Left Ventricular Systolic Dysfunction, Heart Failure, and the Risk of Stroke and Systemic Embolism in Patients With Atrial Fibrillation

Insights From the ARISTOTLE Trial

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Background—We examined the risk of stroke or systemic embolism (SSE) conferred by heart failure (HF) and left ventricular systolic dysfunction (LVSD) in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (ARISTOTLE), as well as the effect of apixaban versus warfarin.

Methods and Results—The risk of a number of outcomes, including the composite of SSE or death (to take account of competing risks) and composite of SSE, major bleeding, or death (net clinical benefit) were calculated in 3 patient groups: (1) no HF/no LVSD (n=8728), (2) HF/no LVSD (n=3207), and (3) LVSD with/without symptomatic HF (n=2736). The rate of both outcomes was highest in patients with LVSD (SSE or death 8.06; SSE, major bleeding, or death 10.46 per 100 patient-years), intermediate for HF but preserved LV systolic function (5.32; 7.24), and lowest in patients without HF or LVSD (1.54; 5.27); each comparison $P<0.0001$. Each outcome was less frequent in patients treated with apixaban: in all ARISTOTLE patients, the apixaban/warfarin hazard ratio for SSE or death was 0.89 (95% confidence interval, 0.81–0.98; $P=0.02$); for SSE, major bleed, or death it was 0.85 (0.78–0.92; $P<0.001$). There was no heterogeneity of treatment effect across the 3 groups.

Conclusions—Patients with LVSD (with/without HF) had a higher risk of SSE or death (but similar rate of SSE) compared with patients with HF but preserved LV systolic function; both had a greater risk than patients without either HF or LVSD. Apixaban reduced the risk of both outcomes more than warfarin in all 3 patient groups.

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Key Words: atrial fibrillation ■ heart failure ■ left ventricular systolic dysfunction ■ stroke

Tools which estimate the risk of stroke in patients with atrial fibrillation are widely used in clinical practice to help in the choice of antithrombotic strategy.[1–3] One of the most commonly used is the cardiac failure, hypertension, age, diabetes mellitus, stroke (doubled) [$CHADS_2$] score.[2] Although $CHADS_2$ and other scores include cardiac failure or congestive heart failure (HF), it is unclear how HF should be defined and whether it is an independent risk factor for thromboembolism.[4–9]

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In a pooled analysis of 3 trials, moderate to severe echocardiographic left ventricular systolic dysfunction (LVSD) was an independent risk factor for stroke in patients with atrial fibrillation, although this was not confirmed in all

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subsequent studies.[10–14] Moreover, several analyses have shown that clinical HF is not an independent risk factor for stroke in patients with atrial fibrillation although left ventricular (LV) function was not documented in most of these studies and it is likely that patients with preserved, as well as reduced ejection fraction (EF) were included among those with HF.[4–14]

To further examine the relationship among ventricular function, clinical HF, and the risk of stroke or systemic embolism (SSE) in patients with atrial fibrillation, we undertook a retrospective analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE).[15,16] We also examined the effect of apixaban, compared with warfarin, according to LV function and HF status.

Methods

Patients

The design and results of ARISTOTLE have been reported in detail.[15,16] In brief, ARISTOTLE was a double-blind, double-dummy, randomized trial comparing apixaban 5 mg twice daily (or 2.5 mg twice daily for patients with ≤2 of the following 3 criteria: age, ≥80 years; body weight, ≤60 kg; or serum creatinine level, ≥1.5 mg/dL) with warfarin (dosed by the investigator to achieve a target international normalized ratio, 2.0–3.0) in patients with atrial fibrillation at risk of stroke. The inclusion criteria were persistent or paroxysmal atrial fibrillation and 1 or more of the following risk factors for stroke: age, ≥75 years; prior stroke, transient ischemic attack (TIA), or systemic embolism; symptomatic HF within 3 months; LVSD that is, EF ≤40%; diabetes mellitus; or hypertension requiring pharmacological treatment. Reasons for exclusion included atrial fibrillation because of a reversible cause; mitral stenosis, a prosthetic heart valve or other indication for oral anticoagulation; need for aspirin in a dose >165 mg/d or combined with clopidogrel; recent stroke (<7 days); increased risk of hemorrhage; anemia with hemoglobin <9 g/dL; creatinine clearance <25 mL/min; active liver disease; other comorbid condition with reduced life expectancy and inability to comply with international normalized ratio monitoring or other study procedures. Institutional review board approval and patient written informed consent were obtained before enrolment.

Trial Outcomes

The primary efficacy outcome was stroke (ischemic or hemorrhagic) or systemic embolism. The key secondary efficacy outcome was death from any cause. The primary safety outcome was major bleeding, defined using the International Society on Thrombosis and Hemostasis criteria. Another predefined efficacy outcome was the composite of stroke, systemic embolism, or death. The following net clinical benefit composite outcomes were also prespecified: stroke, systemic embolism, or major bleeding and stroke, systemic embolism, major bleeding or death from any cause. All primary and secondary efficacy and safety outcome events were adjudicated by a blinded clinical events committee using prespecified criteria.

For this analysis, we also report HF hospitalizations. These were not adjudicated events and but were designated the primary reason for admission by the trial investigators.

Definition of LVSD and HF

Information on investigator reported HF and ventricular function was obtained from the trial case report forms. Information on HF was available from the Inclusion Criteria page (symptomatic congestive HF within 3 months) and the Cardiovascular Disease History page (Does the subject have symptomatic congestive HF?). Similarly, information on LV function was obtained from the Inclusion Criteria page (LV dysfunction with an EF ≤40% by echocardiography, radionuclide study, or contrast angiography) and the Assessment of Left Ventricular Function page which recorded EF or LV dysfunction category (normal, mild, moderate, or severe), whether an evaluation of LV function had been made. Only patients with a report of both HF status and LV function were included in this analysis. These patients were divided into 3 categories: (1) patients with LVSD, with or without symptomatic HF. LVSD was defined as an EF ≤40% or a report of moderate or severe LVSD; (2) patients with HF and preserved EF (>40%), normal LV function, or mild LVSD, collectively referred to as HF with preserved EF (HF-PEF); and (3) patients with no HF and an EF >40% or normal LV function (ie, with neither LVSD nor HF-PEF). The ARISTOTLE prespecified efficacy and safety outcomes were analyzed post hoc in each of these patient groups, as was the effect of apixaban compared with warfarin.

Statistical Analysis

Baseline characteristics were summarized using medians and quartiles for continuous variables and frequencies and percentages for categorical variables. These characteristics were compared across patient groups using Kruskal–Wallis and ANOVA tests. Efficacy and safety end points are presented as rates per 100 patient-years of follow-up. Hazard ratios (HRs) comparing the LVSD and HF-PEF groups with the reference group (no LVSD/no HF) were derived from a Cox proportional hazards model. Withal models were unadjusted except SSE where the following variables were used to derive adjusted HRs for the SSE end point: age, sex, hypertension, diabetes mellitus, coronary artery disease (any of prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), history of stroke/TIA, body mass index, and renal function (eGFR [estimated glomerular filtration rate]). The interactions between the randomized treatment and patient group were computed using a Cox proportional hazards model, which included the randomized treatment, the patient group, and the interaction between the 2 as covariates. Statistical analyses were performed at the Duke Clinical Research Institute using SAS software version 9.22 (SAS Institute, Inc, Cary, NC). All tests were 2-sided and a P value of <0.05 was considered statistically significant.

Results

A total of 18 201 patients were randomized, of which 14 671 (81%) had information on both HF status and LV systolic function. Of these 14 671 patients, 8728 (59%) had no report of symptomatic HF and an EF >40% (n=7473) or normal LV systolic function (n=1101) or mild dysfunction (n=154). A further 3207 patients (22%) had a report of symptomatic HF and an EF >40% (n=2971) or normal LV systolic function (n=181) or mild dysfunction (n=55; ie, the study definition of HF-PEF. Finally, 2736 patients (19%) had an EF ≤40% (n=2623) or moderate or severe dysfunction (n=113). Of these 2736 patients, 1865 (13%) had a report of symptomatic HF and 871 (5.9%) had asymptomatic LVSD.

The median overall follow-up in ARISTOTLE was 18 months.

Baseline Characteristics

Patients With LVSD and HF-PEF

The baseline characteristics of patients with LVSD (with or without symptomatic HF), patients with HF and HF-PEF and those with neither LVSD nor HF (no LVSD/no HF) are shown in Table 1.

Compared with patients with LVSD, patients with HF-PEF were twice as likely to be women, were more likely to have a history of hypertension (although had a similar baseline blood pressure) and more often treated with a calcium channel blocker. Conversely, patients with LVSD were more likely than those with HF-PEF to have a history of myocardial infarction or revascularization procedure, have anemia and

Table 1. Baseline Characteristics

	LVSD (n=2736)	HF-PEF (n=3207)	No LVSD/No HF (n=8728)	*P* Value*
Age (median, 25th–75th)	68 (60–74)	69 (61–75)	71 (64–76)	<0.0001
Age ≥75 y, n (%)	641 (23)	811 (25)	2944 (34)	<0.0001
Female, n (%)	583 (21)	1354 (42)	3068 (35)	<0.0001
Systolic blood pressure (median, 25th–75th), mm Hg	126 (114–138)	130 (120–140)	130 (120–140)	<0.0001
Diastolic blood pressure (median, 25th–75th), mm Hg	80 (70–85)	80 (71–88)	80 (70–86)	<0.0001
Body mass index (median, 25th–75th), kg/m^2	28.1 (24.7–32.0)	29.3 (25.8–33.5)	28.5 (25.3–32.5)	<0.0001
Diabetes mellitus, n (%)	736 (27)	808 (25)	2182 (25)	0.13
Hypertension, n (%)	2059 (75)	2851 (89)	7845 (90)	<0.0001
Documented coronary artery disease, n (%)	1172 (43)	1537 (48)	2538 (29)	<0.0001
History of at least moderate valvular disease, n (%)	817 (30)	800 (25)	1504 (17)	<0.0001
Mitral regurgitation	754 (28)	690 (22)	1255 (14)	<0.0001
Mitral stenosis	17 (<1)	34 (1)	75 (1)	0.19
Aortic regurgitation	171 (6)	210 (7)	361 (4)	<0.0001
Aortic stenosis	57 (2)	95 (3)	170 (2)	0.0033
Left BBB, n (%)	307 (11)	156 (5)	254 (3)	<0.0001
Prior myocardial Infarction, n (%)	763 (28)	572 (18)	934 (11)	<0.0001
Prior percutaneous coronary intervention, n (%)	380 (14)	249 (8)	890 (10)	<0.0001
Prior coronary artery bypass graft, n (%)	339 (12)	182 (6)	576 (7)	<0.0001
Implantable cardioverter defibrillator, n (%)	223 (8)	27 (1)	47 (<1)	<0.0001
Resynchronization device, n (%)	81 (3)	11 (<1)	11 (<1)	<0.0001
Prior stroke or TIA, n (%)	432 (16)	560 (17)	1710 (20)	<0.0001
Anemia, n (%)	216 (8)	267 (8)	637 (7)	0.15
Current smoker, n (%)	302 (11)	265 (8)	653 (7)	<0.0001
Type of atrial fibrillation, n (%)				
Paroxysmal	295 (11)	473 (15)	1642 (19)	<0.0001
Persistent or permanent	2441 (89)	2732 (85)	7085 (81)	
Prior use of vitamin K antagonists, n (%)	1656 (61)	1627 (51)	5459 (63)	<0.0001
Current NYHA Class, n (%)				
I	731 (27)	529 (16)	6374 (73)	<0.0001
II	1373 (50)	1974 (62)	2127 (24)	
III	598 (22)	681 (21)	205 (2)	
IV	33 (1)	23 (<1)	4 (<1)	
LV ejection fraction (median, 25th–75th; n=12 900), n (%)	35 (30–39)	56 (50–62)	60 (55–65)	<0.0001
LV dysfunction classification [n=1714], n (%)				
Normal	16 (7)	181 (77)	1101 (88)	
Mild	14 (6)	55 (23)	154 (12)	
Moderate	123 (55)	0 (0)	0 (0)	
Severe	70 (31)	0 (0)	0 (0)	
CHADS (mean, SD)	2.22 (1.20)	2.67 (1.08)	1.88 (0.99)	<0.001
1	803 (29)	284 (9)	3880 (45)	<0.0001
2	986 (36)	1404 (44)	2911 (33)	
≥3	947 (35)	1519 (47)	1937 (22)	

(*Continued*)

Table 1. (Continued)

	LVSD (n=2736)	HF-PEF (n=3207)	No LVSD/No HF (n=8728)	*P* Value*
Creatinine clearance, n (%)				
Normal (80 mL/min)	1127 (41)	1390 (43)	3670 (42)	<0.0001
Mild impairment (>50–80 mL/min)	1103 (41)	1259 (39)	3698 (43)	
Moderate impairment (>30–50 mL/min)	442 (16)	478 (15)	1239 (14)	
Severe impairment (≤30 mL/min)	52 (2)	72 (2)	86 (1)	
Medications at time of randomization, n (%)				
ACE inhibitor or ARB	2205 (81)	2473 (77)	5802 (66)	<0.0001
Amiodarone	417 (15)	418 (13)	812 (9)	<0.0001
β-Blocker	2043 (75)	2199 (69)	5381 (62)	<0.0001
Aspirin	938 (34)	1026 (32)	2618 (30)	<0.0001
Clopidogrel	66 (2)	59 (2)	168 (2)	0.22
Digoxin	1299 (47)	1258 (39)	2102 (24)	<0.0001
Calcium blocker	430 (16)	846 (26)	3245 (37)	<0.0001
Statin	1184 (43)	1203 (38)	4032 (46)	<0.0001
Diuretic	1992 (73)	2235 (70)	4000 (46)	<0.0001
Aldosterone antagonist	62 (2)	46 (1)	42 (<1)	<0.0001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BBB, bundle branch block; CHADS, cardiac failure, hypertension, age, diabetes mellitus, stroke; HF-PEF, heart failure with preserved ejection fraction; LVSD, left ventricular systolic dysfunction; NYHA, New York Heart Association; and TIA, transient ischemic attack.

*For continuous variables derived from the Kruskal–Wallis test except for CHADS scores (ANOVA).

to be treated with a β-blocker and digoxin (although these differences were small). Patients with LVSD were also more likely than those with HF-PEF to have left bundle-branch block on their ECG and to have an implanted cardioverter defibrillator.

By definition, more patients with HF-PEF were in New York Heart Association functional class II–IV and had a higher median EF (56%) than those with LVSD (35%).

Patients with LVSD were more likely to have persistent (as opposed to paroxysmal AF) than patients with HF-PEF and more likely to have received a vitamin K antagonist before randomization.

There was a substantial difference in the distribution of $CHADS_2$ score between patients with LVSD and those with HF-PEF. The proportion of patients with a score of 1 was 29.4% among those with LVSD compared with 8.9% among those with HF-PEF.

Patients With Neither LVSD Nor HF-PEF

Patients without either LVSD or HF-PEF were older than those in the other 2 groups, less likely to have coronary heart or valvular disease and more likely to have a history of prior stroke or TIA. These patients were also less likely to be treated with an ACE (angiotensin-converting enzyme) inhibitor/ARB (angiotensin receptor blocker), β-blocker, diuretic, amiodarone, or aspirin (but more likely than any other group to be treated with a calcium channel blocker). By definition, more patients in this group than in any other were in New York Heart Association functional class I and had the highest median EF (60%). This group also had the greatest proportion

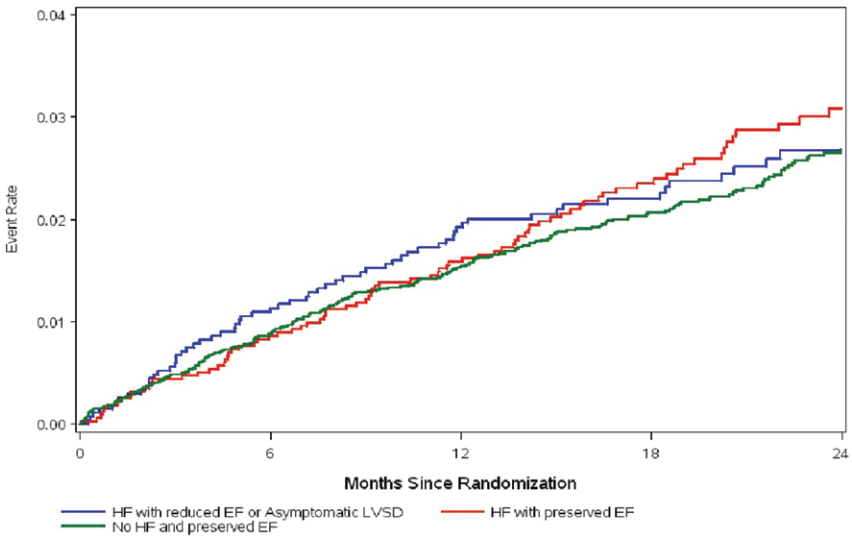

Figure. Cumulative incidence of the primary composite outcome of stroke or systemic embolism in the 3 patient groups: (1) no heart failure (HF)/no left ventricular systolic dysfunction (LVSD), (2) HF/no LVSD, and (3) LVSD with/without symptomatic HF.

Table 2. Association Between HF/LSVD Status and Efficacy, Safety, and Net Benefit Outcomes

	LVSD		HF-PEF		No LVSD/No HF	
	Rate* (n)	HR† (95% CI)	Rate* (n)	HR† (95% CI)	Rate* (n)	*P* Value
Efficacy end points						
Stroke or systemic embolism‡	1.39 (67)	1.01 (0.77–1.33)	1.52 (89)	1.11 (0.87–1.42)	1.37 (224)	0.71
Stroke	1.29 (62)	0.98 (0.74–1.30)	1.39 (81)	1.06 (0.82–1.36)	1.31 (214)	0.89
Ischemic/uncertain type stroke	1.00 (48)	1.02 (0.74–1.41)	1.11 (65)	1.14 (0.86–1.52)	0.97 (159)	0.67
Hemorrhagic stroke	0.29 (14)	0.81 (0.45–1.46)	0.31 (18)	0.86 (0.51–1.46)	0.35 (58)	0.72
Systemic embolism	0.10 (5)	1.21 (0.44–3.37)	0.14 (8)	1.61 (0.67–3.84)	0.08 (14)	0.71
Death from any cause	7.07 (348)	2.96 (2.57–3.42)	4.32 (258)	1.81 (1.55–2.11)	2.40 (400)	<0.0001
Stroke, systemic embolism or death from any cause	8.06 (389)	2.33 (2.05–2.65)	5.32 (311)	1.54 (1.34–1.77)	3.46 (565)	<0.0001
Safety end points						
ISTH major bleeding	3.09 (135)	1.23 (1.01–1.50)	2.55 (134)	1.02 (0.84–1.24)	2.50 (372)	0.11
Intracranial	0.45 (20)	0.75 (0.46–1.22)	0.45 (24)	0.75 (0.48–1.18)	0.60 (90)	0.30
Other location	2.63 (115)	1.38 (1.11–1.72)	2.09 (110)	1.10 (0.88–1.37)	1.89 (282)	0.01
Gastrointestinal	0.95 (42)	1.46 (1.02–2.10)	0.81 (43)	1.26 (0.88–1.80)	0.64 (97)	0.10
Major or clinically relevant nonmajor bleeding	5.53 (237)	1.12 (0.97–1.30)	5.27 (271)	1.07 (0.93–1.23)	4.88 (712)	0.26
GUSTO severe bleeding	0.81 (36)	0.99 (0.68–1.44)	0.75 (40)	0.92 (0.65–1.32)	0.81 (122)	0.91
GUSTO moderate/severe bleeding	2.04 (90)	1.18 (0.93–1.50)	1.61 (85)	0.93 (0.73–1.19)	1.72 (258)	0.26
TIMI major bleeding	1.36 (60)	1.03 (0.77–1.37)	1.26 (67)	0.96 (0.73–1.27)	1.31 (197)	0.92
TIMI major or minor bleeding	2.25 (99)	1.15 (0.91–1.44)	1.91 (101)	0.98 (0.78–1.23)	1.95 (292)	0.45
Any bleeding	21.27 (777)	0.95 (0.88–1.03)	20.70 (907)	0.93 (0.86–1.00)	22.15 (2691)	0.11
Net benefit end points						
Stroke, systemic embolism, or major bleeding	4.15 (195)	1.20 (1.02–1.41)	3.85 (220)	1.12 (0.96–1.31)	3.44 (550)	0.07
Stroke, systemic embolism, major bleeding or death from any cause	10.46 (492)	1.98 (1.77–2.22)	7.24 (414)	1.37 (1.22–1.54)	5.27 (843)	<0.0001
Other end points						
HF hospitalization	5.99 (274)	5.07 (4.21–6.11)	3.24 (185)	2.77 (2.26–3.40)	1.12 (189)	<0.0001

CI indicates confidence interval; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Hemostasis; HF-PEF, heart failure with preserved ejection fraction; HR, hazard ratio; LVSD, left ventricular systolic dysfunction; TIA, transient ischemic attack; and TIMI, Thrombolysis In Myocardial Infarction.

*Rate per 100 patient-years of follow-up.

†Hazard ratio vs no LVSD/no HF group.

‡Adjusted for age, sex, hypertension, diabetes mellitus, coronary artery disease (any of prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), history of stroke/TIA, body mass index and renal function (eGFR [estimated glomerular filtration rate]).

of patients with paroxysmal atrial fibrillation and by far the largest proportion (44.5%) with a $CHADS_2$ score of 1.

Unadjusted Clinical Outcomes

Unadjusted rates of SSE did not differ significantly across the 3 patient groups (Table 2; Figure). The rate of death was highest in those with LVSD, intermediate in patients with HF-PEF, and lowest in subjects with neither LVSD nor HF-PEF. The rate of death was also substantially higher than the rate of SSE in all groups. The relative difference was greatest in patients with LVSD. The rate of the composite outcomes, including death, showed the same pattern across patient groups as death.

Of the 1865 subjects with LVSD and symptomatic HF, 44 experienced SSE (rate 1.35 per 100 patient-years) compared

with 23 among the 871 individuals with asymptomatic LVSD (rate 1.49 per 100 patient-years). For the composite of death or SSE, these figures were 295 (9.02 per 100 patient-years) and 94 (6.05 per 100 patient-years), respectively.

The rate of hospitalization for HF was 2- to 4-fold higher than the rate of SSE in patients with LVSD and HF-PEF, but was lower than the rate of SSE in patients with neither LVSD nor HF.

The rate of bleeding did not differ significantly between patient groups and although the net clinical benefit outcome did, the difference was mainly driven by death.

Adjusted Clinical Outcomes

For the SSE end point, the adjusted rates (per 100/person-years of follow-up) were 1.53, 1.58, and 1.38 for the LVSD, HF-PEF, and no LVSD/no HF groups, respectively. Although the difference among the 3 groups was not statistically significant (P=0.52), regardless of treatment, patients in the LVSD and HF-PEF groups had a slightly higher rate of SSE during follow-up—HR (95% confidence interval), 1.10 (0.83–1.46) for LVSD and 1.15 (0.89–1.48) for HF-PEF.

The relationship between EF, examined as a continuous variable, and risk of SSE was not statistically significant—the HR for each 10% decrease in LVEF was 1.02 (0.94–1.11); P=0.65.

Comparison of Apixaban With Warfarin

The effect of apixaban, compared with warfarin, on the efficacy and safety outcomes is shown in Tables 3 through 5. For all the prespecified efficacy composite outcomes, the HR favored apixaban in each patient group, with no evidence of heterogeneity of treatment effect. This was also the case for all-cause mortality alone. In the whole ARISTOTLE population, the apixaban/warfarin HR for SSE or death was 0.89 (95% confidence interval, 0.81–0.98); P=0.02. The HR also favored apixaban for all definitions of bleeding (except gastrointestinal bleeding in patients with HF-PEF) and all net clinical benefit outcomes in each patient group. In the whole ARISTOTLE population, the apixaban/warfarin HR for SSE, major bleed, or death was 0.85 (0.78–0.92); P<0.001.

Compared with warfarin, apixaban had no effect on HF hospitalization.

Table 3. Treatment Effect by HF/LSVD Status—Efficacy End Points

	Rate (n)			
	Apixaban	Warfarin	HR (95% CI)	Interaction *P* Value
Stroke or systemic embolism*				
LVSD	0.99 (24)	1.80 (43)	0.55 (0.34–0.91)	0.21
HF-PEF	1.51 (44)	1.54 (45)	0.98 (0.65–1.49)	
No LVSD/no HF	1.16 (95)	1.58 (129)	0.74 (0.57–0.96)	
Stroke				
LVSD	0.91 (22)	1.67 (40)	0.54 (0.32–0.91)	0.22
HF-PEF	1.37 (40)	1.40 (41)	0.98 (0.63–1.51)	
No LVSD/no HF	1.09 (89)	1.54 (125)	0.71 (0.54–0.93)	
Ischemic or uncertain type stroke				
LVSD	0.79 (19)	1.21 (29)	0.65 (0.36–1.15)	0.27
HF-PEF	1.20 (35)	1.03 (30)	1.17 (0.72–1.91)	
No LVSD/no HF	0.87 (71)	1.08 (88)	0.81 (0.59–1.10)	
Hemorrhagic stroke				
LVSD	0.12 (3)	0.45 (11)	0.27 (0.08–0.97)	0.64
HF-PEF	0.20 (6)	0.41 (12)	0.50 (0.19–1.34)	
No LVSD/no HF	0.24 (20)	0.46 (38)	0.53 (0.31–0.91)	
Systemic embolism				
LVSD	0.08 (2)	0.12 (3)	0.67 (0.11–3.99)	0.80
HF-PEF	0.14 (4)	0.14 (4)	1.01 (0.25–4.02)	
No LVSD/no HF	0.10 (8)	0.07 (6)	1.34 (0.47–3.86)	
Death from any cause				
LVSD	6.99 (172)	7.15 (176)	0.98 (0.79–1.21)	0.52
HF-PEF	4.05 (121)	4.58 (137)	0.89 (0.69–1.13)	
No LVSD/no HF	2.17 (181)	2.62 (219)	0.83 (0.68–1.01)	
Stroke, systemic embolism or death from any cause				
LVSD	7.76 (188)	8.37 (201)	0.93 (0.76–1.13)	0.63
HF-PEF	5.07 (148)	5.57 (163)	0.91 (0.73–1.14)	
No LVSD/no HF	3.14 (256)	3.79 (309)	0.83 (0.70–0.98)	

CI indicates confidence interval; HF-PEF, heart failure with preserved ejection fraction; HR, hazard ratio; and LVSD, left ventricular systolic dysfunction.

*Adjusted for age, sex, hypertension, diabetes mellitus, coronary artery disease (any of prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting), history of stroke/TIA, body mass index and renal function (eGFR [estimated glomerular filtration rate]).

Table 4. Treatment Effect by HF/LSVD Status—Safety End Points

	Rate (n)			
	Apixaban	Warfarin	HR (95% CI)	Interaction *P* Value
ISTH major bleeding				
LVSD	2.77 (61)	3.41 (74)	0.81 (0.58–1.14)	0.50
HF-PEF	1.95 (52)	3.17 (82)	0.62 (0.44–0.88)	
No LVSD/no HF	2.17 (162)	2.83 (210)	0.77 (0.62–0.94)	
ISTH major bleeding: intracranial				
LVSD	0.18 (4)	0.73 (16)	0.25 (0.08–0.73)	0.23
HF-PEF	0.15 (4)	0.76 (20)	0.20 (0.07–0.58)	
No LVSD/no HF	0.38 (29)	0.81 (61)	0.47 (0.30–0.73)	
ISTH major bleeding: other location				
LVSD	2.59 (57)	2.67 (58)	0.97 (0.67–1.40)	0.64
HF-PEF	1.80 (48)	2.39 (62)	0.76 (0.52–1.10)	
No LVSD/no HF	1.78 (133)	2.01 (149)	0.89 (0.70–1.12)	
ISTH major bleeding: gastrointestinal				
LVSD	0.81 (18)	1.09 (24)	0.74 (0.40–1.36)	0.043
HF-PEF	1.08 (29)	0.53 (14)	2.03 (1.07–3.84)	
No LVSD/no HF	0.59 (45)	0.70 (52)	0.86 (0.57–1.27)	
Major or clinically relevant nonmajor bleeding				
LVSD	5.05 (109)	6.01 (128)	0.84 (0.65–1.08)	0.23
HF-PEF	4.09 (107)	6.50 (164)	0.63 (0.50–0.81)	
No LVSD/no HF	3.90 (287)	5.89 (425)	0.66 (0.57–0.77)	
GUSTO severe bleeding				
LVSD	0.49 (11)	1.14 (25)	0.43 (0.21–0.88)	0.88
HF-PEF	0.45 (12)	1.07 (28)	0.42 90.21–0.83)	
No LVSD/no HF	0.54 (41)	1.08 (81)	0.50 (0.34–0.73)	
GUSTO moderate/severe bleeding				
LVSD	1.71 (38)	2.38 (52)	0.72 (0.47–1.09)	0.74
HF-PEF	1.20 (32)	2.03 (53)	0.59 (0.38–0.92)	
No LVSD/no HF	1.29 (97)	2.16 (161)	0.60 (0.46–0.77)	
TIMI major bleeding				
LVSD	1.07 (24)	1.64 (36)	0.65 (0.39–1.10)	0.92
HF-PEF	0.93 (25)	1.60 (42)	0.59 (0.36–0.96)	
No LVSD/no HF	0.97 (73)	1.66 (124)	0.58 (0.44–0.78)	
TIMI major or minor bleeding				
LVSD	1.85 (41)	2.66 (58)	0.69 (0.46–1.03)	0.83
HF-PEF	1.42 (38)	2.42 (63)	0.59 (0.40–0.88)	
No LVSD/no HF	1.57 (118)	2.34 (174)	0.67 (0.53–0.85)	
Any bleeding				
LVSD	18.72 (356)	24.03 (421)	0.79 (0.68–0.91)	0.48
HF-PEF	17.03 (391)	24.75 (516)	0.70 (0.61–0.80)	
No LVSD/no HF	18.55 (1171)	26.04 (1520)	0.73 (0.67–0.78)	

CI indicates confidence interval; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; HF-PEF, heart failure-preserved ejection fraction; HR, hazard ratio; ISTH, International Society on Thrombosis and Hemostasis; LVSD, left ventricular systolic dysfunction; and TIMI, Thrombolysis In Myocardial Infarction.

Discussion

We found that among a large cohort of patients with atrial fibrillation receiving an oral anticoagulant, unadjusted rates of SSE in those with LVSD or HF-PEF were not higher than in those without LVSD or HF. However, the stroke risk-factor profile differed considerably among these 3 patient groups.

As anticipated, patients with HF-PEF differed from those with LVSD, particularly with respect to the proportion of women and those with a history of hypertension, both of which were greater in subjects with HF-PEF.[17] These 2 factors, plus a higher proportion of patients with symptomatic HF and slightly more elderly individuals, resulted in the HF-PEF

Table 5. Treatment Effect by HF/LSVD Status—Net Benefit and Other End points

	Rate (n)			
	Apixaban	Warfarin	HR (95% CI)	Interaction *P* Value
Stroke, systemic embolism, or major bleeding				
LVSD	3.69 (87)	4.62 (108)	0.80 (0.60–1.05)	0.98
HF-PEF	3.46 (99)	4.24 (121)	0.82 (0.63–1.06)	
No LVSD/no HF	3.04 (243)	3.85 (307)	0.79 (0.67–0.94)	
Stroke, systemic embolism, major bleeding, or death from any cause				
LVSD	10.11 (239)	10.81 (253)	0.93 (0.78–1.12)	0.59
HF-PEF	6.71 (192)	7.76 (222)	0.86 (0.71–1.05)	
No LVSD/no HF	4.78 (383)	5.76 (460)	0.83 (0.73–0.95)	
HF hospitalization				
LVSD	5.89 (135)	6.10 (139)	0.96 (0.76–1.21)	0.62
HF-PEF	3.29 (94)	3.19 (91)	1.03 (0.78–1.38)	
No LVSD/no HF	1.24 (101)	1.08 (88)	1.15 (0.87–1.54)	

CI indicates confidence interval; HF-PEF, heart failure-preserved ejection fraction; HR, hazard ratio; and LVSD, left ventricular systolic dysfunction.

group having higher overall $CHADS_2$ scores. Conversely, patients with LVSD had a considerably higher mortality rate. Consequently, direct comparison of outcomes in these 2 groups is difficult because of their quite different and competing risks, on the one hand of SSE (in those with HF-PEF) and on the other of death (in those with LVSD). Comparison with these 2 groups is further confounded by the fact that to be enrolled in ARISTOTLE, individuals with neither HF nor LVSD had to have other risk factors for SSE. As a result, the no LVSD/no HF group were older and had higher frequencies of hypertension and diabetes mellitus than might have been expected (compared with patients in the HF-PEF and LVSD groups). For the same reason, subjects without LVSD or HF-PEF had the highest frequency of prior stroke or TIA.

Consequently, evaluation of the independent influence of symptomatic HF and LVSD on the risk of SSE required multivariable adjustment. After adjustment, we found that patients with LVSD and those with HF-PEF had a numerically higher risk of SSE than patients with neither LVSD nor HF. Of interest, the adjusted stroke rate was similar in patients with LVSD and HF-PEF, although the difference between these 2 patient groups and those without either LVSD or HF-PEF was not significant. When EF was examined as a continuous variable, there was no apparent relationship with SSE, a finding consistent with a recent large study from France.[18] Indeed, it is uncertain that any transthoracic echocardiographic measure is an independent predictor of stroke.[11–13,19,20] However, N-terminal pro B-type natriuretic peptide was shown to be an independent predictor of stroke risk in the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, although in that analysis only HF was adjusted for and ventricular function was not taken into account.[21]

Despite our findings, we cannot definitively conclude that the clinical syndrome of HF or reduced systolic function do not increase the risk of SSE. All patients in ARISTOTLE received an oral anticoagulant, so it is possible that this treatment largely abrogated the risk of SSE related to LVSD or HF, and LVSD and HF could be risk factors for SSE in patients not receiving an anticoagulant.

One other notable observation in this analysis was that the rate of hospitalization for HF was 2- to 4-fold higher than the rate of SSE in patients with LVSD and HF-PEF, but in patients with neither LVSD nor HF, the rate of SSE was higher than the rate of HF hospitalization. It is also of interest to compare the rates of death and stroke in ARISTOTLE with those in the recently reported warfarin versus aspirin in patients with Reduced Cardiac Ejection Fraction trial (WARCEF) in patients with systolic HF but in sinus rhythm. The rate of death in warfarin-treated patients in WARCEF was 6.63% per year compared with 7.15 in patients with LVSD in ARISTOTLE. The rate of ischemic stroke in WARCEF was 0.72% per year compared with 1.21 (ischemic or unknown cause of stroke) in ARISTOTLE. The higher rates of both events in ARISTOTLE might reflect the older average age, presence of clinically evident atrial fibrillation, and a greater proportion of patients with prior stroke or TIA compared with WARCEF.

The second objective of our analyses was to compare the effects of apixaban with those of warfarin on the prespecified ARISTOTLE efficacy and safety outcomes across the patient groups of interest. In keeping with the overall results of ARISTOTLE, we found that apixaban was superior to warfarin with respect to both types of outcome and there was no evidence of treatment heterogeneity according to LV function or HF status. The figures illustrating composite outcomes, including death (which take account of competing risks), demonstrate that patients treated with apixaban fare better than those receiving warfarin and that patients with HF-PEF and particularly those with LVSD have the greatest absolute benefit (because they are at higher absolute risk).

Our study had a number of limitations. First, it was a retrospective analysis. Second, 19% of patients did not have baseline information on both LV systolic function and HF status. Third, our definition of HF relied on an investigator diagnosis indicated by a check-box and did not fulfil all the criteria recommended in guidelines. Fourth, because of relatively small numbers, we had to combine patients with both symptomatic and asymptomatic LVSD.

In summary, anticoagulated patients with atrial fibrillation and LVSD and those with atrial fibrillation and HF-PEF had a numerically higher adjusted risk of SSE than patients with neither LVSD nor HF, although the difference between the patient groups was not significant. Similarly, there was no relationship between risk of SSE and EF considered as a continuous measure. Apixaban was superior to warfarin with respect to both efficacy and safety outcomes in all patient groups, with the greatest absolute benefit in the highest risk patients with LVSD.

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CLINICAL PERSPECTIVE

We investigated the risk of stroke or systemic embolism in patients with atrial fibrillation and heart failure treated with either warfarin or the direct factor Xa inhibitor apixaban in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (ARISTOTLE). Patients with heart failure had a numerically (but not statistically significant) higher risk of stroke or systemic embolism than those without heart failure. The risk of stroke or systemic embolism in heart failure was similar in patients with preserved and reduced ejection fraction. The superiority of apixaban over warfarin with respect to both efficacy and safety (bleeding) was consistent in patients with and without heart failure. Apixaban is an alternative to warfarin for prevention of stroke or systemic embolism in patients with atrial fibrillation and heart failure.

Circulation
Heart Failure

Left Ventricular Systolic Dysfunction, Heart Failure, and the Risk of Stroke and Systemic Embolism in Patients With Atrial Fibrillation: Insights From the ARISTOTLE Trial

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