Circulation

ORIGINAL RESEARCH ARTICLE

Efficacy and Safety of Apixaban Versus Warfarin in Patients With Atrial Fibrillation and Extremes in Body Weight

Insights From the ARISTOTLE Trial

Editorial, see p 2301

Stefan H. Hohnloser, MD
Marat Fudim, MD
John H. Alexander, MD, MHS
Daniel M. Wojdyla, MS
Justin A. Ezekowitz, MBBCH, MCs
Michael Hanna, MD
Dan Atar, MD, PhD
Ziad Hijazi, MD, PhD
M. Cecilia Bahit, MD
Sana M. Al-Khatib, MD, MHS
Jose Luis Lopez-Sendon, MD, PhD
Lars Wallentin, MD, PhD
Christopher B. Granger, MD
Renato D. Lopes, MD, MHS, PhD

BACKGROUND: Guidelines caution against the use of non–vitamin K antagonist oral anticoagulants in patients with extremely high (>120 kg) or low (≤60 kg) body weight because of a lack of data in these populations.

METHODS: In a post hoc analysis of ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; n=18 201), a randomized trial comparing apixaban with warfarin for the prevention of stroke in patients with atrial fibrillation, we estimated the randomized treatment effect (apixaban versus warfarin) stratified by body weight (≤60, >60–120, >120 kg) using a Cox regression model and tested the interaction between body weight and randomized treatment. The primary efficacy and safety outcomes were stroke or systemic embolism and major bleeding.

RESULTS: Of the 18 139 patients with available weight and outcomes data, 1985 (10.9%) were in the low-weight group (≤60 kg), 15 172 (83.6%) were in the midrange weight group (>60–120 kg), and 982 (5.4%) were in the high-weight group (>120 kg). The treatment effect of apixaban versus warfarin for the efficacy outcomes of stroke/systemic embolism, all-cause death, or myocardial infarction was consistent across the weight spectrum (interaction *P* value>0.05). For major bleeding, apixaban had a better safety profile than warfarin in all weight categories and even showed a greater relative risk reduction in patients in the low (≤60 kg; HR, 0.55; 95% CI, 0.36–0.82) and midrange (>60–120 kg) weight groups (HR, 0.71; 95% CI, 0.61–0.83; interaction *P* value=0.016).

CONCLUSIONS: Our findings provide evidence that apixaban is efficacious and safe across the spectrum of weight, including in low- (≤60 kg) and high-weight patients (>120 kg). The superiority on efficacy and safety outcomes of apixaban compared with warfarin persists across weight groups, with even greater reductions in major bleeding in patients with atrial fibrillation with low to normal weight as compared with high weight. The superiority of apixaban over warfarin in regard to efficacy and safety for stroke prevention seems to be similar in patients with atrial fibrillation across the spectrum of weight, including in low- and very high–weight patients. Thus, apixaban appears to be appropriate for patients with atrial fibrillation irrespective of body weight.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT00412984.

Key Words: atrial fibrillation ■ bleeding ■ non-vitamin K antagonist oral anticoagulants ■ stroke ■ warfarin

Sources of Funding, see page 2299

https://www.ahajournals.org/journal/circ

Clinical Perspective

What Is New?

- Apixaban is efficacious and safe across the spectrum of weight, including in low- (≤60 kg) and high-weight patients (>120 kg).
- The superiority on efficacy and safety outcomes of apixaban compared with warfarin persists across weight groups, with even greater reductions in major bleeding in patients with atrial fibrillation with low to normal weight as compared with high weight.

What Are the Clinical Implications?

- The superiority of apixaban over warfarin with regard to efficacy and safety for stroke prevention seems to be consistent in patients with atrial fibrillation across the spectrum of weight, including in very low– and very high–weight patients.
- Apixaban is more appropriate than warfarin for patients with atrial fibrillation irrespective of body weight.

Obesity is a comorbid condition of increasing prevalence, particularly in Western societies. In the United States, the prevalence rates of obesity and extreme obesity are 35% and 6.4%, respectively.[1] Obesity is an important risk factor for the development and maintenance of atrial fibrillation (AF).[2] Current guidelines recommend the use of fixed-dose non–vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in patients with AF, with some guidance on dose reduction for patients with multiple bleeding risk factors.[3,4] However, the currently available evidence on the use of NOACs in patients with low or high body weight is limited, and data on the efficacy and safety of these compounds in patients with extremes of weight are sparse. A major concern with the use of NOACs in patients with extremes of weight is that fixed dosing schedules in individuals above the average weight of those included in the clinical trials may result in unintentional over- or underdosing, with the consequence of enhanced risk of thromboembolic or bleeding complications. In fact, recent International Society on Thrombosis and Haemostasis (ISTH) guidelines caution against the use of NOACs in patients with extremely high weight (>120 kg) without clear guidance on use NOACs in patients with low (≤60 kg) body weight.[5] Based on this concern and the lack of respective data on this important topic, we conducted a post hoc analysis of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, which randomized patients with AF to apixaban or warfarin therapy. The primary aim of our analysis was to determine the efficacy and safety of NOACs for stroke prevention in patients with AF randomized to apixaban versus warfarin according to body weight.

METHODS

Study Population

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The ARISTOTLE trial (ClinicalTrials.gov NCT00412984) design and results have been previously published.[4,6] Briefly, ARISTOTLE was a double-blind, double dummy, randomized clinical trial of 18 201 patients with AF and at least 1 additional risk factor for stroke or systemic embolism. Risk factors included age ≥75 years; prior stroke, transient ischemic attack, or systemic embolism; heart failure or reduced left ventricular ejection fraction; diabetes mellitus; or hypertension requiring pharmacological treatment. Patients were randomized to treatment with 5 mg of apixaban twice daily (n=9120) or dose-adjusted warfarin (n=9081) with a target international normalized ratio of 2.0 to 3.0. Patients received a reduced dose of 2.5 mg of apixaban twice daily if they had ≥2 of the following criteria: age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL. For the present analyses, we included patients with available baseline measurements of weight.

Institutional review boards at participating centers reviewed and approved the study protocol, and all patients provided written informed consent.

Weight Groups

Weight was assessed at baseline in kilograms. We analyzed weight as a continuous variable, and patients were divided into 3 main groups based on drug dosing criteria (dose reduction ≤60 kg) and ISTH recommendations (no NOAC >120 kg)[5]: low weight (≤60 kg), midrange weight (>60–120 kg), and high weight (>120 kg). For an additional sensitivity analysis, the high-weight group was further subdivided into patients of 121 to 140 kg and >140 kg.

Outcomes

The efficacy outcomes were stroke (ischemic, hemorrhagic, or uncertain type) or systemic embolism, death from any cause, or myocardial infarction at 2 years of follow-up. Safety outcomes included ISTH major bleeding, ISTH clinically relevant nonmajor bleeding, intracranial bleeding, gastrointestinal bleeding, and any bleeding at 2 years of follow-up.[6] An independent clinical events committee whose members were unaware of treatment assignment adjudicated all outcomes according to prespecified criteria.

Statistical Analysis

Baseline categorical variables are presented as counts, and percentages and continuous variables are presented as medians (25th, 75th percentiles). The characteristics were compared across categories of weight using the χ^2 test and Kruskal-Wallis test for continuous variables. Cox regression models were used to estimate the HRs and 95% CIs

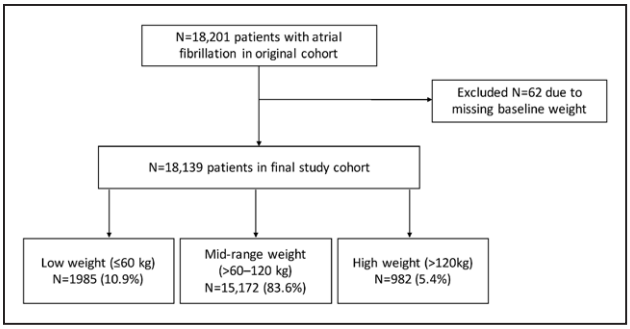

Figure 1. CONSORT flow diagram.

comparing apixaban with warfarin across body weight categories. Analyses of bleeding outcomes included only events occurring during study drug treatment, whereas stroke or systemic embolism and other efficacy outcomes were analyzed using the intention-to-treat principle. Restricted cubic splines were used to allow for nonlinear relationships between body weight and outcomes. Treatment effects were compared in separate models according to weight (both as a categorical variable and continuous), by adding interaction terms to models including body weight and treatment allocation. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC). A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 18 139 patients (99.7% of the entire population) with known baseline body weight at randomization were included in the present analysis and categorized into 3 groups according to body weight: 1985 (10.9%) patients were in the low-weight group (≤60 kg), 15 172 (83.6%) were in the midrange weight group (>60–120 kg), and 982 (5.4%) were in the high-weight group (>120 kg; Figure 1). Throughout study follow-up, there were only small changes in weight in each of the individual weight groups (Table 1). Baseline characteristics across groups of weight are shown in Table 2. Compared with the midrange and low-weight groups, patients in the high-weight group were younger, more likely to be male, and more likely to be randomized in North America. Patients in the low-weight group were more likely to be female and of Asian or Latin American ethnicity; have a history of stroke, transient ischemic attack, or systemic embolism; have abnormal renal function; have higher N-terminal probrain natriuretic peptide levels; and have a CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 yr, diabetes mellitus, stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74, sex category [female]) score of ≥2. Patients in the low-weight group were also more likely to be on a reduced dose of apixaban (27.2% of cases) when compared with those in the midrange or high-weight groups (1.9% and 0.3%, respectively). There were significant differences in concomitant medications among the 3 groups (Table 2).

Treatment Effect of Apixaban Versus Warfarin According to Weight

During a median follow-up of 21.8 months (25th, 75th percentiles [16.3, 28.1 months]), there were 475 stroke or systemic embolic events, 1268 all-cause mortality events, and 786 major bleeding events. The distribution of events by body weight group and treatment assignment is presented in Table 3. The relationship between efficacy and safety outcomes and weight as a continuous variable is presented in Figure 2. Overall, patients treated with apixaban had lower rates of both the efficacy and safety outcomes across most of the weight spectrum compared with patients treated with warfarin. The risk of stroke/systemic embolism, all-cause death, and ISTH major bleeding was higher in patients with lower weight at randomization; however, there was no significant interaction between study treatment (apixaban versus warfarin) and weight on efficacy outcomes such as stroke/systemic embolism, all-cause death, or myocardial infarction. There was a significant interaction between weight and study treatment for the outcome of ISTH major bleeding, suggesting that warfarin was associated with a higher risk of major bleeding in the lower weight range when compared with the higher weight categories; this was not seen with apixaban use.

Efficacy and safety outcomes were further stratified by the specific weight categories (Table 3; Figure I in the online-only Data Supplement) to highlight event rates and interaction testing among the 3 clinically relevant weight groups. The hazards for stroke/systemic embolism in the low-weight group (≤60 kg) were HR, 0.63; 95% CI, 0.41–0.96, those in the midrange weight group (>60–120 kg) were HR, 0.85; 95% CI, 0.70–1.05, and those in the high-weight group (≥120 kg)

Table 1. Change in Body Weight Throughout Study Follow-Up According to Body Weight Group

Change in Weight From Baseline	Body Weight at Screening, Median, 25th–75th (N)			*P* Value
	≤60 kg (N=1985)	>60 to 120 kg (N=15 172)	>120 kg (N=982)	
At 1 y	0.5, −1.0 to 2.0 (1468)	0.0, −2.0 to 2.0 (12 136)	0.0, −4.1 to 2.7 (817)	<0.0001
At 2 y	0.3, −1.0 to 2.4 (521)	0.0, −2.5 to 2.7 (4951)	-0.5, −5.6 to 4.1 (336)	0.0005
At 3 y	0.0, −2.0 to 2.0 (67)	0.0, −3.2 to 2.9 (863)	−1.8, −7.2 to 5.7 (100)	0.6264

Table 2. Baseline Characteristics According to Body Weight Category

Characteristic	Body Weight at Screening			*P* Value
	≤60 kg (N=1985)	>60 to 120 kg (N=15 172)	>120 kg (N=982)	
Age, median (25th, 75th), y	74 (66, 79)	70 (63, 76)	62 (56, 67)	<0.0001
Age ≥80	481 (24.2%)	1938 (12.8%)	7 (0.7%)	<0.0001
Female sex, n (%)	1430 (72.0%)	4809 (31.7%)	154 (15.7%)	<0.0001
Region of enrollment, n (%)				<0.0001
North America	227 (11.4%)	3667 (24.2%)	564 (57.4%)	
Latin America	492 (24.8%)	2881 (19.0%)	84 (8.6%)	
Europe	340 (17.1%)	6672 (44.0%)	306 (31.2%)	
Asia	926 (46.6%)	1952 (12.9%)	28 (2.9%)	
Systolic BP, median (25th, 75th), mm Hg	130, 118–140	130, 120–140	130, 120–140	<0.0001
Previous MI, n (%)	190 (9.6%)	2267 (15.0%)	122 (12.4%)	<0.0001
Previous clinically relevant or spontaneous bleeding, n (%)	286 (14.4%)	2548 (16.8%)	199 (20.3%)	0.0003
Qualifying risk factors, n (%)				
Age ≥75	934 (47.1%)	4665 (30.7%)	55 (5.6%)	<0.0001
Previous stroke, TIA, or SE	544 (27.4%)	2886 (19.0%)	96 (9.8%)	<0.0001
HF or reduced LVEF	736 (37.1%)	5333 (35.2%)	365 (37.2%)	0.1250
Diabetes mellitus	328 (16.5%)	3757 (24.8%)	449 (45.7%)	<0.0001
Hypertension requiring treatment	1546 (77.9%)	13 400 (88.3%)	919 (93.6%)	<0.0001
CHA_2DS_2-VASc, mean (SD)	3.95 (1.52)	3.39 (1.50)	2.71 (1.30)	<0.0001
CHA_2DS_2-VASc score, n (%)				<0.0001
≤1	80 (4.0%)	1342 (8.8%)	175 (17.8%)	
2	255 (12.8%)	3200 (21.1%)	301 (30.7%)	
≥3	1650 (83.1%)	10 630 (70.1%)	506 (51.5%)	
Reduced-dose apixaban/ apixaban placebo, n (%)	539 (27.2%)	289 (1.9%)	3 (0.3%)	<0.0001
Medications at time of randomization, n (%)				
ACE inhibitors or ARB	1159 (59.7%)	10 885 (72.9%)	749 (77.0%)	<0.0001
Amiodarone	212 (10.9%)	1745 (11.7%)	92 (9.5%)	0.0772
β-Blocker	982 (50.6%)	9760 (65.3%)	708 (72.8%)	<0.0001
Aspirin	601 (30.3%)	4703 (31.0%)	314 (32.0%)	0.6326
Clopidogrel	61 (3.1%)	266 (1.8%)	10 (1.0%)	<0.0001
Renal function, n (%)				<0.0001
Normal (80 mL/min)	108 (5.4%)	6467 (42.6%)	943 (96.0%)	
Mild impairment (>50–80 mL/min)	797 (40.2%)	6754 (44.5%)	36 (3.7%)	
Moderate impairment (>30–50 mL/min)	912 (45.9%)	1832 (12.1%)	3 (0.3%)	
Severe impairment (≤30 mL/ min)	166 (8.4%)	104 (0.7%)	0 (0.0%)	
Creatinine ≥1.5	84 (4.2%)	1073 (7.1%)	72 (7.3%)	<0.0001
Biomarkers, median (25th, 75th)				
NT-proBNP, ng/L	1019 (512, 1756)	698 (356, 1211)	523 (288, 944)	<0.0001
Troponin I, ng/L	6.3 (3.6, 12.6)	5.3 (3.3, 9.9)	4.9 (3.0, 9.0)	<0.0001

ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 yr, diabetes mellitus, stroke or transient ischemic attack or thromboembolism, vascular disease, age 65–74, sex category (female); HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal probrain natriuretic peptide; SE, systemic embolism; and TIA, transient ischemic attack.

were HR, 0.39; 95% CI, 0.12–1.22 (interaction *P* value=0.640). Among all efficacy end points, a significant interaction between weight and randomized treatment was only found for hemorrhagic stroke (interaction *P* value=0.042), suggesting that only for this efficacy end point, the relative effectiveness of apixaban versus warfarin was modified by differences in weight. Patients in the low-weight group (≤60 kg) who were on apixaban were at a lower risk of hemorrhagic stroke (HR, 0.16; 95% CI, 0.05–0.54) during follow-up compared with patients on warfarin. In patients in the midrange weight group, the risk of hemorrhagic stroke for apixaban compared with warfarin was also lower (HR, 0.64; 95% CI, 0.42–0.97). In the high-weight group (>120 kg), there were no hemorrhagic strokes in the apixaban arm and 4 in the warfarin arm.

Apixaban was associated with lower event rates for all safety end points when compared with warfarin (Table 3). In the case of ISTH major bleeding, the weight groups were associated with a differential risk. Apixaban had a better safety profile than warfarin in patients

Table 3. Treatment Effect of Apixaban Versus Warfarin According to Body Weight Group

Event	Rate per 100 pt/yr (no.)		HR (95% CI)	Interaction *P* Value*
	Apixaban	Warfarin	Apixaban Versus Warfarin	
Efficacy end points				
Stroke/SE				0.6401
≤60 kg	2.01 (34)	3.20 (52)	0.63 (0.41–0.96)	
61–120 kg	1.23 (173)	1.44 (201)	0.85 (0.70–1.05)	
>120 kg	0.44 (4)	1.13 (11)	0.39 (0.12–1.22)	
Stroke				0.8423
≤60 kg	1.95 (33)	2.95 (48)	0.66 (0.42–1.03)	
61–120 kg	1.14 (161)	1.37 (191)	0.84 (0.68–1.03)	
>120 kg	0.44 (4)	1.03 (10)	0.43 (0.13–1.36)	
Ischemic or uncertain type of stroke				0.9810
≤60 kg	1.77 (30)	1.90 (31)	0.93 (0.57–1.54)	
61–120 kg	0.91 (128)	0.98 (137)	0.93 (0.73–1.18)	
>120 kg	0.44 (4)	0.61 (6)	0.71 (0.20–2.52)	
Hemorrhagic stroke				0.0418
≤60 kg	0.18 (3)	1.10 (18)	0.16 (0.05–0.54)	
61–120 kg	0.25 (36)	0.40 (56)	0.64 (0.42–0.97)	
>120 kg	0.00 (0)	0.41 (4)	—	
All-cause death				0.3614
≤60 kg	7.00 (122)	6.33 (107)	1.10 (0.85–1.43)	
61–120 kg	3.14 (451)	3.75 (535)	0.84 (0.74–0.95)	
>120 kg	3.00 (28)	2.52 (25)	1.19 (0.69–2.04)	
Myocardial infarction				0.8694
≤60 kg	0.64 (11)	0.36 (6)	1.74 (0.64–4.71)	
61–120 kg	0.54 (76)	0.66 (92)	0.82 (0.60–1.11)	
>120 kg	0.33 (3)	0.41 (4)	0.81 (0.18–3.60)	
Safety end points				
Major bleeding				0.0158
≤60 kg	2.33 (36)	4.28 (62)	0.55 (0.36–0.82)	
61–120 kg	2.15 (277)	3.02 (379)	0.71 (0.61–0.83)	
>120 kg	1.55 (13)	2.08 (19)	0.74 (0.37–1.50)	
Major or CRNM bleeding				0.0108
≤60 kg	3.60 (55)	7.06 (101)	0.51 (0.37–0.71)	
61–120 kg	4.20 (532)	5.97 (730)	0.71 (0.63–0.79)	
>120 kg	2.77 (23)	4.83 (43)	0.58 (0.35–0.95)	
Intracranial bleeding				0.1833
≤60 kg	0.32 (5)	1.49 (22)	0.21 (0.08–0.56)	
61–120 kg	0.35 (46)	0.75 (96)	0.47 (0.33–0.67)	
>120 kg	0.00 (0)	0.43 (4)	—	
Gastrointestinal bleeding				0.1730
≤60 kg	0.90 (14)	1.09 (16)	0.84 (0.41–1.72)	
61–120 kg	0.67 (87)	0.79 (100)	0.85 (0.64–1.13)	
>120 kg	0.47 (4)	0.33 (3)	1.44 (0.32–6.42)	
Any bleeding				0.1101
≤60 kg	18.68 (244)	30.86 (344)	0.62 (0.53–0.73)	
61–120 kg	18.15 (1987)	25.29 (2528)	0.73 (0.69–0.78)	
>120 kg	16.44 (119)	25.13 (176)	0.67 (0.53–0.85)	

The distribution of patients in each individual weight group was as follows: N=1985, ≤60 kg; N=15 172, >60 to 120 kg; and N=982, >120 kg. CRNM indicates clinically relevant nonmajor; and SE, systemic embolism.

*Interaction *P* value computed with weight as continuous variable.

in the low (≤60 kg; HR, 0.55; 95% CI, 0.36–0.82) and midrange weight (>60–120 kg) groups (HR, 0.71; 95% CI, 0.61–0.83; interaction *P* value=0.016). However, in patients in the high-weight group (≥120 kg), despite an absolute lower risk of major bleeding, the relative risk between apixaban and warfarin was comparable (HR, 0.47; 95% CI, 0.37–1.50). Patients randomized to receive apixaban were at a lower risk of major or clinically relevant nonmajor bleeding across all 3 weight groups; however, the effect size was largest in the low-weight (≤60 kg; HR, 0.51; 95% CI, 0.37–0.71) and high-weight (≥120 kg) groups (HR, 0.58; 95% CI, 0.35–0.95), when compared with the midrange (>60–120 kg) group (HR, 0.71; 95% CI, 0.63–0.79; interaction *P* value=0.011). For all other safety outcomes (intracranial, gastrointestinal, or any bleeding), there were no significant interactions between apixaban and warfarin treatment effects and weight.

Treatment Effect of Apixaban Versus Warfarin in the High-Weight Group

In the high-weight category (>120 kg), there was no significant difference in the occurrence of efficacy outcomes associated with either apixaban or warfarin, but there was a lower risk of major and clinically relevant nonmajor bleeding (HR, 0.58; 95% CI, 0.35–0.95) or any bleeding with apixaban (HR, 0.67; 95% CI, 0.53–0.85) as compared with warfarin. The high-weight group was further stratified into 2 groups: 121 to 140 kg (n=724 [4%]) and >140 kg (n=258 [1.4%]). Baseline characteristics for the respective groups can be found in Table I in the online-only Data Supplement. The randomized treatment effect by body weight for the high-weight groups is shown in Table 4. The risk of stroke or systemic embolism associated with apixaban was lower than for warfarin in patients weighing 121 to 140 kg (HR, 0.21; 95% CI, 0.05–0.95). In the

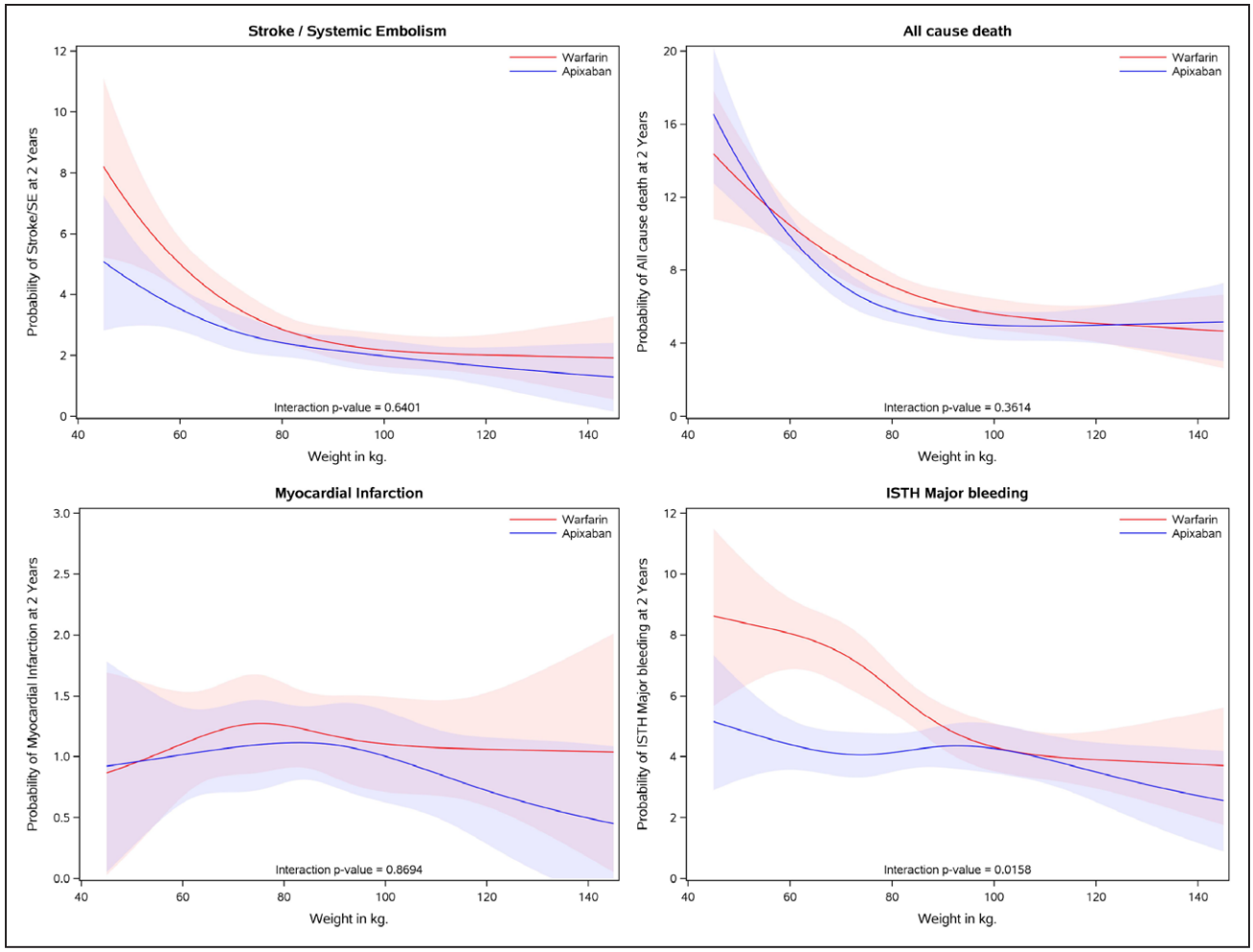

Figure 2. Efficacy and safety outcomes for apixaban vs warfarin, with weight as a continuous variable.
ISTH indicates International Society on Thrombosis and Haemostasis; and SE, systemic embolism.

>140 kg patient cohort, there were only 2 events in the apixaban group and 1 in the warfarin group, making it impossible to compare the 2 groups. There was no difference between apixaban and warfarin in relation to all-cause death for either of the weight groups (121–140 kg: HR, 1.23; 95% CI, 0.64–2.35; and >140 kg: HR, 1.14; 95% CI, 0.43–3.04). Patients in the 121 to 140 kg weight group randomized to apixaban were at comparable risk for major bleeding as those receiving warfarin (HR, 0.99; 95% CI, 0.46–2.10) but tended to have lower rates of any bleeding (HR, 0.61; 95% CI, 0.46–0.80). In the >140 kg weight group, there were no stroke/systemic embolic events in those receiving apixaban, but there were 5 stroke/systemic embolic events in those receiving warfarin. All-cause bleeding was comparable between both treatment arms (HR, 0.89; 95% CI, 0.57–1.39).

DISCUSSION

The present post hoc analysis of the ARISTOTLE trial represents the largest study in patients with AF evaluating the efficacy and safety of a NOAC in relation to body weight. The main finding is that apixaban is safe and efficacious in patients with AF with extremes of body weight. There was no interaction showing any attenuation of the treatment effect of apixaban compared with warfarin in extreme body weights.

Current guidelines and product labeling provide only limited guidance for NOAC use and dosing in patients with low body weight but none for the high body weight population. In fact, use of NOACs in the high-weight population is cautioned against.[5] To date there are no large randomized trials that have tested the efficacy and safety of NOACs in the low-weight or high-weight population. Given the absence of randomized trial data, one can gain some insight from the available pharmacodynamic and pharmacokinetic data for NOAC use. In a small study comprising 54 healthy volunteers (18 with body weight ≤50 kg, 18 with body weight 65–85 kg, and 19 body weight ≥120 kg), Upreti et al.[7] determined both plasma and urine levels of apixaban and measured antifactor Xa activity following administration of a single 10-mg dose of apixaban. Maximum blood

Table 4. Treatment Effect of Apixaban Versus Warfarin in High Weight Subgroups

Event	Rate (No.)		HR (95% CI)
	Apixaban	Warfarin	Apixaban Versus Warfarin
Efficacy end points			
Stroke/SE			
121–140 kg	0.29 (2)	1.41 (10)	0.21 (0.05–0.95)
>140 kg	0.85 (2)	0.38 (1)	2.35 (0.21–25.95)
Stroke			
121–140 kg	0.29 (2)	1.27 (9)	0.23 (0.05–1.07)
>140 kg	0.85 (2)	0.38 (1)	2.35 (0.21–25.95)
Ischemic or uncertain type of stroke			
121–140 kg	0.29 (2)	0.84 (6)	0.34 (0.07–1.72)
>140 kg	0.85 (2)	0.00 (0)	—
Hemorrhagic stroke			
121–140 kg	0.00 (0)	0.42 (3)	—
>140 kg	0.00 (0)	0.38 (1)	—
All-cause death			
121–140 kg	2.88 (20)	2.34 (17)	1.23 (0.64–2.35)
>140 kg	3.35 (8)	2.98 (8)	1.14 (0.43–3.04)
Myocardial infarction			
121–140 kg	0.29 (2)	0.28 (2)	1.05 (0.15–7.44)
>140 kg	0.43 (1)	0.76 (2)	0.54 (0.05–5.92)
Safety end points			
Major bleeding			
121–140 kg	2.06 (13)	2.09 (14)	0.99 (0.46–2.10)
>140 kg	0.00 (0)	2.05 (5)	—
Major or CRNM bleeding			
121–140 kg	2.54 (16)	5.55 (36)	0.46 (0.26–0.84)
>140 kg	3.51 (7)	2.90 (7)	1.21 (0.42–3.46)
Intracranial bleeding			
121–140 kg	0.00 (0)	0.44 (3)	—
>140 kg	0.00 (0)	0.41 (1)	—
Gastrointestinal bleeding			
121–140 kg	0.62 (4)	0.15 (1)	4.27 (0.48–38.24)
>140 kg	0.00 (0)	0.82 (2)	—
Any bleeding			
121–140 kg	15.15 (85)	25.63 (132)	0.61 (0.46–0.80)
>140 kg	20.86 (34)	23.74 (44)	0.89 (0.57–1.39)

The distribution of patients in each individual weight group was as follows: N=724, 121–140 kg and N=258, >140 kg. CRNM indicates clinically relevant nonmajor; and SE, systemic embolism.

levels of the drug and areas under the concentration versus time curve were found to be 31% (90% CI, 18% to 41%) and 23% (90% CI, 9% to 35%) lower in the high-weight patients. On the other hand, the time to maximum concentration of apixaban in the high-weight group was similar to that in the reference group (65–85 kg) and amounted to 3.9 h (1.0–6.0). The authors concluded from their findings that adjustment of the apixaban dose based on body weight is not necessary.

Notably, our post hoc analysis supports previous retrospective subgroup analyses of other smaller NOAC trials, which demonstrated that the use of NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) in the high-weight population appears to be efficacious and safe when compared with warfarin, irrespective of the underlying condition (AF or venous thromboembolism).[8–12] These findings are also supported by meta-analyses of major NOAC trials in AF and venous thromboembolism in the high-weight groups.[13–15] The meta-analysis by Proietti et al[14] suggests a potential relationship between weight and major adverse outcomes in patients with AF in randomized, controlled trials, as well as observational cohort studies. Investigators reported a lower risk for stroke/systemic embolic events (OR, 0.75; 95% CI, 0.66–0.84 and OR, 0.62; 95% CI, 0.54–0.70, respectively) in obese patients treated with NOACs.[14] For major bleeding, only obese patients were at lower risk compared with normal weight patients (OR, 0.84; 95% CI, 0.72–0.98). Proietti et al[14] concluded that there might be an obesity paradox in patients with AF, particularly for all-cause and cardiovascular death but also for stroke/systemic embolic events because it was also seen in the EORP-AF General Pilot Registry (EURObservational Research Programme Atrial Fibrillation).[16] Interestingly, a treatment benefit favoring NOACs over warfarin for both efficacy and safety was seen only in normal weight but not in overweight/obese patients. Evidence for a potential obesity paradox has also been reported for apixaban utilizing data from the ARISTOTLE trial.[17] Here, higher body mass index was associated with a lower risk of the composite end point of all-cause mortality, stroke, systemic embolism, and myocardial infarction compared with a normal body mass index.[17] There was no significant association between obesity and major bleeding. Although our analysis of the ARISTOTLE trial confirms the preserved treatment effects of apixaban in patients with high body weight, we are the first to present the findings for patients with extremely high body weight (121–140 kg and >140 kg). In both the 121 to 140 kg and >140 kg groups, the benefits of apixaban over warfarin in reducing stroke, death, and bleeding were preserved.

In the ARISTOTLE trial dose-reduction criteria were applied to patients who had at least 2 high risk criteria (age ≥80 years, body weight ≤60 kg, or a serum creatinine level ≥1.5 mg/dL). These criteria were based on pharmacokinetic modeling,[7,18,19] and a reduction of the apixaban dose from 5 mg to 2.5 mg was intended to avoid increased blood drug levels and thus decrease the risk of bleeding. In the ARISTOTLE trial, 831 patients (4.6%) had 2 or 3 dose-reduction criteria and were receiving the reduced dose of apixaban. The safety and effectiveness of the reduced dose of apixaban appeared

to be unchanged from the standard dose of apixaban in patients with ≤1 high risk criteria.[20] Further, 5 mg of apixaban twice daily appeared to be safe and efficacious in patients with only 1 dose-reduction criterion, despite a higher risk of stroke or systemic embolism and major bleeding in this population. Our analysis confirms and extends the findings by Alexander et al[20] because it shows that the effectiveness of apixaban is consistent across weight categories. Importantly, patients treated with apixaban (versus warfarin) with weight in the low to midrange had an even greater reduction in major bleeding when compared with patients with higher weight (>120 kg; interaction *P* value=0.016). Finally, patients in the predefined low-weight category of ≤60 kg, of whom only 27% were on a reduced dose of apixaban, were found to have better efficacy and safety outcomes with apixaban as compared with warfarin.

Limitations

The present findings are based on results obtained from a post hoc analysis utilizing weight measurements at baseline. Subgroup analyses are subject to many limitations because of their retrospective nature. Furthermore, the relationship between changes in weight over time and outcomes cannot be assessed, although changes in weight throughout follow-up were small. Although residual confounding can never be excluded, this was a randomized clinical trial, and comparisons were only made between randomized groups (warfarin versus apixaban), thus minimizing the risk of confounding. Finally, our results cannot necessarily be generalized to the general population given differences in our trial population from the general population.

Conclusions

The data obtained from the large ARISTOTLE trial provided evidence that apixaban is efficacious and safe across the spectrum of weight, including low- (≤60 kg) and high-weight patients (>120 kg). The superiority on efficacy and safety outcomes of apixaban compared with warfarin persists across weight groups, with even greater reduction in major bleeding in patients with AF with low to normal weight as compared with high weight.

ARTICLE INFORMATION

Received September 13, 2018; accepted January 11, 2019.

Guest Editor for this article was Brian Olshansky, MD.

The online-only Data Supplement, podcast, and transcript are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/circulationaha.118.037955.

Correspondence

Renato D. Lopes, MD, PhD, MHS, Duke Clinical Research Institute, Duke University School of Medicine, 2400 Pratt St, Durham, NC 27710. Email renato.lopes@duke.edu

Affiliations

Johann Wolfgang Goethe University, Frankfurt, Germany (S.G.G.). Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (M.F., J.H.A., D.M.W., S.M.A.-K., C.B.G., R.D.L.). University of Alberta, Alberta, Canada (J.A.E.). Bristol-Myers Squibb, Princeton, NJ (M.H.). University of Oslo, Norway (D.A.). Uppsala Clinical Research Center, Uppsala University, Sweden (Z.H., L.W.). Fundación INECO Rosario, Department of Cardiology, INECO Neurociencias Orono, Santa Fe, Argentina (M.C.B.). Hospital Universitario La Paz, Madrid, Spain (J.L.L.-S.).

Sources of Funding

This work was supported by Bristol-Myers Squibb and Pfizer, Inc.

Disclosures

Dr Hanna is a former employee of Bristol-Myers Squibb and was employed there during completion of this study. Dr Hohnloser received consulting fees/honoraria from Bayer HealthCare, Medtronic, Bristol-Myers Squibb, Daiichi Sankyo, Sanofi Aventis, Abbott, Boehringer Ingelheim, and Pfizer. Dr Fudim was supported by American Heart Association Grant 17MCPRP33460225 and National Institutes of Health T32 grant 5T32HL007101 and received consulting fees/honoraria from Coridea and AxonTherapies. Dr Alexander received consulting fees/honoraria from Bristol-Myers Squibb, CSL Behring, Pfizer, Portola, and VasoPrep Surgical and research grants from Boehringer Ingelheim, Bristol-Myers Squibb, CSL Behring, Sanofi, and Tenax Therapeutics. Dr Ezekowitz received research funding from the National Institutes of Health and Alere Inc. Dr Hijazi received consulting fees/honoraria from Bristol-Myers Squibb/Pfizer, Roche Diagnostics. Dr Wallentin received institutional research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Merck & Co, and Roche Diagnostics. Dr Granger received consulting fees/honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Gilead Sciences, Inc., GlaxoSmithKline, Hoffman LaRoche, Janssen, Medtronic Inc., Novartis, Pfizer, The Medicines Company, and Verseon and research grants from Armetheon, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi, GlaxoSmithKline, Janssen, Medtronic Foundation, Novartis Corporation, Pfizer, and The Medicines Company. Dr Lopes received research grants from Amgen, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Medtronic PLC, and Sanofi-Aventis and consulting/advisory board fees from Bristol-Myers Squibb/Pfizer, Bayer, and Boehringer Ingelheim. The other authors report no conflicts of interest.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA.* 2014;311:806–814. doi: 10.1001/jama.2014.732
2. Lavie CJ, Pandey A, Lau DH, Alpert MA, Sanders P. Obesity and atrial fibrillation prevalence, pathogenesis, and prognosis: effects of weight loss and exercise. *J Am Coll Cardiol.* 2017;70:2022–2035. doi: 10.1016/j.jacc.2017.09.002
3. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, Oldgren J, Sinnaeve P, Camm AJ, Kirchhof P; ESC Scientific Document Group. Updated European Heart Rhythm Association practical guide on the use of non–vitamin-K antagonist anticoagulants in patients with nonvalvular atrial fibrillation: executive summary. *Eur Heart J.* 2017;38:2137–2149. doi: 10.1093/eurheartj/ehw058
4. 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; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–992. doi: 10.1056/NEJMoa1107039
5. Martin K, Beyer-Westendorf J, Davidson BL, Huisman MV, Sandset PM, Moll S. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2016;14:1308–1313. doi: 10.1111/jth.13323
6. 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; ARISTOTLE Investigators. Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (AR-

ISTOTLE) trial: design and rationale. *Am Heart J.* 2010;159:331–339. doi: 10.1016/j.ahj.2009.07.035
7. Upreti VV, Wang J, Barrett YC, Byon W, Boyd RA, Pursley J, LaCreta FP, Frost CE. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. *Br J Clin Pharmacol.* 2013;76:908–916. doi: 10.1111/bcp.12114
8. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369:799–808. doi: 10.1056/NEJMoa1302507
9. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Špinar J, Ruzyllo W, Ruda M, Koretsune Y, Betcher J, Shi M, Grip LT, Patel SP, Patel I, Hanyok JJ, Mercuri M, Antman EM; ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369:2093–2104. doi: 10.1056/NEJMoa1310907
10. 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; RELY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561
11. 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; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891. doi: 10.1056/NEJMoa1009638
12. Balla SR, Cyr DD, Lokhnygina Y, Becker RC, Berkowitz SD, Breithardt G, Fox KAA, Hacke W, Halperin JL, Hankey GJ, Mahaffey KW, Nessel CC, Piccini JP, Singer DE, Patel MR. Relation of risk of stroke in patients with atrial fibrillation to body mass index (from patients treated with rivaroxaban and warfarin in the rivaroxaban once daily oral direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation trial). *Am J Cardiol.* 2017;119:1989–1996. doi: 10.1016/j.amjcard.2017.03.028
13. Di Minno MN, Lupoli R, Di Minno A, Ambrosino P, Scalera A, Dentali F. Effect of body weight on efficacy and safety of direct oral anticoagulants in the treatment of patients with acute venous thromboembolism: a meta-analysis of randomized controlled trials. *Ann Med.* 2015;47:61–68. doi: 10.3109/07853890.2014.982064
14. Proietti M, Guiducci E, Cheli P, Lip GY. Is there an obesity paradox for outcomes in atrial fibrillation?: A systematic review and meta-Analysis of non–vitamin K antagonist oral anticoagulant trials. *Stroke.* 2017;48:857–866. doi: 10.1161/STROKEAHA.116.015984
15. Boonyawat K, Caron F, Li A, Chai-Adisaksopha C, Lim W, Iorio A, Lopes RD, Garcia D, Crowther MA. Association of body weight with efficacy and safety outcomes in phase III randomized controlled trials of direct oral anticoagulants: a systematic review and meta-analysis. *J Thromb Haemost.* 2017;15:1322–1333. doi: 10.1111/jth.13701
16. Boriani G, Laroche C, Diemberger I, Fantecchi E, Meeder J, Kurpesa M, Baluta MM, Proietti M, Tavazzi L, Maggioni AP, Lip GYH; EORP-AF General Pilot Registry Investigators. Overweight and obesity in patients with atrial fibrillation: sex differences in 1-year outcomes in the EORP-AF General Pilot Registry. *J Cardiovasc Electrophysiol.* 2018;29:566–572. doi: 10.1111/jce.13428
17. Sandhu RK, Ezekowitz J, Andersson U, Alexander JH, Granger CB, Halvorsen S, Hanna M, Hijazi Z, Jansky P, Lopes RD, Wallentin L. The "obesity paradox" in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *Eur Heart J.* 2016;37:2869–2878. doi: 10.1093/eurheartj/ehw124
18. Frost CE, Song Y, Shenker A, Wang J, Barrett YC, Schuster A, Harris SI, LaCreta F. Effects of age and sex on the single-dose pharmacokinetics and pharmacodynamics of apixaban. *Clin Pharmacokinet.* 2015;54:651–662. doi: 10.1007/s40262-014-0228-0
19. Chang M, Yu Z, Shenker A, Wang J, Pursley J, Byon W, Boyd RA, LaCreta F, Frost CE. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. *J Clin Pharmacol.* 2016;56:637–645. doi: 10.1002/jcph.633
20. Alexander JH, Andersson U, Lopes RD, Hijazi Z, Hohnloser SH, Ezekowitz JA, Halvorsen S, Hanna M, Commerford P, Ruzyllo W, Huber K, Al-Khatib SM, Granger CB, Wallentin L; Apixaban for Reduction of Stroke and Other Thromboembolic Complications in Atrial Fibrillation (ARISTOTLE) Investigators. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. *JAMA Cardiol.* 2016;1:673–681. doi: 10.1001/jamacardio.2016.1829