Blood Pressure Control and Risk of Stroke or Systemic Embolism in Patients With Atrial Fibrillation: Results From the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial

Meena P. Rao, MD, MPH; Sigrun Halvorsen, MD, PhD; Daniel Wojdyla, MS; Laine Thomas, PhD; John H. Alexander, MD, MHS; Elaine M. Hylek, MD, MPH; Michael Hanna, MD; M. Cecilia Bahit, MD; Renato D. Lopes, MD, PhD; Raffaele De Caterina, MD, PhD; Cetin Erol, MD; Shinya Goto, MD, PhD; Fernando Lanas, MD; Basil S. Lewis, MD; Steen Husted, MD, DSc; Bernard J. Gersh, MB, ChB, DPhil; Lars Wallentin, MD, PhD; Christopher B. Granger, MD; on behalf of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Steering Committee and Investigators

Background—Patients with atrial fibrillation (AF) and hypertension are at high risk for stroke. Previous studies have shown elevated risk of stroke in patients with AF who have a history of hypertension (regardless of blood pressure [BP] control) and in patients with elevated BP. We assessed the association of hypertension and BP control on clinical outcomes.

Methods and Results—In ARISTOTLE (n=18 201), BP was evaluated as history of hypertension requiring treatment and elevated BP (systolic ≥140 and/or diastolic ≥90 mm Hg) at study entry and any point during the trial. Hazard ratios (HRs) were derived from Cox proportional hazards models including BP as a time-dependent covariate. A total of 15 916 (87.5%) patients had a history of hypertension requiring treatment. In patients with elevated BP measurement at any point during the trial, the rate of stroke or systemic embolism was significantly higher (HR, 1.53; 95% confidence interval [CI], 1.25−1.86), as was hemorrhagic stroke (HR 1.85; 95% CI, 1.26−2.72) and ischemic stroke (HR, 1.50; 95% CI, 1.18−1.90). Rates of major bleeding were lower in patients with a history of hypertension (HR, 0.80; 95% CI, 0.66−0.98) and nonsignificantly lower in patients with elevated BP at study entry (HR, 0.89; 95% CI, 0.77−1.03). The benefit of apixaban versus warfarin on preventing stroke or systemic embolism was consistent among patients with and without a history of hypertension (*P* interaction=0.27), BP control at baseline (*P* interaction=0.43), and BP control during the trial (*P* interaction=0.97).

Conclusions—High BP measurement at any point during the trial was independently associated with a substantially higher risk of stroke or systemic embolism. These results strongly support efforts to treat elevated BP as an important strategy to optimally lower risk of stroke in patients with AF.

Clinical Trial Registration—URL: https://ClinicalTrials.gov/. Unique identifier: NCT00412984. (*J Am Heart Assoc*.2015;4: e002015 doi: 10.1161/JAHA.115.002015)

Key Words: apixaban • atrial fibrillation • blood pressure control • stroke • systemic embolism

Hypertension is the most common comorbid condition in patients with atrial fibrillation (AF) and is present in approximately 80% to 90% of patients with AF enrolled in recent clinical trials.[1–5] In AF, hypertension has been found to be an independent risk factor for stroke and patients with both AF and hypertension have an increased risk of stroke

when compared with patients with either condition alone.[6,7] Antihypertensive therapies significantly reduce the risk of stroke in patients with hypertension; however, few studies have focused on patients with hypertension and AF.[8,9]

Previous studies have found elevated risk of stroke in patients with AF who have a history of hypertension (regardless of blood pressure [BP] control), whereas other studies found an elevated risk of stroke in all patients with AF without previous history of hypertension with systolic blood pressure (SBP) levels ≥140 mm Hg.[10–12] Thus, in order to define the potential benefit of BP control in patients with AF, a clearer understanding of the association between stroke risk and BP control is needed.

The risk of stroke in patients with AF can be reduced with anticoagulation, and vitamin K antagonists (VKAs) have historically been the most commonly used therapy. Apixaban is an oral direct factor Xa inhibitor that was found to be superior to warfarin in preventing stroke or systemic embolism (SE) in patients with AF in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[5] Given that uncontrolled elevation in SBP is a risk factor for intracranial hemorrhage and patients taking anticoagulants are at high risk for bleeding, it is not only relevant to determine the association between a history of hypertension requiring therapy and BP control with clinical outcomes as above, but also to determine whether patients with AF and hypertension benefit from novel oral anticoagulants in the same way as those without hypertension.[13]

Methods

Study Population

The design and results of the ARISTOTLE study have been previously published.[5,14] Briefly, ARISTOTLE was a double-blind, double-dummy, randomized trial comparing apixaban 5 mg twice-daily (2.5 mg twice-daily for patients with at least 2 of the following: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL) with warfarin (target international normalized ratio, 2.0–3.0) in patients with documented AF or flutter and at least 1 additional risk factor for stroke (age >75 years; previous stroke, transient ischemic attack [TIA], or SE; symptomatic heart failure within 3 months or systolic dysfunction with a left ventricular ejection fraction [LVEF] <40%; diabetes mellitus; and hypertension requiring pharmacological treatment). Patients were not enrolled if they had a reversible cause for their AF, mitral stenosis, prosthetic heart valve, or other indication for oral anticoagulation, need for aspirin >165 mg daily or need for both aspirin and clopidogrel, stroke within the previous 7 days, and severe renal insufficiency. A total of 18 201 patients were enrolled.

Institutional review board approval and participant written informed consent were obtained before enrollment.

Blood Pressure

BP was recorded at screening; preceding to dosing on day 1; and at the quarterly, annual, and end of treatment period visits (around every 6 months). Though no standardized method for BP measurement was specified in the trial protocol, appropriate methods of collecting BP recordings were reviewed during site training. Median duration of follow-up in this study was 1.8 years.

BP control was evaluated in 3 ways: history of hypertension requiring treatment, elevated BP (SBP ≥140 mm Hg and/or diastolic BP [DBP] ≥90 mm Hg) at study entry, and elevated BP (mean of last 2 BP measurements as having SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) at any point during the trial. These categories were not mutually exclusive.

Study Outcomes

The primary efficacy outcome was stroke or SE. The primary safety outcome was major bleeding as defined by the International Society on Thrombosis and Hemostasis (ISTH).[15] Key secondary outcomes included death from any cause, cardiovascular mortality, myocardial infarction (MI), ischemic stroke, hemorrhagic stroke, major or clinically relevant nonmajor (CRNM) bleeding, and any bleeding.

Statistical Analysis

Baseline characteristics are presented as medians with 25th and 75th percentiles for continuous variables and counts (proportions) for categorical variables. Event rates are presented per 100 patient-years of follow-up. Hazard ratios (HRs) along with 95% confidence intervals (CIs) are derived from Cox regression models. The probability of primary efficacy and safety endpoints are presented as Kaplan-Meier curves. Efficacy and safety endpoints were compared in patients with and without baseline history of treated hypertension and with and without elevated BP at study entry. Patients with and without hypertension were compared using adjusted HRs. For each endpoint, previously developed adjustment models were based on a set of clinically relevant variables. The randomized treatment effect was assessed by history of hypertension status. The interaction between randomized treatment and history of hypertension was tested by adding an interaction term to the Cox regression model. We also investigated the relationship between elevated BP during the trial and subsequent outcomes using a Cox regression model with a time-dependent covariate for elevated BP during follow-up. For this analysis, an elevation

in BP was based on the mean of the 2 most recent BP values (to reduce variability). The average of the BP measured at screening and randomization was used until the first postrandomization measurement was collected. At the time of event, patients were analyzed according to mean of the 2 BPs taken at the visit preceding the event. For each endpoint, HRs were adjusted for potential confounders. All statistical analyses were performed using SAS software (version 9.0; SAS Institute Inc., Cary, NC). Whereas we prospectively collected BPs at each visit with the plan to evaluate the impact of various clinical variables with outcomes, this specific analysis was not preplanned. In all analyses, a $P<0.05$ was considered statistically significant. No corrections for multiple testing were performed.

Results

Baseline Characteristics

Of the 18 201 patients enrolled in the ARISTOTLE study, 15 916 (87.5%) had a history of hypertension requiring pharmacological treatment. Of these patients, 20% had SBP $\geq$140 mm Hg, 6% had DBP $\geq$90 mm Hg, and 17% had both at baseline. Of the 2285 patients without a history of hypertension at enrollment, 21% had elevated BP (SBP $\geq$140 mm Hg and/or DBP $\geq$90 mm Hg) at study entry. In regard to the 7229 patients (45% of the study population) with elevated BP at study entry, 93% had a history of hypertension. Of the 10 972 patients without elevated BPs at study entry, 83% had a history of hypertension (Figure 1).

Patients with a history of hypertension were 2 years younger than those without a history of hypertension, but more likely to have previous diabetes or coronary artery disease (CAD; Table 1). Patients without a history of hypertension at baseline were more likely to have previous heart failure, stroke, or renal dysfunction. As expected, the overall

Total Patients (N=18,201)	SBP ≥140 and/or DBP ≥90 mm Hg (N=7229)	SBP <140 and DBP <90 mm Hg (N=10,972)
History of hypertension (N=15,916)	6748	9168
No history of hypertension (N=2285)	481	1804

Figure 1. Number of patients according to history of hypertension. DBP indicates diastolic blood pressure; SBP, systolic blood pressure.

CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were higher in patients with a history of hypertension, whereas no difference in HAS-BLED scores was noted between the 2 groups. Aspirin therapy and statins were used more frequently in patients with a history of hypertension who also had more coronary disease. Digoxin was used more frequently in patients without a history of hypertension at baseline who had more heart failure.

Clinical Outcomes

Risk of stroke or systemic embolism was higher in patients with a history of hypertension (HR, 1.33; 95% CI, 1.00–1.76) or with elevated BP at study entry (HR, 1.24; 95% CI, 1.03–1.49). Similarly, rates of hemorrhagic stroke (HR, 1.59; 95% CI, 0.87–2.91 and HR, 1.19; 95% CI, 0.82–1.73) and rates of ischemic stroke (HR, 1.27; 95% CI, 0.91–1.78 and HR, 1.29; 95% CI, 1.04–1.61) were higher in both groups, although not statistically significant. Rates of major bleeding were lower in both groups respectively (HR, 0.82; 95% CI, 0.67–1.01 and HR, 0.97; 95% CI, 0.83–1.12; Table 2).

During the trial, 50% of patients had elevated BP at some point during the trial (mean of 2 previous BP measurements having SBP $\geq$140 mm Hg and/or DBP $\geq$90 mm Hg). After adjustment for baseline characteristics that are listed in Figure 2, elevated BP at any point during the course of the trial was significantly associated with subsequent increased risk of stroke or SE (HR, 1.53; 95% CI, 1.25–1.86) and hemorrhagic stroke (HR, 1.85; 95% CI, 1.26–2.72; Figure 2). The association with stroke and SE was consistent according to a history of hypertension, previous stroke, and renal insufficiency. With longer duration of exposure to high BP, the association with stroke or SE trended in the same direction as those with a single mean BP measurement elevation; however, this trend was not statistically significant. An association was also noted between elevation in BP at any point during the trial and major or CRNM bleeding or any bleeding, although major bleeding itself was not significantly increased.

The benefit of apixaban versus warfarin in preventing stroke or SE was consistent among patients with and without a history of hypertension (*P* interaction=0.27; Table 3), elevated BP at study entry (*P* interaction=0.43), and elevation in BP during the trial (*P* interaction=0.97).

Discussion

In ARISTOTLE, patients with AF and hypertension are an important large subgroup of patients. In this analysis, the benefits of apixaban when compared with warfarin in reducing stroke or SE, mortality, and major bleeding were consistent regardless of a history of hypertension, BP at baseline, and BP

Table 1. Baseline Characteristics According to History of HTN at Study Entry

	History of HTN (n=15 916)	No History of HTN (n=2285)	P Value*
Age, median (25th, 75th), y	70 (63, 76)	72 (61, 78)	<0.0001
Female sex, n (%)	5756 (36.2)	660 (28.9)	<0.0001
Systolic BP, median (25th, 75th), mm Hg	130 (120, 140)	122 (110, 132)	<0.0001
Diastolic BP, median (25th, 75th), mm Hg	80 (72, 88)	75 (70, 80)	<0.0001
Weight, median (25th, 75th), kg	83 (71, 96)	75 (64, 89)	<0.0001
Previous stroke, TIA, or systemic embolism, n (%)	2952 (18.5)	586 (25.6)	<0.0001
Diabetes, n (%)	4085 (25.7)	462 (20.2)	<0.0001
Heart failure or reduced LVEF, n (%)	5376 (33.8)	1075 (47.0)	<0.0001
Coronary artery disease, n (%)	5486 (34.5)	556 (24.4)	<0.0001
Renal function, n (%)			<0.0001
Normal (80 mL/min)	6739 (42.5)	779 (34.3)	
Mild impairment (>50–80 mL/min)	6555 (41.3)	1032 (45.5)	
Moderate impairment (>30–50 mL/min)	2322 (14.6)	425 (18.7)	
Severe impairment (≤30 mL/min)	238 (1.5)	32 (1.4)	
$CHADS_2$, mean (SD)	2.2 (1.11)	1.5 (0.88)	<0.0001
$CHADS_2$ score, no. (%)			<0.0001
≤1	4782 (30.0)	1401 (61.3)	
2	5972 (37.5)	544 (23.8)	
≥3	5162 (32.4)	340 (14.9)	
CHA_2DS_2-VASc, mean (SD)	3.5 (1.52)	2.7 (1.24)	<0.0001
CHA_2DS_2-VASc score, no. (%)			<0.0001
0–2	4288 (26.9)	1087 (47.6)	
3–5	9940 (62.5)	1152 (50.4)	
>5	1688 (10.6)	46 (2.0)	
HAS-BLED, mean (SD)	1.8 (1.05)	1.7 (1.05)	0.2401
HAS-BLED score, no. (%)			0.5179
0–1	6501 (40.8)	960 (42.0)	
2	5765 (36.2)	803 (35.1)	
≥3	3650 (22.9)	522 (22.8)	

Table 1. Continued

	History of HTN (n=15 916)	No History of HTN (n=2285)	P Value*
Baseline medication, n (%)			
Amiodarone	1819 (11.6)	232 (10.5)	0.1465
Beta-blocker	10 280 (65.5)	1202 (54.6)	<0.0001
Aspirin	5026 (31.6)	606 (26.5)	<0.0001
Clopidogrel	300 (1.9)	38 (1.7)	0.4626
Digoxin	4869 (31.0)	959 (43.5)	<0.0001
Calcium blocker	5297 (33.7)	270 (12.3)	<0.0001
Statin	6707 (42.7)	766 (34.8)	<0.0001
Nonsteroidal anti-inflammatory agent	1329 (8.5)	191 (8.7)	0.7439
Gastric antacid drugs	2949 (18.8)	401 (18.2)	0.5161
ACE inhibitor or ARB	12 019 (76.5)	813 (36.9)	<0.0001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; HTN, hypertension; LVEF, left ventricular ejection fraction; TIA, transient ischemic attack.
*P value compares patients with history vs no history of HT, ignoring randomized treatment.

measurements during the trial. Patients with a history of hypertension and those with elevated BP (SBP ≥140 mm Hg and/or DBP ≥90 mm Hg) at baseline had a higher risk of stroke or SE, although this finding was not statistically significant. However, a significantly higher risk of stroke was observed with elevated BP at any time during the trial. Thus, the main novel finding of this analysis was that elevated BP measurements (a mean SBP ≥140 mm Hg and/or mean DBP ≥90 mm calculated from 2 BP measurements) at any point during the trial were associated with a subsequent 50% increase in risk of stroke or SE (HR, 1.53; 95% CI, 1.25–1.86).

Previous studies looking at hypertension and AF have not shown a consistent association in outcomes. The Stroke Prevention using an Oral Thrombin Inhibitor in AF (SPORTIF) III and IV trials showed an increase in the rate of stroke or SE in patients with AF and SBP levels ≥140 mm Hg during the follow-up period of the trial.[10,11] The Stroke Prevention in Atrial Fibrillation (SPAF) III trial showed an elevated risk of stroke or SE in patients with AF and a history of hypertension without SBP greater than 150 mm Hg.[12] When looking at BP reduction, a substudy of the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) demonstrated a 38% (95% CI, 6–59) reduction in major vascular events with a BP reduction of 7.3/3.4 mm Hg among the 476 patients with cerebrovascular disease and AF; however because of the small number of events, the results were not statistically significant.[9] On the other hand, the use of irbesartan in the ACTIVE-I trial, which was associated with a 6.8-mm Hg

Table 2. Association Between History of Hypertension at Baseline and Elevated Blood Pressure at Baseline* With Outcomes

	Past Medical History of Hypertension at Baseline				SBP ≥140 mm Hg and/or DBP ≥90 mm Hg at Baseline			
	Yes	No	Unadjusted HR (95% CI) (Yes vs No)	Adjusted* HR (95% CI) (Yes vs No)	Yes	No	Unadjusted HR (95% CI) (Yes vs No)	Adjusted* HR (95% CI) (Yes vs No)
	Rate	Rate			Rate	Rate		
Efficacy endpoints								
Stroke or systemic embolism	1.45 (422)	1.32 (55)	1.10 (0.83–1.45)	1.33 (1.00–1.76)	1.58 (209)	1.34 (267)	1.18 (0.99–1.42)	1.24 (1.03–1.49)
Ischemic/uncertain type stroke	1.02 (297)	0.96 (40)	1.06 (0.76–1.48)	1.27 (0.91–1.78)	1.13 (150)	0.93 (186)	1.22 (0.98–1.51)	1.29 (1.04–1.61)
Hemorrhagic stroke	0.36 (106)	0.29 (12)	1.26 (0.69–2.29)	1.59 (0.87–2.91)	0.39 (52)	0.33 (66)	1.18 (0.82–1.70)	1.19 (0.82–1.73)
Death from any cause	3.58 (1067)	4.81 (205)	0.74 (0.64–0.86)	0.73 (0.61–0.88)	3.44 (466)	3.93 (804)	0.87 (0.78–0.98)	1.08 (0.87–1.36)
Cardiovascular death	1.83 (547)	2.46 (105)	0.74 (0.60–0.92)	0.81 (0.63–1.05)	1.75 (238)	2.02 (413)	0.87 (0.74–1.02)	1.00 (0.73–1.37)
MI	0.58 (171)	0.50 (21)	1.16 (0.74–1.83)	1.15 (0.73–1.82)	0.56 (75)	0.58 (117)	0.96 (0.72–1.29)	1.15 (0.85–1.54)
Safety endpoints								
ISTH major bleeding	2.53 (671)	3.15 (118)	0.80 (0.66–0.98)	0.82 (0.67–1.01)	2.43 (293)	2.73 (495)	0.89 (0.77–1.03)	0.97 (0.83–1.12)
Major or CRNM bleeding	4.96 (1288)	5.49 (202)	0.90 (0.78–1.05)	0.91 (0.78–1.06)	4.80 (566)	5.18 (922)	0.93 (0.83–1.03)	0.98 (0.88–1.09)
Any bleeding	21.65 (4722)	22.59 (694)	0.96 (0.89–1.04)	0.98 (0.90–1.06)	21.04 (2097)	22.27 (3309)	0.95 (0.90–1.00)	1.01 (0.95–1.07)

Adjustment variables: stroke/systemic embolism, ischemic/uncertain type stroke, hemorrhagic stroke: age, region, weight (spline), diabetes, at least moderate valvular disease, previous stroke, TIA, or systemic embolism, previous VKA use, and type of AF. All-cause death and cardiovascular death: age (spline), sex, region, systolic and diastolic blood pressure (spline), weight (spline), at least moderate valvular disease, left BBB, history of MI, previous stroke, TIA or systemic embolism, anemia, smoking, previous VKA use, NYHA class, CHADS2 score, and renal function. MI: age (spline), region, diabetes, coronary artery disease, history of MI, NYHA class, and renal function. Bleeding endpoints: age, sex, region, coronary artery disease, history of MI, history of bleeding, anemia, CHADS2 score, and renal function. AF indicates atrial fibrillation; BBB, bundle branch block; CI, confidence interval; CRNM, clinically relevant nonmajor; DBP, diastolic blood pressure; HR, hazard ratio; ISTH, International Society on Thrombosis and Hemostasis; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischemic attack; VKA, vitamin K antagonist.

*Elevated blood pressure: SBP ≥140 mm Hg and/or DBP ≥90 mm Hg.

†Rates per 100 patient-years.
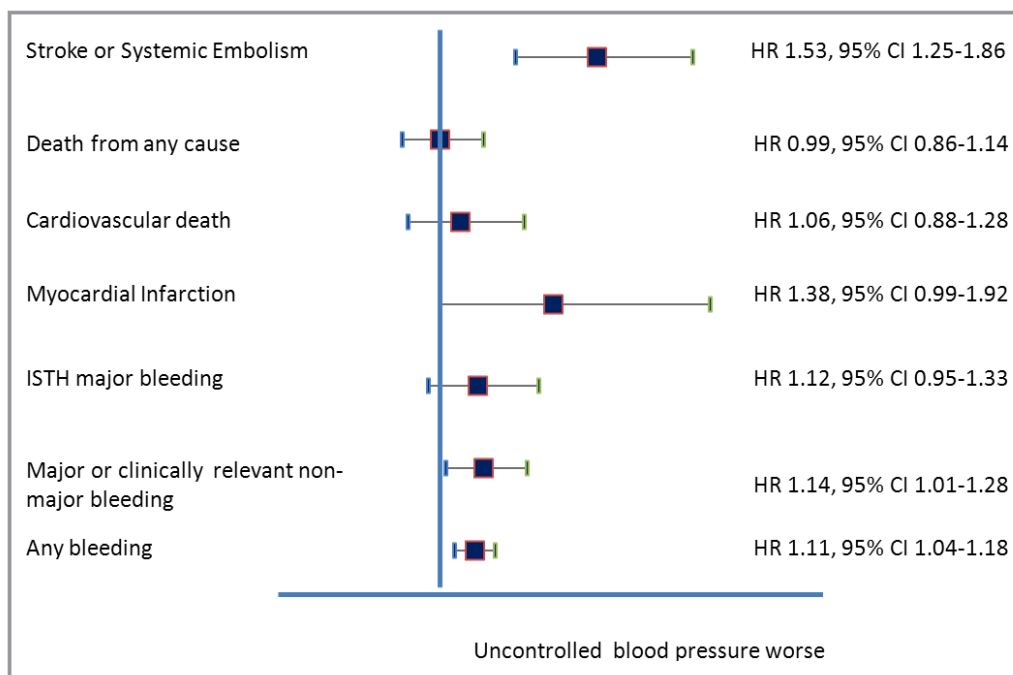
Figure 2. Adjusted HRs and 95% CI for the association between elevated blood pressure at any point during the trial and efficacy and safety endpoints. *Elevated blood pressure is defined as the mean of 2 most recent blood pressure measurements having an SBP >140 mm Hg and/or DBP >90 mm Hg. Stroke or systemic embolism outcome was adjusted by age, region, weight, diabetes, moderate valvular disease, previous stroke/TIA/embolism, type of AF, and previous VKA use. Death from any cause, cardiovascular death, and myocardial infarction were adjusted by age, sex, region, weight, moderate valvular disease, left BBB, history of MI, previous stroke/TIA/embolism, anemia, smoking status, previous VKA use, NYHA class, CHADS2 score, and renal function. Major bleeding or clinically relevant nonmajor bleeding and any bleeding were adjusting by age, sex, region, CAD, previous MI, history of bleeding, anemia, CHADS2 score, and renal function. AF indicates atrial fibrillation; BBB, bundle branch block; CAD, coronary artery disease; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; ISTH, International society on Thrombosis and Hemostasis; MI, myocardial infarction; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischemic attack; VKA, vitamin K antagonist.

reduction in SBP, did not significantly reduce the rate of stroke (relative risk, 0.91; 95% CI, 0.79−1.05).

This study looked at those patients with a history of hypertension requiring treatment, elevated BP at study entry, and elevated BP at any point during the trial and found the most significant finding to be that those patients with elevated BP at any point during the trial had a significantly increased risk of stroke or SE, thereby clearly establishing an association between elevated BP over time and the risk of stroke. Overall, these results underscore the importance of continuous BP control to lower the risk of stroke or SE in patients with AF.

Another important observation is that even for patients enrolled in a large clinical trial, 42% of patients who had a history of hypertension had elevated BP at study entry and 50% of all patients had elevated BP at some point during the trial (mean of 2 previous BP measurements having SBP ≥140 mm Hg and/or DBP ≥90 mm Hg). This highlights an opportunity to focus on BP management in those patients with AF, including those with a previous diagnosis of

hypertension. Additionally, only 7% of patients with elevated BP at baseline had no history of hypertension, suggesting that recognition of elevated BP, even among patients without a history of hypertension, is an important issue.

Patients without a history of hypertension had significant differences in baseline risk factors compared to those with a history of hypertension attributable to enrollment criteria for this study. However, despite these differences, the overall CHADS$_2$ and CHA$_2$DS$_2$-VASc scores were higher for those patients with a history of hypertension at baseline, as expected.

Limitations

Given the large cohort of patients included in this study, this analysis of BP at baseline, and, particularly, of BP over time, is one of the most complete analyses in patients with AF to date. However, given the observational nature of this analysis, we cannot determine whether the associations we describe are cause and effect. These analyses should be interpreted

Table 3. Association Between Treatment Effect of Apixaban Versus Warfarin and Outcomes by History of Hypertension at Baseline

	History of Hypertension			No History of Hypertension			Interaction P Value
	Apixaban Rate* (n)	Warfarin Rate* (n)	HR (95% CI)	Apixaban Rate* (n)	Warfarin Rate* (n)	HR (95% CI)	
Efficacy endpoints							
Stroke/SE	1.31 (191)	1.59 (231)	0.82 (0.68–0.10)	0.99 (21)	1.67 (34)	0.60 (0.35–1.02)	0.27
Ischemic/uncertain type of stroke	1.00 (146)	1.04 (151)	0.96 (0.77–1.21)	0.75 (16)	1.17 (24)	0.64 (0.34–1.21)	0.24
Hemorrhagic stroke	0.24 (36)	0.48 (70)	0.51 (0.34–0.76)	0.19 (4)	0.39 (8)	0.49 (0.15–1.61)	0.93
Death from any cause	3.38 (505)	3.77 (562)	0.90 (0.79–1.01)	4.53 (98)	5.09 (107)	0.89 (0.67–1.17)	0.96
CV death	1.75 (262)	1.91 (285)	0.92 (0.77–1.08)	2.13 (46)	2.81 (59)	0.76 (0.51–1.11)	0.38
MI	0.51 (75)	0.66 (96)	0.78 (0.57–1.05)	0.71 (15)	0.29 (6)	2.44 (0.95–6.28)	0.02
Safety endpoints							
ISTH major bleeding	2.07 (277)	3.00 (394)	0.69 (0.59–0.80)	2.60 (50)	3.73 (68)	0.70 (0.48–1.00)	0.96
Major or CRNM bleeding	4.00 (527)	5.94 (761)	0.68 (0.61–0.76)	4.54 (86)	6.50 (116)	0.70 (0.53–0.93)	0.82
Any bleeding	17.91 (2042)	25.76 (2680)	0.71 (0.67–0.75)	19.29 (314)	26.31 (380)	0.75 (0.64–0.87)	0.55

CI indicates confidence interval; CRNM, clinically relevant nonmajor; CV, cardiovascular; HR, hazard ratio; ISTH, International Society on Thrombosis and Hemostasis; MI, myocardial infarction; SE, systemic embolism.

*Rates are presented as 100 patient-years.

with caution given that they are subgroup analyses that were not preplanned and thus subject to the play of chance. In analysis of treatment effect of apixaban versus warfarin, there was a significant interaction whereby MI with apixaban was lower than with warfarin among patients with history of hypertension, but higher among patients without hypertension. Given the small number of events and lack of a clinically meaningful mechanism for this finding, this is most likely attributable to the play of chance.

Conclusion

In patients with AF and hypertension, having any elevated BP measurements was independently associated with a substantially higher risk of stroke or SE (HR, 1.53; 95% CI, 1.25–1.86). These data strongly support a focus to recognize and treat elevated BP to optimally reduce the risk of stroke in all patients with AF.

Sources of Funding

Disclosures

References

1. Tsang TS, Petty GW, Barnes ME, O'Fallon WM, Bailey KR, Wiebers DO, Sicks JD, Christianson TJ, Seward JB, Gersh BJ. The prevalence of atrial fibrillation in incident stroke cases and matched population controls in Rochester, Minnesota: changes over three decades. *J Am Coll Cardiol*. 2003;42:93–100.

2. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the Unites States, 1985–1999: implications for primary prevention. *Circulation*. 2003;108:711–716.

3. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.

4. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.

5. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.

6. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.

7. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial fibrillation. *JAMA*. 2001;285:2864–2870.

8. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risk of stroke and of coronary heart disease. *Br Med Bull*. 1994;50:272–298.

9. Arima H, Hart RG, Colman S, Chalmers J, Anderson C, Rodgers A, Woodward M, MacMahon S, Neal B. Perinodpril-based blood pressure lowering reduces major vascular events in patients with atrial fibrillation and prior stroke or transient ischemic attack. *Stroke*. 2005;36:2164–2169.

10. Lip GY, Frison L, Grind M. Effect of hypertension on anticoagulated patients with atrial fibrillation. *Eur Heart J*. 2007;28:752–759.

11. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding during antithrombotic therapy: recent data and ideas. *Stroke*. 2005;36:1588–1593.

12. Zabalgoitia M, Halperin JL, Pearce LA, Blackshear JL, Asinger RW, Hart RG. Transesophageal echocardiographic correlates of clinical risk of thromboembolism in nonvalvular atrial fibrillation. Stroke Prevention in Atrial Fibrillation III Investigators. *J Am Coll Cardiol*. 1998;31:1622–1626.

13. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized control trials. *Arch Intern Med*. 1994;154:1449–1457.

14. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, Gersh BJ, Granger CB, Hanna M, Horowitz J, Hylek EM, McMurray JJ, Verheugt FW, Wallentin L. Apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. *Am Heart J*. 2010;159:331–339.

15. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3:692–694.