JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 64, NO. 15, 2014

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jacc.2014.07.967

ORIGINAL INVESTIGATIONS

Amiodarone, Anticoagulation, and Clinical Events in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial

Greg Flaker, MD,* Renato D. Lopes, MD, PhD,† Elaine Hylek, MD, MPH,‡ Daniel M. Wojdyla, MS,† Laine Thomas, PhD,† Sana M. Al-Khatib, MD, MHS,† Renee M. Sullivan, MD,* Stefan H. Hohnloser, MD,§ David Garcia, MD,‖ Michael Hanna, MD,¶ John Amerena, MBBS,# Veli-Pekka Harjola, MD, PhD,** Paul Dorian, MD,†† Alvaro Avezum, MD, PhD,‡‡ Matyas Keltai, MD, DSc,§§ Lars Wallentin, MD, PhD,‖‖ Christopher B. Granger, MD,† for the ARISTOTLE Committees and Investigators

ABSTRACT

BACKGROUND Amiodarone is an effective medication in preventing atrial fibrillation (AF), but it interferes with the metabolism of warfarin.

OBJECTIVES This study sought to examine the association of major thrombotic clinical events and bleeding with the use of amiodarone in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.

METHODS Baseline characteristics of patients who received amiodarone at randomization were compared with those who did not receive amiodarone. The interaction between randomized treatment and amiodarone was tested using a Cox model, with main effects for randomized treatment and amiodarone and their interaction. Matching on the basis of a propensity score was used to compare patients who received and who did not receive amiodarone at the time of randomization.

RESULTS In ARISTOTLE, 2,051 (11.4%) patients received amiodarone at randomization. Patients on warfarin and amiodarone had time in the therapeutic range that was lower than patients not on amiodarone (56.5% vs. 63.0%; $p < 0.0001$). More amiodarone-treated patients had a stroke or a systemic embolism (1.58%/year vs. 1.19%/year; adjusted hazard ratio [HR]: 1.47, 95% confidence interval [CI]: 1.03 to 2.10; $p = 0.0322$). Overall mortality and major bleeding rates were elevated, but were not significantly different in amiodarone-treated patients and patients not on amiodarone. When comparing apixaban with warfarin, patients who received amiodarone had a stroke or a systemic embolism rate of 1.24%/year versus 1.85%/year (HR: 0.68, 95% CI: 0.40 to 1.15), death of 4.15%/year versus 5.65%/year (HR: 0.74, 95% CI: 0.55 to 0.98), and major bleeding of 1.86%/year versus 3.06%/year (HR: 0.61, 95% CI: 0.39 to 0.96). In patients who did not receive amiodarone, the stroke or systemic embolism rate was 1.29%/year versus 1.57%/year (HR: 0.82, 95% CI: 0.68 to 1.00), death was 3.43%/year versus 3.68%/year (HR: 0.93, 95% CI: 0.83 to 1.05), and major bleeding was 2.18%/year versus 3.03%/year (HR: 0.72, 95% CI: 0.62 to 0.84). The interaction p values for amiodarone use by apixaban treatment effects were not significant.

CONCLUSIONS Amiodarone use was associated with significantly increased stroke and systemic embolism risk and a lower time in the therapeutic range when used with warfarin. Apixaban consistently reduced the rate of stroke and systemic embolism, death, and major bleeding compared with warfarin in amiodarone-treated patients and patients who were not on amiodarone. (J Am Coll Cardiol 2014;64:1541–50) © 2014 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

$CHADS_2$ = congestive heart failure, hypertension, age, diabetes, and stroke

CI = confidence interval

HR = hazard ratio

INR = international normalized ratio

LVEF = left ventricular ejection fraction

MI = myocardial infarction

TIA = transient ischemic attack

TTR = time in therapeutic range

Amiodarone is the most effective antiarrhythmic drug for the prevention of atrial fibrillation (AF) (1–3), and it is recommended for patients with frequent, symptomatic AF recurrences, especially in the presence of structural heart disease (4). However, several potential drawbacks may limit the use of amiodarone in patients with AF.

SEE PAGE 1551

Warfarin is prescribed frequently to prevent stroke in patients with AF. Because amiodarone interferes with warfarin metabolism through the CYP 2C9 pathway, the international normalized ratio (INR) values are more difficult to maintain in a therapeutic range of 2 to 3 (5–8). This leads to a suboptimal time in the therapeutic range (TTR), which is associated with increased clinical events (9,10). Noncardiovascular side effects are also concerns with amiodarone. In addition to well-known hepatic, thyroid, neurologic, and ophthalmologic side effects, amiodarone occasionally causes pulmonary toxicity, which may be life-threatening (11,12), and it has also been associated with an increased risk of cancer (13–15). An analysis from the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) study noted excess noncardiovascular deaths with amiodarone (16).

We studied the effects of amiodarone on outcomes in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. The first set of objectives compared the effects of randomized apixaban or warfarin treatment on stroke and systemic embolism, death, and bleeding events in relation to amiodarone use at the time of randomization. In the second set of objectives, we compared the rates of cardiovascular death and noncardiovascular death in relation to amiodarone use.

METHODS

STUDY POPULATION. The design and results of the ARISTOTLE trial have been reported (17,18). Patients eligible for this study had AF documented on 2 occasions, at least 2 weeks apart within the 12 months before enrollment. AF was documented by electrocardiogram or rhythm strip, Holter monitor, or intracardiac recording, and lasted >1 minute. In addition, at least 1 of the following risk factors for stroke was required: age ≥75 years; previous stroke, transient ischemic attack (TIA), or systemic embolism; symptomatic heart failure within the previous 3 months or left ventricular ejection fraction (LVEF) ≤40%; and diabetes or hypertension requiring

From the *University of Missouri, Columbia, Missouri; †Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; ‡Boston University Medical Center, Boston, Massachusetts; §J.W. Goethe-University, Frankfurt, Germany; ||Division of Hematology, University of Washington, Seattle, Washington; ¶Bristol-Myers Squibb, Princeton, New Jersey; #Geelong Cardiology Research Center, Deakin University, Victoria, Australia; **Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland; ††St. Michael's Hospital, Toronto, Ontario, Canada; ‡‡Danta Pazzanese Institute of Cardiology, São Paulo, Brazil; §§Hungarian Institute of Cardiology, Semmelweis University, Budapest, Hungary; and the ||||Cardiology and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden. This study was sponsored by Bristol-Myers Squibb and Pfizer. Dr. Flaker has received grants from Boehringer Ingelheim and Sanofi Aventis; and consulting fees from Bristol-Myers Squibb, Boehringer Ingelheim, Pfizer, Daiichi Sankyo, and Sanofi-Aventis. Dr. Lopes has received grants from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, and Daiichi Sankyo; and consulting fees from Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, GlaxoSmithKline, and Pfizer. Dr. Hylek has received consulting fees and honoraria from Bristol-Myers Squibb, Daiichi Sankyo, Boehringer Ingelheim, Johnson & Johnson, Pfizer, and Bayer; research grants from Bristol-Myers Squibb; and is a member of the advisory boards for Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Janssen, Pfizer, and Roche. Dr. Hohnloser has received grants from Sanofi Aventis and St. Jude Medical; consulting fees from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Boston Scientific, Cardiome, Gilead, Johnson & Johnson, Pfizer, Portola, Sanofi Aventis, Servier, St. Jude Medical, and Zoll; and lecture fees from Bayer Healthcare, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Sanofi Aventis, St. Jude Medical, and Medtronic. Dr. Garcia has received consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Pfizer, Bayer Healthcare, and CSL Behring; and fees for the development of educational materials from Boehringer Ingelheim. Dr. Harjola has received consulting fees from Bristol-Myers Squibb/Pfizer. Dr. Dorian has received consulting fees and honoraria from Sanofi Aventis, Bayer Healthcare, Bristol-Myers Squibb, Pfizer, Servier, and Boehringer Ingelheim. Dr. Avezum has received research grants from AstraZeneca, Bayer, Bristol-Myers Squibb, Pfizer, and Boehringer Ingelheim; and consulting fees and honoraria from AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, and Pfizer. Dr. Wallentin has received consulting fees and honoraria from Abbott, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Regado Biosciences, Boehringer Ingelheim, Athera Biotechnologies, and AstraZeneca; and research grants from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Merck/Schering-Plough, and Bristol-Myers Squibb/Pfizer. Dr. Granger has received research grants and consulting fees from Boehringer Ingelheim, Bristol-Myers Squibb, Bayer Healthcare, Daiichi Sankyo, Sanofi Aventis, and Pfizer. All other authors have reported that they have no relationships relevant to this paper to disclose.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

You can also listen to this issue's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received March 13, 2014; revised manuscript received June 17, 2014, accepted July 8, 2014.

pharmacological therapy. Key exclusion criteria were AF due to a reversible cause, moderate or severe mitral stenosis, conditions other than AF that required anticoagulation (e.g., a prosthetic heart valve), stroke within the previous 7 days, need for aspirin >165 mg/day or for both aspirin and clopidogrel, and renal insufficiency with a creatinine level >2.5 mg/dl or a creatinine clearance of <25 ml/min.

RANDOMIZATION. Patients were randomized to receive either warfarin or apixaban. Warfarin was adjusted to achieve a target INR of 2.0 to 3.0. Apixaban was administered in doses of 5 mg twice daily or 2.5 mg twice daily in patients with 2 of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dl.

CLINICAL OUTCOMES. The primary efficacy outcome of the study was stroke, which as defined as the abrupt onset of a nontraumatic, focal neurological deficit lasting at least 24 h, or systemic embolism, which was defined as symptoms consistent with acute loss of blood to a noncerebral artery confirmed by autopsy, angiography, vascular imaging, or some other objective testing. Secondary endpoints included myocardial infarction (MI) and death. Death was classified as cardiovascular (stroke, systemic embolism, MI, sudden death, heart failure, or indeterminate) or noncardiovascular (bleeding, malignancy, infection, trauma, pulmonary). The primary safety outcome was International Society of Thrombosis and Hemostasis major bleeding, which was defined as 1) bleeding that resulted in a decrease in hemoglobin of ≥2 g/dl over a 24-h period; 2) bleeding leading to a transfusion of ≥2 units of packed red blood cells; 3) bleeding occurring in a critical site; or 4) bleeding leading to death. A clinical events committee blinded to treatment assignment adjudicated all primary and secondary outcomes.

STATISTICAL ANALYSIS. The baseline characteristics of those patients who received amiodarone at the time of randomization were compared with those who did not receive amiodarone. Continuous characteristics are reported as medians and 25th and 75th percentiles and compared using the Wilcoxon rank-sum test. Categorical variables are reported as frequencies and percentages and compared using chi-square tests. Events are summarized as rates per 100 patient-years of follow-up and the number of events. Kaplan-Meier curves were used to graphically describe the incidence of the primary efficacy and safety events by randomized treatment and amiodarone use at randomization. Hazard ratios (HRs) that compared randomized treatments (apixaban vs. warfarin) in patients on or off amiodarone were derived from Cox proportional hazards models. The interaction between randomized treatment and amiodarone was tested using a Cox model, with main effects for randomized treatment and amiodarone and their interaction. Propensity score–based matching was used to compare patients on and off amiodarone at the time of randomization. Variables included in the propensity score were selected from 35 baseline patient characteristics believed to be important in the selection of antiarrhythmic drug therapy. Candidate variables for inclusion in the propensity analysis were 1) demographic characteristics, including age, sex, and country of enrollment; 2) medical conditions, including a history of MI, coronary artery disease, pulmonary disease, intracranial bleeding, congestive heart failure, cardiomyopathy, valvular heart disease, congenital heart disease, unstable angina, diabetes mellitus, hepatic or renal disease, ventricular fibrillation and/or ventricular tachycardia cardiac arrest, stroke and/or TIA, peripheral artery disease, noncerebral thromboembolic event, and either carotid stent or carotid endarterectomy; 3) characteristics of AF or flutter, including duration of most recent episode; 4) findings on physical examination, including systolic blood pressure and body mass index; and 5) medications at the time of randomization, including beta-blockers and diuretics. Each patient on amiodarone was matched with 3 patients not on amiodarone enrolled in the same country. Countries where amiodarone was rarely or never used (≤3 patients) were excluded from this analysis (Finland, Malaysia, Norway, Puerto Rico, Singapore, and Turkey). Overall, 844 patients from these countries were excluded from this propensity analysis. Finally, to ensure that treatment effects with amiodarone did not vary between randomized therapies, the tests of interactions between amiodarone and randomized therapy were repeated with propensity-matched samples.

All statistical analyses were performed with SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina) and R version 3.0.1 (Vienna, Austria).

RESULTS

There were 18,201 patients enrolled in ARISTOTLE. Amiodarone status was known at randomization in 17,907 patients; 2,051 (11%) patients received amiodarone at randomization and 15,856 patients did not receive amiodarone. The mean follow-up was 21.7 months for amiodarone patients and 21.8 months for patients not on amiodarone.

There were marked geographic differences in the use of amiodarone. Amidarone use was 17.9% in Latin

TABLE 1 Baseline Characteristics of Patients Stratified by Amiodarone Use at Randomization and Study Drug Assignment

	Amiodarone			No Amiodarone			
	Overall (n = 2,051)	Apixaban (n = 1,009)	Warfarin (n = 1,042)	Overall (n = 15,856)	Apixaban (n = 7,954)	Warfarin (n = 7,902)	p Value*
Age, yrs	68 (60, 74)	68 (61, 74)	68 (60, 74)	70 (63, 76)	70 (63, 76)	70 (63, 76)	<0.0001
Age ≥75 yrs	481 (23.5)	228 (22.6)	253 (24.3)	5,102 (32.2)	2,569 (32.3)	2,533 (32.1)	<0.0001
Female	730 (35.6)	363 (36.0)	367 (35.2)	5,598 (35.3)	2,820 (35.5)	2,778 (35.2)	0.7980
Region							<0.0001
North America	291 (14.2)	151 (15.0)	140 (13.4)	291 (14.2)	2,071 (26.0)	2,065 (26.1)	
Latin America	614 (29.9)	303 (30.0)	311 (29.8)	614 (29.9)	1,412 (17.8)	1,395 (17.7)	
Europe	875 (42.7)	411 (40.7)	464 (44.5)	875 (42.7)	3,205 (40.3)	3,138 (39.7)	
Asia Pacific	271 (13.2)	144 (14.3)	127 (12.2)	271 (13.2)	1,266 (15.9)	1,304 (16.5)	
Systolic BP, mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	0.5417
Weight, kg	82 (71, 95)	82 (70, 95)	83 (71, 95)	82 (70, 96)	82 (70, 96)	82 (70, 96)	0.6567
BMI, kg/m^2	29 (25, 33)	29 (25, 33)	29 (25, 33)	28 (25, 33)	29 (25, 33)	28 (25, 33)	0.0702
Previous stroke, TIA, or SE	321 (15.7)	165 (16.4)	156 (15.0)	3,150 (19.9)	1,552 (19.5)	1,598 (20.2)	<0.0001
Previous stroke or TIA	310 (15.1)	160 (15.9)	150 (14.4)	3,059 (19.3)	128 (1.6)	1,556 (19.7)	<0.0001
Previous SE	26 (1.3)	11 (1.1)	15 (1.4)	240 (1.5)	2,745 (34.5)	112 (1.4)	0.3863
HF or reduced LVEF	911 (44.4)	435 (43.1)	476 (45.7)	5,438 (34.3)	2,745 (34.5)	2,693 (34.1)	<0.0001
LVEF, %	55 (42, 62)	55 (42, 62)	55 (42, 62)	56 (47, 64)	56 (47, 63)	56 (47, 64)	<0.0001
Previous MI	325 (15.9)	165 (16.4)	160 (15.4)	2,229 (14.1)	1,140 (14.3)	1,089 (13.8)	0.0288
PAD	91 (4.5)	46 (4.6)	45 (4.6)	786 (5.0)	391 (33.2)	395 (5.1)	0.3056
Documented history of CAD	761 (37.2)	372 (36.9)	389 (37.4)	5,202 (32.8)	2,636 (33.2)	2,566 (32.5)	<0.0001
NYHA functional class at screening							<0.0001
I	912 (44.5)	443 (43.9)	469 (45.1)	8,579 (54.2)	4,250 (53.5)	4,329 (54.9)	
II	839 (41.0)	415 (41.2)	424 (40.8)	5,708 (36.1)	2,899 (36.5)	2,809 (35.6)	
III	284 (13.9)	145 (14.4)	139 (13.4)	1,487 (9.4)	772 (9.7)	715 (9.1)	
IV	13 (0.6)	5 (0.5)	8 (0.8)	57 (0.4)	23 (0.3)	23 (0.3)	
Previous PCI	164 (8.0)	83 (8.2)	81 (7.8)	1468 (9.3)	749 (9.4)	719 (9.1)	0.0616
Previous CABG	109 (5.3)	59 (5.8)	50 (4.8)	1085 (6.8)	565 (7.1)	520 (6.6)	0.0090
Previous pacemaker/ICD/ resynchronization device	200 (9.8)	102 (10.1)	98 (9.4)	1,511 (9.5)	766 (9.6)	745 (9.4)	0.7478
Hypertension requiring treatment	1,819 (88.7)	900 (89.2)	919 (88.2)	13,885 (87.6)	6,946 (87.3)	6,939 (87.3)	0.1465
Hypertrophic cardiomyopathy	46 (2.2)	23 (2.3)	23 (2.2)	396 (2.5)	196 (2.5)	200 (2.5)	0.4874
Valvular heart disease	370 (18.1)	201 (20.0)	169 (16.2)	2,828 (17.8)	1,407 (17.7)	1,421 (18.0)	0.8147
Congenital heart disease	38 (1.9)	20 (2.0)	18 (1.7)	250 (1.6)	130 (1.6)	120 (1.5)	0.3476
Admitted with unstable angina	198 (9.7)	107 (10.6)	91 (8.7)	1,295 (8.2)	644 (8.1)	651 (8.2)	0.0213
Cardiac arrest (VT/VF)	23 (1.1)	10 (1.0)	13 (1.2)	121 (0.8)	60 (0.8)	61 (0.8)	0.0868
Previous clinically relevant or spontaneous bleeding	282 (13.8)	139 (13.8)	143 (13.7)	2,733 (17.2)	1,371 (17.2)	1,362 (17.2)	<0.0001
Previous intracranial bleeding	12 (0.6)	4 (0.4)	8 (0.8)	89 (0.6)	44 (0.6)	45 (0.6)	0.8914
History of fall within previous year	71 (4.0)	44 (5.0)	27 (3.0)	680 (4.7)	340 (4.7)	340 (4.7)	0.1740
History of pulmonary disease	354 (17.3)	168 (16.7)	186 (17.9)	3,007 (19.0)	1,507 (19.0)	1,500 (19.1)	0.0628
Diabetes	448 (21.8)	234 (23.2)	214 (20.5)	4,052 (25.6)	2,028 (25.5)	2,024 (25.6)	0.0003
History of thyroid disease	214 (10.5)	110 (10.9)	104 (10.0)	1,811 (11.4)	934 (11.8)	877 (11.1)	0.1894
Type of AF							<0.0001
Paroxysmal	701 (34.2)	343 (34.0)	358 (34.4)	2,035 (12.8)	1,006 (12.7)	1,029 (13.0)	
Persistent or permanent	1,350 (65.8)	666 (66.0)	684 (65.6)	13,818 (87.2)	6,946 (87.3)	6,872 (87.0)	
Time from first occurrence of AF, mo							<0.0001
<6	625 (30.6)	301 (29.9)	324 (31.2)	4,302 (27.2)	2,152 (27.1)	2,150 (27.3)	
6–24	437 (21.4)	207 (20.6)	230 (22.2)	3,016 (19.1)	1,533 (19.3)	1,483 (18.8)	
>24	983 (48.1)	499 (49.6)	484 (46.6)	8,487 (53.7)	4245 (53.5)	4,242 (53.9)	
Duration of most recent episode, day							<0.0001
<1	103 (5.1)	54 (5.5)	49 (4.8)	571 (3.6)	289 (3.6)	282 (3.6)	
1	422 (20.9)	214 (21.6)	208 (20.3)	1,889 (12.0)	957 (12.1)	932 (11.9)	
2–5	156 (7.7)	80 (8.1)	76 (7.4)	657 (4.2)	334 (4.2)	323 (4.1)	
6–13	111 (5.5)	54 (5.5)	57 (5.6)	618 (3.9)	328 (4.2)	290 (3.7)	
≥14	1,223 (60.7)	588 (59.4)	635 (62.0)	11,988 (76.2)	5,978 (75.8)	6,010 (76.7)	

Continued on the next page

TABLE 1 Continued

	Amiodarone			No Amiodarone			
	Overall (n = 2,051)	Apixaban (n = 1,009)	Warfarin (n = 1,042)	Overall (n = 15,856)	Apixaban (n = 7,954)	Warfarin (n = 7,902)	p Value*
History of cardioversion	449 (21.9)	233 (23.1)	216 (20.7)	1,346 (16.9)	1,278 (16.2)	<0.0001	
Previous use of VKA for >30 days	998 (48.7)	484 (48.0)	514 (49.3)	9,274 (58.5)	4,659 (58.6)	4,615 (58.4)	<0.0001
$CHADS_2$	2.0 ± 1.0	2.0 ± 1.0	2.0 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	2.1 ± 1.1	0.0003
$CHADS_2$ score							0.0008
≤1	734 (35.8)	351 (34.8)	383 (36.8)	5,317 (33.5)	2,674 (33.6)	2,643 (33.4)	
2	769 (37.5)	380 (37.7)	389 (37.3)	5,660 (35.7)	2,838 (35.7)	2,822 (35.7)	
CHA_2DS_2-VASc score	3.2 ± 1.5	3.3 ± 1.5	3.2 ± 1.5	3.4 ± 1.5	3.4 ± 1.5	3.4 ± 1.5	<0.0001
CHA_2DS_2-VASc score							<0.0001
≤2	692 (33.7)	333 (28.6)	359 (34.5)	4,554 (28.7)	2,293 (28.8)	2,261 (28.6	
3–4	968 (47.2)	479 (48.9)	489 (46.9)	7,662 (48.3)	3,801 (47.8)	3,861 (48.9)	
≥5	391 (19.1)	197 (22.5)	194 (18.6)	3,640 (23.0)	1,860 (23.4)	1,780 (22.5)	
HAS-BLED score	1.6 ± 1.0	1.6 ± 1.0	1.6 ± 1.0	1.8 ± 1.1	1.8 ± 1.0	1.8 ± 1.1	<0.0001
HAS-BLED score							<0.0001
0–1	981 (47.8)	470 (46.6)	511 (49.0)	6,270 (39.5)	3,163 (39.8)	3,107 (39.3)	
2	712 (34.7)	358 (35.5)	354 (34.0)	5,790 (36.5)	2,885 (36.3)	2,905 (36.8)	
≥3	358 (17.5)	181 (17.9)	177 (17.0)	3,796 (23.9)	1,906 (23.9)	1,890 (23.9)	
Medications at randomization							
ACE inhibitor or ARB	1,544 (75.3)	763 (75.6)	781 (75.0)	1,1288 (71.2)	5,701 (71.7)	5,587 (70.7)	0.0001
Beta-blocker	1,106 (53.9)	536 (53.1)	570 (54.7)	1,0376 (65.4)	5,261 (66.1)	5,115 (64.7)	<0.0001
Aspirin	742 (36.2)	377 (37.4)	365 (35.0)	4,890 (30.8)	2,482 (31.2)	2,408 (30.5)	<0.0001
Clopidogrel	40 (2.0)	19 (1.9)	21 (2.0)	298 (1.9)	151 (1.9)	147 (1.9)	0.8244
Digoxin	463 (22.6)	225 (22.3)	238 (22.8)	5,365 (33.8)	2,691 (33.8)	2,674 (33.8)	<0.0001
Calcium channel blocker	480 (23.4)	230 (22.8)	250 (24.0)	5,087 (32.1)	2,514 (31.6)	2,573 (32.6)	<0.0001
Statin	780 (38.0)	388 (38.5)	392 (37.6)	6,693 (42.2)	3,362 (42.3)	3,331 (42.2)	0.0003
NSAID	123 (6.0)	60 (5.9)	63 (6.0)	1,397 (8.8)	692 (8.7)	705 (8.9)	<0.0001
Gastric antacid drugs	348 (17.0)	170 (16.8)	178 (17.1)	3,002 (18.9)	1,513 (19.0)	1,489 (18.8)	0.0317
Theophylline	8 (0.4)	3 (0.3)	5 (0.5)	121 (0.8)	56 (0.7)	65 (0.8)	0.0601
Diuretic	1,172 (57.1)	585 (58.0)	587 (56.3)	8,531 (53.8)	4,238 (53.3)	4,293 (54.3)	0.0043
Chronic renal disease	196 (9.6)	79 (7.8)	117 (11.2)	1296 (8.2)	662 (8.3)	634 (8.0)	0.0319
Renal function							0.0158
Normal: 80 ml/min	818 (39.9)	406 (40.2)	412 (39.5)	6,576 (41.5)	3,294 (41.4)	3,282 (41.5)	
Mild impairment: >50–80 ml/min	840 (41.0)	420 (41.6)	420 (40.3)	6,625 (41.8)	3,330 (41.9)	3,295 (41.7)	
Moderate impairment: >30–50 ml/min	360 (17.6)	165 (16.4)	195 (18.7)	2,351 (14.8)	1,176 (14.8)	1,175 (14.9)	
Severe impairment: ≤30 ml/min	29 (1.4)	17 (1.7)	12 (1.2)	236 (1.5)	117 (1.5)	119 (1.5)	
Chronic renal disease or moderate/severe renal function	523 (25.5)	236 (23.4)	287 (27.5)	3,382 (21.3)	1,697 (21.3)	1,685 (21.3)	<0.0001
Chronic liver disease	70 (3.4)	35 (3.5)	35 (3.4)	439 (2.8)	227 (2.9)	212 (2.7)	0.0985
Chronic liver or renal disease	563 (27.5)	255 (25.3)	308 (29.6)	3,682 (23.2)	1,853 (23.3)	1,829 (23.1)	<0.0001

Values are median (25th, 75th percentiles), n (%), or mean ± SD. *For comparison between amiodarone patients (n = 2,051) and no amiodarone patients (n = 15,856).

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; BMI = body mass index; BP = blood pressure; CABG = coronary artery bypass grafting; CAD = coronary artery disease; $CHADS_2$ = congestive heart failure, hypertension, age, diabetes, and stroke; CHA_2DS_2-VASc = congestive heart failure/LV dysfunction, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA/thromboembolism, vascular disease, age 65-74 years, sex; HAS-BLED = hypertension, abnormal liver/renal function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (age ≥65 years), drugs/alcohol concomitantly; HF = heart failure; ICD = implantable cardioverter defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSAID = nonsteroidal anti-inflammatory drugs; NYHA = New York Heart Association; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SE = systemic embolism; TIA = transient ischemic attack; VF = ventricular fibrillation; VKA = vitamin K antagonist; VT = ventricular tachycardia.

America, 12% in Europe, 9.5% in the Asian Pacific countries, and 6.6% in North America.

In general, patients who received amiodarone were younger (median age 68 years vs. 70 years; $p < 0.001$), were more likely to have heart failure or a reduced LVEF (44.4% vs. 34.3%; $p < 0.0001$), were less likely to have diabetes (21.8% vs. 25.6%; $p = 0.0003$), and were less likely to have had a previous stroke, TIA, or systemic embolism (15.7% vs. 19.9%; $p < 0.0001$). The $CHADS_2$ score was 2.0 ± 1.0 for patients on amiodarone and 2.1 ± 1.1 for patients not on amiodarone ($p = 0.0003$). The CHA_2DS_2-VASc score was 3.2 ± 1.5 for patients on amiodarone and 3.4 ± 1.5 for patients not on amiodarone. More patients on amiodarone had paroxysmal AF compared with those not on amiodarone (34.2% vs. 12.8%; $p < 0.0001$).

In patients assigned to warfarin, the mean TTR was 56.5% in patients who received amiodarone and

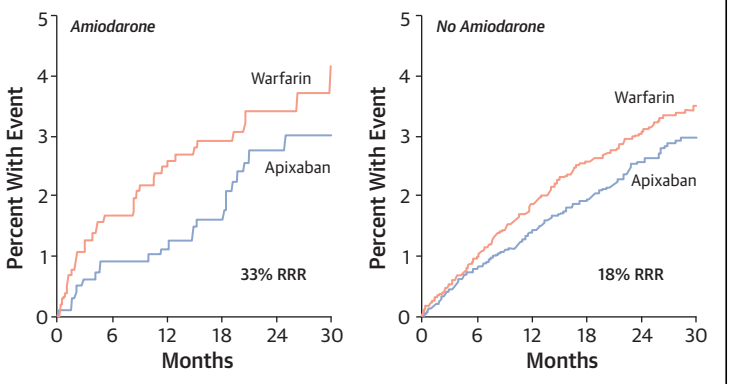


FIGURE 1 Kaplan-Meier Curves of Stroke or Systemic Embolism

Stroke or systemic embolism by amiodarone use at randomization in patients treated with apixaban or warfarin. RRR = relative risk ratio.

63.0% in patients who did not receive amiodarone ($p < 0.0001$). For those patients who received amiodarone versus those who did not, the mean times of follow-up below range (INR <2) were 28.5% and 24.2%, respectively ($p < 0.0001$). The mean times of follow-up above range (INR >3) were 15% and 12.8%, respectively ($p < 0.0001$).

APIXABAN VERSUS WARFARIN. Of the 2,051 patients who received amiodarone at baseline, 1,009 patients were assigned to apixaban and 1,042 were assigned to warfarin. There were no significant differences in selected stroke risk factors or in selected bleeding risk factors between patients receiving either apixaban or warfarin (Table 1).

For patients who received amiodarone, the rate of stroke or systemic embolism was 1.24%/year for patients assigned to apixaban and 1.85%/year for patients assigned to warfarin (HR: 0.68, 95% CI: 0.40 to 1.145). In patients who did not receive amiodarone, the rate of stroke or systemic embolism was 1.29%/year when assigned to apixaban and 1.57%/year when assigned to warfarin (HR: 0.82; 95% CI: 0.68 to 1.00) (Figure 1, Table 1). The interaction p value was 0.4776. For patients who received amiodarone, the rate of all-cause death was 4.15%/year when assigned to apixaban and 5.65%/year when assigned to warfarin (HR: 0.74; 95% CI: 0.55 to 0.98). In patients who did not receive amiodarone, the rate of all-cause death was 3.43%/year when assigned to apixaban and 3.68%/year when assigned to warfarin (HR: 0.93; 95% CI: 0.83 to 1.05). The interaction p value was 0.1366. Other efficacy analyses, including rates of cardiovascular death and noncardiovascular death, are shown in Table 2.

In terms of safety endpoints, in patients who received amiodarone at baseline, the rate of major bleeding was 1.86%/year when assigned to apixaban and 3.06%/year when assigned to warfarin (HR: 0.61; 95% CI: 0.39 to 0.96). In patients who did not receive amiodarone at baseline, the rate of major bleeding was 2.18%/year when assigned to apixaban and 3.03%/year in patients assigned to warfarin (HR: 0.72; 95% CI: 0.62 to 0.84) (Figure 2). The interaction p value was 0.4894. The rates of combined major and clinically relevant nonmajor bleeding in patients who received and did not receive amiodarone at baseline are shown in Table 2.

MAJOR EVENTS ASSOCIATED WITH THE USE OF AMIODARONE. Using a propensity score-adjusted analysis, patients who received amiodarone had a significantly higher rate of stroke or systemic embolism compared with those who did not receive

TABLE 2 Observed Rates and Number of Events for Efficacy and Safety Endpoints in Patients With Amiodarone and No Amiodarone at Randomization and by Study Drug Assignment

	Amiodarone				No Amiodarone				Interaction
Event	Overall	Apixaban	Warfarin	HR (95% CI)*	Overall	Apixaban	Warfarin	HR (95% CI)*	p Value
Efficacy endpoints									
Stroke or SE	1.55 (58)	1.24 (23)	1.85 (35)	0.68 (0.40-1.15)	1.43 (416)	1.29 (189)	1.57 (227)	0.82 (0.68-1.00)	0.4776
All-cause death	4.91 (187)	4.15 (78)	5.65 (109)	0.74 (0.55-0.98)	3.56 (1060)	3.43 (514)	3.68 (546)	0.93 (0.83-1.05)	0.1366
CV death	2.63 (100)	2.34 (44)	2.90 (56)	0.81 (0.54-1.20)	1.82 (541)	1.74 (260)	1.90 (281)	0.92 (0.77-1.09)	0.5611
Non-CV death	1.58 (60)	1.38 (26)	1.76 (34)	0.79 (0.47-1.31)	1.13 (335)	1.10 (165)	1.15 (170)	0.96 (0.78-1.19)	0.4728
MI	0.27 (10)	0.21 (4)	0.32 (6)	0.68 (0.19-2.41)	0.61(179)	0.58 (85)	0.65 (94)	0.90 (0.90-1.20)	0.6790
Safety endpoints									
Major bleeding	2.46 (82)	1.86 (31)	3.06 (51)	0.61 (0.39-0.96)	2.60 (690)	2.18 (293)	3.03 (397)	0.72 (0.62-0.84)	0.4894
Major/CRNM bleeding	5.12 (167)	3.92 (64)	6.31 (103)	0.63 (0.46-0.86)	4.99 (1298)	4.10 (542)	5.92 (756)	0.70 (0.62-0.78)	0.5226
Intracranial bleeding	0.74 (25)	0.30 (5)	1.19 (20)	0.25 (0.10-0.67)	0.54 (146)	0.35 (47)	0.74 (99)	0.46 (0.33-0.66)	0.2456

Values are %/year (n). *Hazard ratios are apixaban versus warfarin.

CI = confidence interval; CRNM = clinically relevant non-major; CV = cardiovascular; HR = hazard ratio; other abbreviations as in Table 1.

amiodarone. The rate of stroke or systemic embolism was 1.58%/year in patients who received amiodarone and 1.19% in those who did not receive amiodarone (adjusted HR: 1.47; 95% CI: 1.03 to 2.10; p = 0.0322). Patients who received amiodarone had numerically, but not significantly, higher rates of all-cause death (4.76% vs. 4.09%; adjusted HR: 1.16; 95% CI: 0.95 to 1.41), cardiovascular death (2.65% vs. 2.26%; adjusted HR: 1.2; 95% CI: 0.91 to 1.55), and noncardiovascular death (1.49% vs. 1.09%; HR: 1.27; 95% CI: 0.88 to 1.82). There were no significant differences in MI and major bleeding between those who received and those who did not receive amiodarone (Table 3).

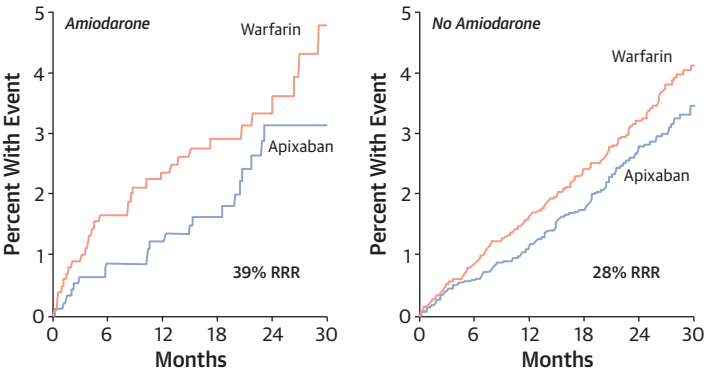


FIGURE 2 Kaplan-Meier Curves of Major Bleeding

International Society of Thrombosis and Hemostasis (ISTH) major bleeding by amiodarone use at randomization in patients treated with apixaban or warfarin. Abbreviation as in Figure 1.

DISCUSSION

This analysis from the ARISTOTLE study included 2,051 patients who received amiodarone, which represented one of the largest experiences to date with amiodarone for AF in a clinical trial. The main findings were as follows: 1) amiodarone use was associated with a significantly increased risk of stroke and systemic embolism, and a lower time in the TTR when used with warfarin; 2) apixaban consistently reduced the rate of stroke and systemic embolism, death, and major bleeding compared with warfarin in amiodarone patients and patients not on amiodarone (Central Illustration); and 3) the relative reductions in stroke and systemic embolism, mortality, and major bleeding with apixaban compared with warfarin were similar with and without amiodarone use.

The quality of anticoagulation, as assessed by the mean TTR during the trial, was 56.5% in patients treated with warfarin combined with amiodarone. In clinical trials, TTR values of 62% to 66% were achieved (19–22), and were accepted as an indication of effective anticoagulation. In ARISTOTLE, the mean TTR was 63% in patients who did not receive amiodarone and who were assigned to warfarin. Despite the difference in TTR, there was a consistent risk reduction in stroke and systemic embolism, mortality, and major bleeding with apixaban compared with warfarin, regardless of treatment with amiodarone. These findings were in accordance with our previous observation on the lack of interaction between INR control and the benefits of apixaban compared with warfarin in the overall ARISTOTLE trial (23). These data suggested that apixaban is an attractive choice to prevent stroke and systemic embolism, lower mortality, and reduce major bleeding, irrespective of whether the patient receives or does not receive amiodarone.

The use of class IA antiarrhythmic drugs in AF has been associated with excess mortality (24,25). Whether class IC or class III agents, including amiodarone, are associated with higher mortality in patients with AF has been controversial. Excess mortality has not been noted in a pooled analysis of class IC and class III drugs after cardioversion (26). However, antiarrhythmic drug therapy in the AFFIRM study, which included amiodarone, sotalol, and 6 class I antiarrhythmic drugs, was associated with excess mortality (27), and noncardiovascular mortality was increased in patients on amiodarone (15,16). Reports of increased cancer rates with amiodarone have been published (13,14).

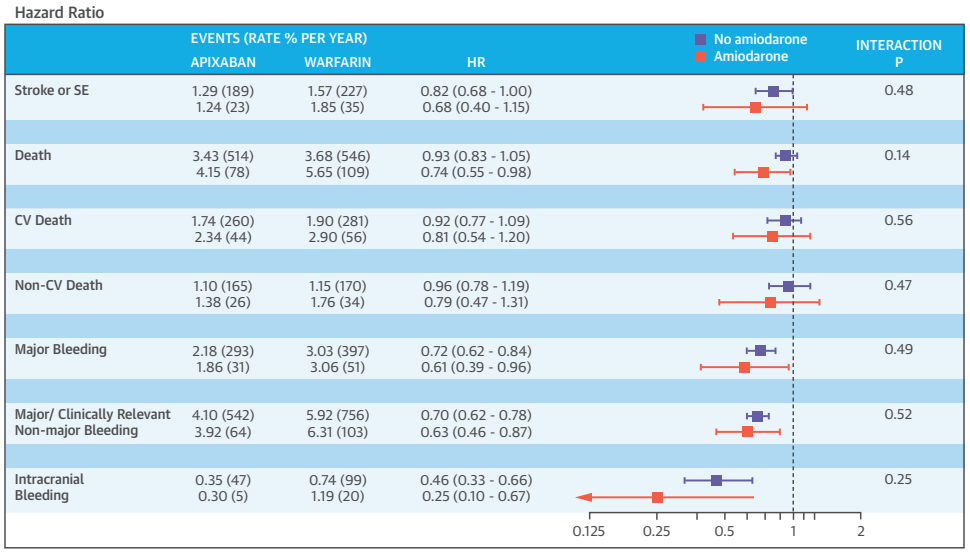
Despite these concerns, the use of amiodarone in ARISTOTLE was substantial; 11% of patients received this drug. There was wide geographic variability in amidarone use; its use was more likely in Latin America and less likely in North America. The reason

TABLE 3 Observed Rates and Number of Events in Patients Included in the Propensity-Matched Analysis*

Endpoint	Amiodarone Rates (Events)	No Amiodarone Rates (Events)	HR (95% CI)†	p Value
Stroke/SE	1.58 (50)	1.19 (115)	1.47 (1.03–2.10)	0.0322
All-cause death‡	4.76 (156)	4.09 (409)	1.16 (0.95–1.41)	0.1577
CV death‡	2.65 (87)	2.26 (226)	1.19 (0.91–1.55)	0.2104
Non-CV death‡	1.49 (49)	1.09 (109)	1.27 (0.88–1.82)	0.1964
MI	0.30 (10)	0.51 (51)	0.58 (0.27–1.25)	0.1646
Major bleeding	2.40 (74)	2.09 (199)	1.15 (0.85–1.53)	0.3656

Values are n (%). Rate per 100 patient-years of follow-up in patients included in this analysis. Patients on amiodarone were matched with patients not on amiodarone in 1:3 ratio on the basis of variables associated with each endpoint. Sample sizes were: 1,755 amiodarone/5,265 nonamiodarone for stroke/SE; 1,780 amiodarone/5,340 nonamiodarone for all-cause, CV and non-CV death; 1,818 amiodarone/5,454 nonamiodarone for myocardial infarction; and 1,828 amiodarone/5,484 nonamiodarone for major bleeding. *Patients from the following countries were excluded from this analysis: Finland, Hong Kong, Malaysia, Norway, Puerto Rico, Singapore, Sweden, and Turkey. †The hazard ratios compare amiodarone with no amiodarone. ‡Causes of death are classified as CV, non-CV, and unknown cause.

Abbreviations as in Tables 1 and 2.



CENTRAL ILLUSTRATION **Patient Outcomes by Amiodarone Use at Randomization**

Event rates and hazard ratios (HRs) comparing apixaban to warfarin by amiodarone use at randomization. CV = cardiovascular; SE = systemic embolism.

for these differences was uncertain, but it might represent differences in the patient population, regional differences in perceptions about the merits of rhythm control, or differences in the availability of catheter-based techniques for rhythm control.

The reason for the suggestion of a higher rate of stroke and systemic embolism in patients who received amiodarone versus patients who did not receive amiodarone is unclear. There is no a priori reason for class III antiarrhythmic medications to be thrombogenic. In the AFFIRM study, amiodarone was the most frequently used medication in the rhythm control arm, and there were no differences in cerebrovascular events in patients assigned to the rhythm control arm compared with the rate control arm (15). The multichannel blocker, dronedarone, with class III properties and negligible effects on INR values, was associated with a reduction in stroke in patients with paroxysmal or persistent AF (28), but was also associated with an increased stroke risk in patients with permanent AF (29). These data suggest that the thromboembolic risk is likely related to characteristics of the AF population, rather than the specific antiarrhythmic drug. In the present analysis, the mean TTR in patients who received amiodarone and warfarin was low, and the majority of values were below the accepted therapeutic range. It is possible that less effective anticoagulation with amiodarone could contribute to the observed association with stroke or systemic embolism in the warfarin group, where the HR for stroke or systemic embolism with amiodarone was somewhat greater, although there was no significant interaction. These findings indicate that special efforts are needed to maintain an in-range INR in patients who receive warfarin and amiodarone. These findings provide an additional rationale to prefer apixaban more than warfarin in patients who require amiodarone.

The concern about cancer and amiodarone use in humans was based on the results from a meta-analysis of 15 trials, 4 of which reported cancer deaths. Of 1,609 patients who received amiodarone, 13 (0.8%) died of cancer. In comparison, of 1,597 patients who received placebo, 4 (0.3%) died of cancer (13). A more recent retrospective cohort study from Taiwan included patients who received amiodarone for >28 days without antecedent malignancy (14). Of 6,418 patients followed for a median of 2.57 years, 280 cancers developed, which was higher than would be expected. Cancer was not an endpoint of the ARISTOTLE trial, and the follow-up time was relatively brief for the detection of any possible association of amiodarone with cancer.

STUDY LIMITATIONS. This was a retrospective evaluation of the ARISTOTLE database; therefore, it was subject to all the biases inherent to this type of analysis. Amiodarone use was defined at the time of randomization, and its use was not systematically

collected throughout the study. The duration of amiodarone use before entry into the study was not determined. At baseline, patients were classified with either paroxysmal or persistent and/or permanent AF, and patients with persistent and permanent AF were not separated into different groups. Patients who did not receive amiodarone at the time of randomization might have received it in the past. The follow-up was too brief to detect important long-term problems with the medication, including the development of cancer. Finally, because patients who received or did not receive amiodarone were not randomized, there were important differences between them. Although we attempted to compensate for these differences with a propensity score method, assumptions were made in the development of this scoring system, and there might have been residual unmeasured confounding. Therefore, the possibility of confounding factors or even the play of chance as a cause for the associations between amiodarone use and outcomes could not be excluded.

CONCLUSIONS

In a contemporary clinical trial involving patients with AF at risk for stroke, amiodarone use was substantial and varied by geographic region. Anticoagulation quality, as assessed by TTR, was lower in warfarin-treated patients who received amiodarone, and amiodarone use was associated with a significantly higher risk of stroke and systemic embolism. The relative effects of apixaban versus warfarin on stroke and systemic embolism, mortality, and major bleeding were consistent in patients who received and patients who did not receive amiodarone.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Greg Flaker, University of Missouri, 1 Hospital Drive, CE306, Columbia, Missouri 65212. E-mail: flakerg@missouri.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Amiodarone is effective in preventing AF, but it can interfere with warfarin metabolism and potentially increase the risk of thromboembolic events or bleeding. Newer target-specific oral anticoagulants have less interaction with amiodarone.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Compared with warfarin, in the ARISTOTLE trial, the factor Xa inhibitor, apixaban, reduced rates of stroke and systemic embolism, death, and major bleeding in patients with nonvalvular AF, whether or not they were concurrently treated with amiodarone.

TRANSLATIONAL OUTLOOK: Randomized studies of amiodarone and other antiarrhythmic medications in anticoagulated patients with AF could clarify the generalizability of these findings and better guide treatment decisions in clinical practice.

REFERENCES

1. Roy D, Talajic M, Dorian P, et al. Amiodarone to prevent recurrence of atrial fibrillation. Canadian Trial of Atrial Fibrillation Investigators. N Engl J Med 2000;342:913–20.

2. Singh BN, Singh SN, Reda DJ, et al., for the Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) Investigators. Amiodarone versus sotalol for atrial fibrillation. N Engl J Med 2005; 352:1861–72.

3. AFFIRM First Antiarrhythmic Drug Substudy Investigators. Maintenance of sinus rhythm in patients with atrial fibrillation: an AFFIRM substudy of the first antiarrhythmic drug. J Am Coll Cardiol 2003;42:20–9.

4. Camm AJ, Lip GY, De Caterina R, et al. ESC Committee for Practice Guidelines. 2012 focused update of the ESC guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace 2012;14:1385–413.

5. Flaker GC, Pogue J, Yusuf S, et al., for the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE) Investigators. Cognitive function and anticoagulation control in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2010;3:277–83.

6. Kerin NZ, Blevins RD, Goldman L, et al. The incidence, magnitude, and time course of the amiodarone-warfarin interaction. Arch Intern Med 1988;148:1779–81.

7. Sanoski CA, Bauman JL. Clinical observations with the amiodarone/warfarin interaction: dosing relationships with long-term therapy. Chest 2002; 121:19–23.

8. Wallentin L, Yusuf S, Ezekowitz M, et al., for the RE-LY Investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975–83.

9. Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2008;1:84–91.

10. Connolly S, Pogue J, Eikelboom J, et al., ACTIVE W Investigators. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation 2008;118:2029–37.

11. Greenspon AJ, Kidwell GA, Hurley W, et al. Amiodarone-related postoperative adult respiratory distress syndrome. Circulation 1991;84:407–15.

12. Sobol SM, Rakita L. Pneumonitis and pulmonary fibrosis associated with amiodarone treatment: a possible complication of a new antiarrhythmic drug. Circulation 1982;65:819–24.

13. Piccini JP, Berger JS, O'Connor CM. Amiodarone for the prevention of sudden cardiac death: a meta-analysis of randomized controlled trials. Eur Heart J 2009;30:1245–53.

14. Su VY, Hu YW, Chou KT, et al. Amiodarone and the risk of cancer: a nationwide population-based study. Cancer 2013;119:1699–705.

15. Steinberg J, Sadaniantz A, Kron J, et al. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) study. Circulation 2004; 109:1973–80.

16. Saksena S, Slee A, Waldo AL, et al. Cardiovascular outcomes in the AFFIRM Trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management): An assessment of individual antiarrhythmic drug therapies compared with rate control with propensity score-matched analyses. J Am Coll Cardiol 2011;58:1975–85.

17. Lopes RD, Alexander JH, Al-Khatib SM, et al., ARISTOTLE Investigators. Apixaban for reduction in stroke and other ThromboembоLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J 2010;159:331–9.

18. Granger CB, Alexander JH, McMurray JJ, et al., for the ARISTOTLE Committee and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

19. ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidigrel Trial with Ibesartan 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., for the RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

21. Albers GW, Diener HC, Frison L, et al., for the SPORTIF Executive Steering Committee for the SPORTIF V Investigators. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. JAMA 2005; 293:690–8.

22. Olsson SB, Executive Steering Committee of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003;362: 1691–8.

23. Wallentin L, Lopes RD, Hanna M, et al., for the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. Circulation 2013;127:2166–76.

24. Coplen SE, Antman EM, Berlin JA, et al. Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation 1990;82:1106–16.

25. Flaker GC, Blackshear JL, McBride R, et al. Antiarrhythmic drug therapy and cardiac mortality in atrial fibrillation. The Stroke Prevention in Atrial Fibrillation Investigators. J Am Coll Cardiol 1992; 20:527–32.

26. Lafuente-Lafuente C, Mouly S, Longas-Tejero MA, et al. Antiarrhythmic drugs for maintaining sinus rhythm after cardioversion of atrial fibrillation. A systematic review of randomized controlled trials. Arch Intern Med 2006;166:719–28.

27. Corley SD, Epstein AE, DiMarco JP, et al., for the AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm management (AFFIRM) Study. Circulation 2004; 109:1509–13.

28. Connolly SJ, Crijns HJ, Torp-Pedersen C, et al., for the ATHENA Investigators. Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. Circulation 2009;120:1174–80.

29. Connolly SJ, Camm AJ, Halperin JL, et al., for the PALLAS Investigators. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 2011;365:2268–76.

KEY WORDS antiarrhythmia agents, anticoagulants, antithrombotic agents, factor Xa, stroke, thromboembolism, warfarin