirin and aspirin alone, a conclusion that is inconsistent with the

B

Subgroup	Total No. of Patients	Clopidogrel plus Aspirin %/yr	Aspirin Only	P Value for Interaction
Overall	7554	2.37	3.31	
Age				0.08
<65 yr	1866	1.34	1.40	
65–74 yr	2549	2.08	3.61	
≥75 yr	3138	3.37	4.40	
Sex				0.70
Male	4397	1.91	2.58	
Female	3157	3.03	4.33	
Stroke or TIA				0.94
Yes	992	4.52	6.30	
No	6561	2.07	2.93	
Hypertension				0.46
Yes	6427	2.33	3.33	
No	1125	2.60	3.20	
Systolic blood pressure				0.54
≥136 mm Hg	3771	2.43	3.55	
<136 mm Hg	3777	2.30	3.07	
Congestive heart failure				0.86
Yes	2496	2.85	3.90	
No	5054	2.16	3.05	
MI or CAD				0.13
Yes	2208	2.81	3.29	
No	5345	2.20	3.32	
Diabetes				0.31
Yes	1462	3.14	3.80	
No	6089	2.19	3.20	
$CHADS_2$ score				0.62
>1	4645	2.98	4.00	
1	2698	1.64	2.40	
VKA therapy				0.02
Yes	645	2.70	1.99	
No	6906	2.34	3.45	
Atrial fibrillation				0.44
Permanent	4814	2.75	3.98	
Persistent or paroxysmal	2723	1.76	2.23	
Reason for enrollment in ACTIVE A				0.56
Risk of bleeding	1731	3.31	4.62	
Physician's judgment that VKA inappropriate	3757	2.16	2.88	
Patient's preference not to take VKA, only reason	1964	1.86	3.05	
Region				0.35
North America	738	2.10	3.61	
Western Europe and Israel	2331	2.59	2.78	
Eastern Europe	2473	1.99	3.14	
South America	1562	2.63	3.90	
Asia–Pacific	322	3.49	5.12	
South Africa	128	1.44	3.37	



significant 28% reduction in the risk of stroke shown in ACTIVE A. However, most patients in ACTIVE W (77%) had previously been treated with a vitamin K antagonist. Among the patients in ACTIVE W who were not receiving a vitamin K antagonist at the time of enrollment, the reduction in the rate of stroke was only 29%.

In conclusion, we found that treatment with

clopidogrel plus aspirin, as compared with aspirin alone, reduced the rate of major vascular events among patients with atrial fibrillation who were at increased risk for stroke and for whom therapy with a vitamin K antagonist was considered to be unsuitable. This reduction was primarily due to a reduction in the risk of stroke. There was a significant increase in the risk of major hemorrhage.

Supported by grants from Sanofi-Aventis and Bristol-Myers Squibb.

Dr. Connolly reports receiving consulting fees, lecture fees, and grant support from Sanofi-Aventis, Bristol-Myers Squibb, and Boehringer Ingelheim and grant support from Portola Pharmaceuticals; Dr. Hohnloser, consulting fees, lecture fees, and grant support from Sanofi-Aventis and Bristol-Myers Squibb, consulting fees from Cardiome and ARYx Therapeutics, and lecture fees and grant support from St. Jude Medical; Dr. Pfeffer, consulting fees and grant support from Sanofi-Aventis and Bristol-Myers Squibb; Dr. Yusuf, consulting fees, lecture fees, and grant support from Sanofi-Aventis and Bristol-Myers Squibb, consulting fees and lecture fees from AstraZeneca and Boehringer Ingelheim, and lecture fees and grant support from GlaxoSmithKline. No other potential conflict of interest relevant to this article was reported.

APPENDIX

The ACTIVE committee members and investigators are as follows: **Operations Committee:** S.J. Connolly (principal investigator), S. Yusuf (steering committee chair), J. Camm, S. Chrolavicius (project manager), P. Commerford, M. Flather, R.G. Hart, S.H. Hohnloser, C. Joyner (chair of event adjudication committee), M. Pfeffer, C. Gaudin (sponsor representative), M. Blumenthal (sponsor representative), C. Marchese (sponsor representative); **Writing Group**: S.J. Connolly, J. Pogue, S. Chrolavicius, R. Hart, M. Pfeffer, S. Hohnloser, S. Yusuf; **Steering Committee:** I. Anand, H. Arthur, A. Avezum, A. Budaj, L. Ceremuzynski, R. De Caterina, R. Diaz, P. Dorian, G. Flaker, K.A.A. Fox, M.G. Franzosi, S. Goldhaber, S. Golitsyn, C. Granger, D. Halon, A. Hermosillo, D. Hunt, P. Jansky, N. Karatzas, M. Keltai, O. Kozan, F. Lanas, C.P. Lau, J.Y. Le Heuzey, B.S. Lewis, J. Morais, C. Morillo, E. Paolasso, R.J. Peters, M. Pfisterer, L. Piegas, A. Pipilis, E. Sitkei, K. Swedberg, M. Talajic, V. Valentin, W. Van Mieghem, J. Varigos, plus members of the operations committee; **Events Adjudication Committee:** S. Ameriso, M. Atra, A. Avezum, O. Berwanger, C. Bonilla, N. Bornstein, A. Budaj, T. Chamiec, Y.K. Chan, Y. Cottin, L. Csiba, J. Cybulski, A. Czepiel, H. De Raedt, R. Diaz, H. Dvorakova, J. Eikelboom, O. Ergene, G. Fodor, M. Galli, E. Gardinale, S. Golitsyn, C. Granger, B. Gross, P. Goodfield, D. Halon, O. Happola, J. Healey, D. Himbert, D. Hunt, F. Jacobsson, P. Jansky, P. Kalvach, N. Karatzas, M. Keltai, B. Kies, M. Laine, A. Lam, J.Y. Le Heuzey, B.S. Lewis, S. Lewis, D. Leys, A.P. Maggioni, A. Massaro, B.M. Mayosi, B. Norrving, T. Okay, L. Olah, J.O. Osende, A. Oto, A. Peeters, M. Penicka, A. Perakis, L. Piegas, A. Pipilis, G. Pizzolato, F. Rafti, J. Renkin, A. Siva, P.G. Steg, B. Stockins, E. Strozynska, K. Swedberg, F. Turazza, L. Vanderhoven, S. Vizel, P. Widimsky, J. Zaborski; **Stroke Advisory Committee:** G. Albers, G. Hankey, R.G. Hart, B. Norrving, A. Shuaib, J. Silva; **Data Safety Monitoring Board:** D.G. Wyse (chair) J.A. Cairns, M. Gent, J. Hirsh, J. Marler, E. Pritchett, J. Wittes; **Project Office:** H. Beresh (research coordinator), L. Floyd, Z. Gasic, I. Holadyk-Gris, M. Lawrence (events adjudication coordinator), I. Moro, S. Perry, J. Roberts, T. Rodrigues, L. Robinson, C. Stevens, L. Worthy, F. Yuan; **Investigators who recruited at least 3 patients** (number of patients enrolled in each country): *Argentina* (517): R.A. Ahuad Guerrero, O. Allall, L.M. Amuchastegui, M. Boskis, M.H. Bustamante Labarta, C.R. Castellanos, P. Chiale, C.A. Cuneo, A. Czcczuo, A.J. Gabito, M. Garrido, L.A. Guzmán, E.G. Hasban, A.R. Hershson, M.A. Hominal, J.G. Krauss, H.L. Luciardi, E.M. Marzetti, O.R. Montaña, R.F. Rabinovich, H.R. Ramos, A.S. Sanchez, P.O. Schygiel, G.M. Sumay, D.R. Vogel, C.J. Zaidman; *Australia* (182): G.M. Aroney, D.T. Ashby, M.A. Barlow, P. Cooke, D.B. Cross, M.A. Fitzpatrick, P. Garrahy, J. Karrasch, G.I. Nelson, D. Rees, S.D. Roger, J. Rogers, B.B. Singh, J.F. Stickland, J.H. Waites, W.F. Walsh; *Austria* (55): J. Eichinger, K. Huber, F. Leisch; *Belgium* (119): J. Boland, V.M. Conraads, F.J.C. Cools, L. De Roy, D. El Allaf, G.H. Mairesse, B. Vankelecom; *Brazil* (662): J. Abrantes, D. Armaganijan, J. Atié, C. Blacher, L.C. Bodanese, J.C.F. Braga, M.V. Braile, H. Chaves, O.R. Coelho, C.L.P. Cunha, G.G. De Lima, A.A.V. de Paola, J.P. Esteves, A. Francischetti, A.E. Francischetti, A.M. Lorga-Filho, L.N. Maia, D.M. Marcussi, J.A. Marin-Neto, Z.M. Meneghelo, R. Mourilhe Rocha, P.R. Nogueira, W. Oigman, M. Paiva, D.B. Précoma, W. Rabelo, A. Rabelo, Jr., S. Rassi, A. Rassi, Jr., G. Reis, P.R. Rossi, J.M. Rossi Neto, J.K. Saraiva, D.C. Sobral-Filho, S.L. Zimmermann; *Canada* (304): T.A. Ashton, R. Bhargava, S. Carroll, R. Chehayeb, S.P. Connors, C. Constance, P. Costi, B. Coutu, E. Crystal, J.D. Douketis, C. Fortin, B.A. Fox, M.K. Gupta, A.D. Krahn, R. Kuritzky, K. Kwok, R. Leader, P. Ma, I. Mangat, C.R. Maranda, M.F. Matangi, G. Moddel, A. Mukherjee, S. Nawaz, M. Palaic, A.S. Pandey, T.M. Rebane, M. Ruel, J.L. Sapp, M.P. Senaratne, R. St-Hilaire, P. Talbot, T.B. To, M. Vakani, M.A. Weigel, Z. Wulffhart, L. Yao, D. Zaniol; *Chile* (160): C.R. Conejeros, R. Corbalán, G.R. Dussaillant, E. Escobar, M.E. Hassi, C.A. Parra, B.A. Varleta; *Czech Republic* (426): L. Berka, V. Dedek, J. Florian, O. Hejhal, M. Herold, Z. Klimsa, I. Kotik, J. Simon, K. Smetana, J. Spinar, L. Špinarová, F. Tousek; *Denmark* (39): S. Husted, T. Nielsen, S. Pehrson, C. Tuxen; *Finland* (58): V.P. Harjola, H.V. Huikuri, R.V.J. Kettunen, J.H. Melin, K. Peuhkurinen; *France* (171): R. Carlioz, D. Coisne, E. Decoulx, P. Defaye, J.M. Demarcq, K. Gacem, D.L. Galley, H.M. Lardoux, P. Mabo, M. Mansour, T.G. Olive, J.E. Poulard, C.F. Pruvot, J.L. Rey; *Germany* (747): W.R. Bauer, G. Baumann, G. Berghöfer, G. Boehm, M.M. Borggrefe, G. Brücker, H. Darius, G.Z. Duray, S.B. Felix, P. Fink, H. Fritz, R. Haberl, S. Hoffmann, T. Horacek, D.W. Kalusche, W. Kasper, H.A. Katus, H.H. Klepzig, U. Loos, R. Merher, T. Munzel, J. Neuzner, H.R. Ochs, B. Pieske, B.W. Pollock, A. Schmidt, M. Schumacher, K. Seidl, U. Speier, S.G. Spitzer, G. Stenzel, H. Volkmann, J. Wunderlich, U. Zacharzowsky; *Greece* (91): H. Antonakoudis, N. Georgakopoulos, J.A. Goudevenos, T.A. Iliopoulos, I. Kallikazaros, V.N. Pyrgakis, P. Skoufas; *Hong Kong* (86): W.K. Chan, H.W. Chan, J.W.H. Fung, S.K. Li, K.S. Wong; *Hungary* (218): T. Forster, P. Kárpáti, K. Keltai, A. Kovacs, G. Kurta, Z. Laszlo, J. Rapi, L. Regos, L. Rostas, I. Szakál, J. Tomcsanyi, C. Toth; *Israel* (124): L. Bloch, N. Khader, E. Klainman, D. Koukoui, C. Lotan, A. Marmor, M.Z. Omary, L.H. Reisin, Z. Vered, D. Zeltser, R. Zimlichman; *Italy* (291): L. Bianconi, D. Bicego, D. Cosmi, F. Filigheddu, A. Garini, M. Lunati, L. Moretti, L. Mos, A.E. Pontiroli, G. Renda, S. Ricci, P. Rossi, M. Santonastaso, G.A. Scioli, M. Stramba-Badiale, P. Terrosu; *Malaysia* (26): R. Omar, T.K. Ong, W.A. Wan Ahmad; *Mexico* (223): R. Alvarado, C. Calvo, J.A. Cordero-Cabra, I. Hernández, C. Jerjes-Sanchez, S. Lara, E. Lopez Rosas, L. Molina, E. Morales, F. Petersen-Aranguren, E.M. Picos Bovio, G. Pozas, F.J. Robles Torres; *the Netherlands* (101): K. Holwerda, D.J.A. Lok, R. Nierop, M.G.C. Pieterse, R. van der Heijden, L. van Kempen; *Norway* (34): B.K. Oie, T.M. Omland, J. Otterstad, C. von Brandis; *Poland* (1061): M. Bronisz, K. Chizynski, T. Czerski, M. Dluzniewski, J. Gessek, A. Gieroba, J.R. Gniot, J. Gorny, H. Halaczuiewicz, K. Janik, M. Janion, O. Jerzykowska, T. Kawka-Urbanek, K. Kincel, S. Kocon, J. Kopaczewski, W. Krasowski, M. Makuch, S. Malinowski, Z. Miastkowski, M. Mickiewicz-Pawlowska, P. Miekus, E. Obrebska-Tabaczka, M. Ogorek, E. Piasecka-Krysiak, A.W. Piepiorka, W. Piotrowski, W. Pluta, E. Puzio, J. Rekosz, W. Sinkiewicz, M. Stopinski, R. Szelemej, M. Tendera, M. Trusz-Gluza, M. Wilkoszynski, B. Zalska; *Portugal* (46): E. Antunes, M.O. Carrageta, J. de Sousa, L. Martins, M.I. Mendonca, I. Sil-

vestre; *Russia* (655): E.V. Akatova, V. Aleksandrov, E.A. Antuch, G. Arutyunov, B. Bart, Y.B. Belousov, I.I. Chernichka, P. Dovgalevsky, N. Gratsiansky, A.Y. Ivleva, O.A. Kislyak, V.Y. Mareyev, E.B. Maykov, V. Milyagin, T.N. Novikova, E.P. Panchenko, O. Reshetko, E. Semernin, B.A. Sidorenko, A. Sinopalnikov, V. Skvortsova, A. Solomatin, T.S. Sukhinina, Z.A. Suslina, Y. Titkov, V. Tsyrline; *Singapore* (38): B. Chan, D. Foo, A.R. Omar, W.S. Teo; *South Africa* (128): B.G. Brown, I.O. Ebrahim, G.J. Gibson, E. Klug, J.D. Marx, P.S. Mntla, A. Okreglicki, M. Pretorius, J.S. Roos, F. Snyders, L.J. van Zyl; *Spain* (80): L. Cano, J. Garcia-Puig, A. Hernandez-Madrid, J.M. Mostaza, M.D. Orriach, X. Sabate, X. Viñolas; *Sweden* (98): P. Blomström, F. Jacobsson, L. Johansson, L. Klintberg, M. Lycksell, O. Nilsson, G. Rasmanis, K.E. Saldeen Nilehn, G. Ulvenstam; *Switzerland* (37): R.W. Baumgartner, M. François, A. Gallino, T. Moccetti, B.E. Tettenborn; *Taiwan* (172): H.-T. Chou, J.-Y. Kuo, W.-T. Lai, J.L. Lin, L.-J. Lin, D.-F. Yeih; *Turkey* (22): M. Bakar, B. Ilerigelen, E. Kumral, Y. Nisanci, Z.I. Savas; *United Kingdom* (149): Y. Adgey, M.J. Brack, J. Cleland, P.P. Davey, J. Davies, S.K. Glen, K. Jennings, T. Levy, G.Y.H. Lip, A.J. Moriarty, C. Pearson, J.A. Purvis, M.P. Pye, I. Savelieva, R. Senior, T.G. Trouton; *United States* (434): I.S. Ahmed, M. Amin, J.L. Anderson, R.A. Bauernfeind, K. Belew, S.D. Bilazarian, R.A. Black, M.E. Burton, J.E. Cebe, Y.S. Chandrashekhar, C. Chen, D. Das, D.M. Denny, V. Desai, R.N. Fahmy, G.J. Fishbein, M.D. Gelernt, J. Gerber, M.C. Goldberg, P.G. Grena, M.B. Honan, J.J. Hunter, J. Jacobson, N.F. Jarmukli, K. Klancke, J.F. Kobayashi, S.J. Lewis, T. Little, I. Mallis, A.M. Marani, J.J. Marshall, P. Meltzer, F.J. Menapace, P.G. O'Neill, D.J. Pearce, A. Quick, S. Ravipudi, M. Sackett, D.M. Salerno, A. Schussheim, K. Sheikh, U.R. Shettigar, C.B. Treasure, H. Vidaillet, N. Vijay, D. Wagner, J.L. Walker, S.L. Winters, D.R. Young, R.G. Zoble.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.

2. 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.

3. van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. JAMA 2002;288:2441-8.

4. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edition). Chest 2008;133:Suppl:546S-592S.

5. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation — executive summary: 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). J Am Coll Cardiol 2006;48:854-906. [Erratum, J Am Coll Cardiol 2007;50:562.]

6. Connolly SJ, Eikelboom J, O'Donnell M, Pogue J, Yusuf S. Challenges of establishing new antithrombotic therapies in atrial fibrillation. Circulation 2007;116:449-55.

7. Hylek EM, D'Antonio J, Evans-Molina C, Shea C, Henault LE, Regan S. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke 2006;37:1075-80.

8. 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.

9. Waldo AL, Becker RC, Tapson VF, Colgan KJ. Hospitalized patients with atrial fibrillation and a high risk of stroke are not being provided with adequate anticoagulation. J Am Coll Cardiol 2005;46:1729-36.

10. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. Ann Intern Med 1999;131:927-34.

11. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494-502.

12. ACTIVE Writing Group of the ACTIVE Investigators. 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.

13. Connolly SJ, Yusuf S, Budaj A, et al. Rationale and design of ACTIVE: the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events. Am Heart J 2006;151:1187-93.

14. Cannon CP, Battler A, Brindis RG, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes: a report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). J Am Coll Cardiol 2001;38:2114-30.

15. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607-21.

16. Watson T, Shantsila E, Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. Lancet 2009;373:155-66.

17. Mitusch R, Siemens HJ, Garbe M, Wagner T, Sheikhzadeh A, Diederich KW. Detection of a hypercoagulable state in nonvalvular atrial fibrillation and the effect of anticoagulant therapy. Thromb Haemost 1996;75:219-23.

18. Lip GY, Lowe GD, Rumley A, Dunn FG. Increased markers of thrombogenesis in chronic atrial fibrillation: effects of warfarin treatment. Br Heart J 1995;73:527-33.

19. Li-Saw-Hee FL, Blann AD, Lip GY. Effects of fixed low-dose warfarin, aspirin-warfarin combination therapy, and dose-adjusted warfarin on thrombogenesis in chronic atrial fibrillation. Stroke 2000;31:828-33.

20. Atalar E, Haznedaroglu IC, Acil T, et al. Patients with paroxysmal atrial fibrillation but not paroxysmal supraventricular tachycardia display evidence of platelet activation during arrhythmia. Platelets 2003;14:407-11.

21. Yamauchi K, Furui H, Taniguchi N, Sotobata I. Plasma beta-thromboglobulin and platelet factor 4 concentrations in patients with atrial fibrillation. Jpn Heart J 1986;27:481-7.

22. Heeringa J, Conway DS, van der Kuip DA, et al. A longitudinal population-based study of prothrombotic factors in elderly subjects with atrial fibrillation: the Rotterdam Study 1990–1999. J Thromb Haemost 2006;4:1944-9.

23. Kamath S, Chin BS, Blann AD, Lip GY. A study of platelet activation in paroxysmal, persistent and permanent atrial fibrillation. Blood Coagul Fibrinolysis 2002;13:627-36.

24. Helgason CM, Hoff JA, Kondos GT, Brace LD. Platelet aggregation in patients with atrial fibrillation taking aspirin or warfarin. Stroke 1993;24:1458-61.

25. Müller I, Massberg S, Zierhut W, et al. Effects of aspirin and clopidogrel versus oral anticoagulation on platelet function and on coagulation in patients with nonvalvular atrial fibrillation (CLAFIB). Pathophysiol Haemost Thromb 2002;32:16-24.