Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial

Renato D Lopes, Sana M Al-Khatib, Lars Wallentin, Hongqiu Yang, Jack Ansell, M Cecilia Bahit, Raffaele De Caterina, Paul Dorian, J Donald Easton, Cetin Erol, Justin A Ezekowitz, Bernard J Gersh, Christopher B Granger, Stefan H Hohnloser, John Horowitz, Elaine M Hylek, John J V McMurray, Puneet Mohan, Dragos Vinereanu, John H Alexander

Background The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial showed that apixaban is better than warfarin at prevention of stroke or systemic embolism, causes less bleeding, and results in lower mortality. We assessed in this trial's participants how results differed according to patients' $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores, used to predict the risk of stroke and bleeding.

Methods ARISTOTLE was a double-blind, randomised trial that enrolled 18 201 patients with atrial fibrillation in 39 countries. Patients were randomly assigned apixaban 5 mg twice daily (n=9120) or warfarin (target international normalised ratio 2·0–3·0; n=9081). The primary endpoint was stroke or systemic embolism. The primary safety outcome was major bleeding. We calculated $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores of patients at randomisation. Efficacy analyses were by intention to treat, and safety analyses were of the population who received the study drug. ARISTOTLE is registered with ClinicalTrials.gov, number NCT00412984.

Findings Apixaban significantly reduced stroke or systemic embolism with no evidence of a differential effect by risk of stroke ($CHADS_2$ 1, 2, or ≥3, p for interaction=0·4457; or CHA_2DS_2VASc 1, 2, or ≥3, p for interaction=0·1210) or bleeding (HAS-BLED 0–1, 2, or ≥3, p for interaction=0·9422). Patients who received apixaban had lower rates of major bleeding than did those who received warfarin, with no difference across all score categories ($CHADS_2$, p for interaction=0·4018; CHA_2DS_2VASc, p for interaction=0·2059; HAS-BLED, p for interaction=0·7127). The relative risk reduction in intracranial bleeding tended to be greater in patients with HAS-BLED scores of 3 or higher (hazard ratio [HR] 0·22, 95% CI 0·10–0·48) than in those with HAS-BLED scores of 0–1 (HR 0·66, 0·39–1·12; p for interaction=0·0604).

Interpretation Because apixaban has benefits over warfarin that are consistent across patient risk of stroke and bleeding as assessed by the CHADS2, CHA2DS2VASc, and HAS-BLED scores, these scores might be less relevant when used to tailor apixaban treatment to individual patients than they are for warfarin. Further improvement in risk stratification for both stroke and bleeding is needed, particularly for patients with atrial fibrillation at low risk for these events.

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Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA (R D Lopes MD, S M Al-Khatib MD, H Yang PhD, Prof C B Granger MD, J H Alexander MD); **Uppsala Clinical Research Centre, Uppsala University, Uppsala, Sweden** (Prof L Wallentin MD); **Lenox Hill Hospital, New York, NY, USA** (Prof J Ansell MD); **ECLA Estudios Cardiológicos Latinoamérica, Rosario, Argentina** (M C Bahit MD); **University-Chieti, Chieti, Italy** (Prof R De Caterina MD); **University of Toronto, St Michael's Hospital, Toronto, ON, Canada** (Prof P Dorian MD); **University of California San Francisco, San Francisco, CA, USA** (Prof J D Easton MD); **Ankara University, Ankara, Turkey** (Prof C Erol MD); **University of Alberta, Edmonton, AB, Canada** (J A Ezekowitz MBBCh); **Mayo Clinic, Rochester, MN, USA** (Prof B J Gersh MB ChB); **JW Goethe-University, Frankfurt, Germany** (Prof S H Hohnloser MD); **University of Adelaide, Adelaide, SA, Australia** (Prof J Horowitz MD); **Boston University Medical Center, Boston, MA, USA** (E M Hylek MD); **Western Infirmary, Glasgow, UK** (Prof J J V McMurray MD); **Bristol-Myers Squibb, Princeton, NJ, USA** (P Mohan MD); **and Carol Davila University of Medicine and Pharmacy, Bucharest, Romania** (Prof D Vinereanu MD)

Introduction

Although warfarin reduces the risk of stroke in patients with atrial fibrillation by 64%[1] and is classified as a class I recommendation in practice guidelines,[2–4] its limitations have contributed to its underuse in clinical practice. These limitations have led to the development of new oral anticoagulants, including direct thrombin inhibitors and factor Xa inhibitors for patients with atrial fibrillation.[5–9]

In view of the known bleeding risks of warfarin, risk scores for thromboembolism and bleeding in patients with atrial fibrillation have been developed to help inform therapeutic decisions. Of the risk scores available to assess the risk of thromboembolism in patients with atrial fibrillation, the $CHADS_2$ score (which assigns one point each for congestive heart failure [C], hypertension [H], age 75 years or older [A], and diabetes [D], and two points for a previous stroke [S_2] or transient ischaemic attack) and CHA_2DS_2VASc score (which assigns points to additional risk factors, such as female sex, age 65–75 years, and vascular disease) are the most widely used.[10–12] The recently developed bleeding score HAS-BLED is used to quantify the risk of bleeding associated with anticoagulant use.[13] Although these three scores help to estimate the risk of stroke and bleeding in patients with atrial fibrillation and to guide decisions about the use of oral anticoagulation, the extent to which these scores can help to guide to guide decisions about which type of oral anticoagulation therapy to use is uncertain.

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

Correspondence to:
Dr Renato D Lopes,
Duke University Medical Center,
Box 3850, Durham, NC 27705,
USA
renato.lopes@duke.edu

(ARISTOTLE) trial compared apixaban (a novel oral direct factor Xa inhibitor) with warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke.[14] We analysed the ARISTOTLE population to assess the efficacy and safety of apixaban compared with warfarin according to $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores for stroke prevention in patients with atrial fibrillation.

Methods

The ARISTOTLE trial: study design and participants

The details of the ARISTOTLE trial have been published previously.[7,14] Briefly, ARISTOTLE was a double-blind, double-dummy, randomised clinical trial that enrolled patients with atrial fibrillation and at least one $CHADS_2$ risk factor for stroke or systemic embolism. Recruitment took place between Dec 19, 2006, and April 2, 2010, in 1034 centres in 39 countries. The approval of the institutional review board at each institution was obtained before the inception of the study, and patients gave written informed consent.

	Score
$CHADS_2$ risk factors	
History of CHF	1
Hypertension	1
Age ≥75 years	1
Diabetes mellitus	1
Previous stroke, TIA, or systemic embolism	2
CHA_2DS_2VASc risk factors	
CHF or LV dysfunction	1
Hypertension	1
Age ≥75 years	2
Age 65–74 years	1
Diabetes mellitus	1
Stroke or TIA	2
Vascular disease (previous MI, PAD, previous PCI, previous CABG, or aortic plaque)	1
Female sex	1
HAS-BLED risk factors	
Hypertension (systolic BP >160 mm Hg)	1
Abnormal renal function (dialysis, transplant, serum Cr ≥200 µmol/L [2·6 mg/dL])	1
Abnormal liver function (chronic hepatic disease; bilirubin >2×ULN; AST, ALT, and ALP >3×ULN)	1
History of stroke	1
History of bleeding	1
Labile INR (INR <2 or >3 in patients on warfarin before randomisation)	1
Age >65 years	1
Use of antiplatelets, NSAIDs, or anti-inflammatory drugs	1
Drug or alcohol abuse	1

CHF=congestive heart failure. TIA=transient ischaemic attack. LV=left ventricular. MI=myocardial infarction. PAD=peripheral artery disease. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. BP=blood pressure. Cr=creatinine. ULN=upper limit of normal. AST=aspartate transaminase. ALT=alanine transaminase. ALP=alkaline phosphatase. INR=international normalised ratio. NSAIDs=non-steroidal anti-inflammatory drugs.

Table 1: **$CHADS_2$, CHA_2DS_2VASc, and HAS-BLED score calculators**

Procedures and endpoints

Patients were randomly assigned (1:1) to receive either warfarin (target international normalised ratio [INR] 2·0–3·0) or apixaban (5 mg twice daily) by a 24-h central computerised and interactive voice-response system. Randomisation was stratified according to whether patients had received warfarin previously. Participants, investigators, members of all committees, and the sponsor staff undertaking the study were masked to individual participant treatment assignments.

The primary endpoint of the main ARISTOTLE trial was stroke or systemic embolism. The primary safety outcome was major bleeding, which was classified according to the International Society on Thrombosis and Haemostasis (ISTH) criteria. The median length of follow-up was 1·8 years (IQR 1·5–2·4).[7,14]

Secondary endpoints included myocardial infarction, all-cause mortality, intracranial bleeding, Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or moderate bleeding, any bleeding, and net clinical events (stroke or systemic embolism, ISTH major bleeding, and all-cause mortality). All endpoints were adjudicated by a blinded clinical events committee with prespecified criteria.[7,14]

To compare efficacy, safety, and balance of efficacy and safety of apixaban and warfarin across patient risk categories, we calculated $CHADS_2$ (1, 2, ≥3), CHA_2DS_2VASc (1, 2, ≥3), and HAS-BLED (0–1, 2, ≥3) scores for every patient according to the sum of risk factors present at randomisation (table 1).[11–13]

Statistical analysis

The efficacy analyses (stroke or systemic embolism, myocardial infarction, and mortality) included all randomly assigned patients (intention to treat) and all events from the time of randomisation until the efficacy cutoff date (predefined as Jan 30, 2011). The safety (bleeding) analyses included all patients who received at least one dose of study drug and included all events from the first dose of study drug until 2 days after the last dose.

We assessed outcomes by categories of $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores with the Cox proportional hazards model, which was stratified by previous warfarin (or vitamin K antagonist) use. We defined event rate in this study as the number of patients who had events divided by the sum of days to first event across all patients. In the descriptive statistics we present categorical variables as number and percentage and continuous variables as median and IQR. We used SAS (version 9.2) for the analyses.

ARISTOTLE is registered with ClinicalTrials.gov, number NCT00412984.

Role of the funding source

PM is an employee of Bristol-Myers Squibb and participated with the other authors in the study design, data

collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all data, and the coauthors and steering committee members had final responsibility for the decision to submit for publication.

Results

The ARISTOTLE trial enrolled 18 201 patients and randomly assigned 9081 to receive warfarin and 9120 to receive apixaban. At randomisation, median $CHADS_2$ scores (2·0 [IQR 1·0–3·0] in patients assigned to apixaban *vs* 2·0 [1·0–3·0] in those assigned to warfarin), median CHA_2DS_2VASc scores (3·0 [2·0–4·0] *vs* 3·0 [2·0–4·0]), and median HAS-BLED scores (2·0 [1·0–2·0] *vs* 2·0 [1·0–2·0]) were generally well balanced across treatment groups. Baseline characteristic data for the components of the $CHADS_2$ score have been published previously.[7]

For the additional components of the CHA_2DS_2VASc score at baseline, 3539 (38·8%) patients assigned to apixaban were aged 65–74 years compared with 3513 (38·7%) patients assigned to warfarin, 2318 (25·4%) patients in the apixaban group had vascular disease compared with 2182 (24·0%) in the warfarin group, and 3234 (35·5%) in the apixaban group were women compared with 3182 (35·0%) in the warfarin group. The components of the HAS-BLED score were also distributed evenly at baseline: systolic blood pressure of greater than 160 mm Hg (320 [3·5%] in the apixaban group *vs* 323 [3·6%] in the warfarin group); severe renal disease (estimated serum creatinine ≥200 µmol/L; 31 [0·3%] *vs* 33 [0·4%]); abnormal liver function or chronic liver disease (266 [2·9%] *vs* 245 [2·7%]); history of stroke (1045 [11·5%] *vs* 1082 [11·9%]); history of bleeding (1525 [16·7%] *vs* 1515 [16·7%]); labile INR less than 2 or greater than 3 in patients receiving warfarin before randomisation (3138 [34·4%] *vs* 3135 [34·5%]); older than 65 years (6104 [66·9%] *vs* 6044 [66·6%]); use of other drugs such as antiplatelet agents or non-steroidal anti-inflammatory drugs (3541 [38·8%] *vs* 3487 [38·4%]); and consumption of more than 8 units of alcohol per week before randomisation (228 [2·5%] *vs* 226 [2·5%]).

Patients with $CHADS_2$ scores of 3 or higher were older, had more comorbidities, and more often had persistent or permanent atrial fibrillation than did patients with $CHADS_2$ scores of 2 or lower (table 2). As expected, the same result was seen for the CHA_2DS_2VASc and HAS-BLED score categories (data not shown).

The relation between $CHADS_2$ and HAS-BLED scores (figure 1) was slight but highly significant (weighted Kappa 0·1783 [95% CI 0·1669–0·1897]; p<0·0001). Similar results were seen for the relation between CHA_2DS_2VASc and HAS-BLED (weighted Kappa 0·1447 [95% CI 0·1377–0·1518]; p<0·0001).

In patients receiving warfarin, the median time in therapeutic range (TTR) was lower in patients with

	$CHADS_2$ score 1 (n=6183)	$CHADS_2$ score 2 (n=6516)	$CHADS_2$ score ≥3 (n=5502)
Age (years)	67·0 (60–71)	71·0 (63–77)	75·0 (67–79)
Female	1876 (30·3%)	2355 (36·1%)	2185 (39·7%)
Region			
Asia Pacific	1149 (18·6%)	845 (13·0%)	922 (16·8%)
Europe	2309 (37·3%)	2710 (41·6%)	2324 (42·2%)
Latin America	1183 (19·1%)	1289 (19·8%)	996 (18·1%)
North America	1542 (24·9%)	1672 (25·7%)	1260 (22·9%)
Systolic blood pressure (mm Hg)	130·0 (120–140)	130·0 (120–140)	130·0 (120–140)
Weight (kg)	83·0 (71–97)	83·0 (70–96)	79·9 (68–93)
Previous myocardial infarction	588 (9·5%)	925 (14·2%)	1072 (19·5%)
Previous spontaneous bleeding	954 (15·4%)	1012 (15·5%)	1074 (19·5%)
History of fall within previous year	175 (2·8%)	259 (4·0%)	319 (5·8%)
Type of atrial fibrillation			
Persistent or permanent	5112 (82·7%)	5587 (85·7%)	4713 (85·7%)
Paroxysmal	1070 (17·3%)	928 (14·2%)	788 (14·3%)
Previous use of vitamin K antagonist	3594 (58·1%)	3624 (55·6%)	3183 (57·9%)
Qualifying risk factors			
Age ≥75 years	572 (9·3%)	2350 (36·1%)	2756 (50·1%)
Previous stroke, TIA, or SE	36 (0·6%)	309 (4·7%)	3193 (58·0%)
Heart failure or reduced LVEF	993 (16·1%)	2626 (40·3%)	2832 (51·5%)
Diabetes	197 (3·2%)	1826 (28·0%)	2524 (45·9%)
Hypertension needing treatment	4782 (77·3%)	5972 (91·7%)	5162 (93·8%)
Drugs at time of randomisation			
ACE inhibitor or ARB	3887 (62·9%)	4811 (73·8%)	4134 (75·1%)
β blocker	3821 (61·8%)	4156 (63·8%)	3505 (63·7%)
Aspirin	1753 (28·4%)	2064 (31·7%)	1815 (33·0%)
Clopidogrel	90 (1·5%)	103 (1·6%)	145 (2·6%)
Digoxin	1722 (27·9%)	2148 (33·0%)	1958 (35·6%)
Calcium-channel blocker	1747 (28·3%)	2011 (30·9%)	1809 (32·9%)
Statins	2198 (35·5%)	2627 (40·3%)	2639 (48·0%)
NSAIDs	508 (8·2%)	525 (8·1%)	487 (8·9%)
Gastric antacid drugs	984 (15·9%)	1158 (17·8%)	1208 (22·0%)
Renal function			
>80 mL/min	3262 (52·8%)	2662 (40·9%)	1594 (29·0%)
51–80 mL/min	2391 (38·7%)	2678 (41·1%)	2518 (45·8%)
31–50 mL/min	478 (7·7%)	1057 (16·2%)	1212 (22·0%)
≤30 mL/min	25 (0·4%)	87 (1·3%)	158 (2·9%)

Data are median (IQR) or number (%).TIA=transient ischaemic attack. SE=systemic embolism. LVEF=left ventricular ejection fraction. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. NSAIDs=non-steroidal anti-inflammatory drugs.

Table 2: **Baseline characteristics according to $CHADS_2$ score**

		HAS-BLED score			
		0–1	2	≥3	Total
$CHADS_2$ score	1	3203 (18%)	2051 (11%)	929 (5%)	**6183 (34%)**
	2	2807 (15%)	2461 (14%)	1248 (7%)	**6516 (36%)**
	≥3	1451 (8%)	2056 (11%)	1995 (11%)	**5502 (30%)**
	Total	**7461 (41%)**	**6568 (36%)**	**4172 (23%)**	**18 201 (100%)**

Figure 1: **Correlation between $CHADS_2$ and HAS-BLED scores**
Data are number of patients with both scores out of the total study population of 18 201 patients (%).

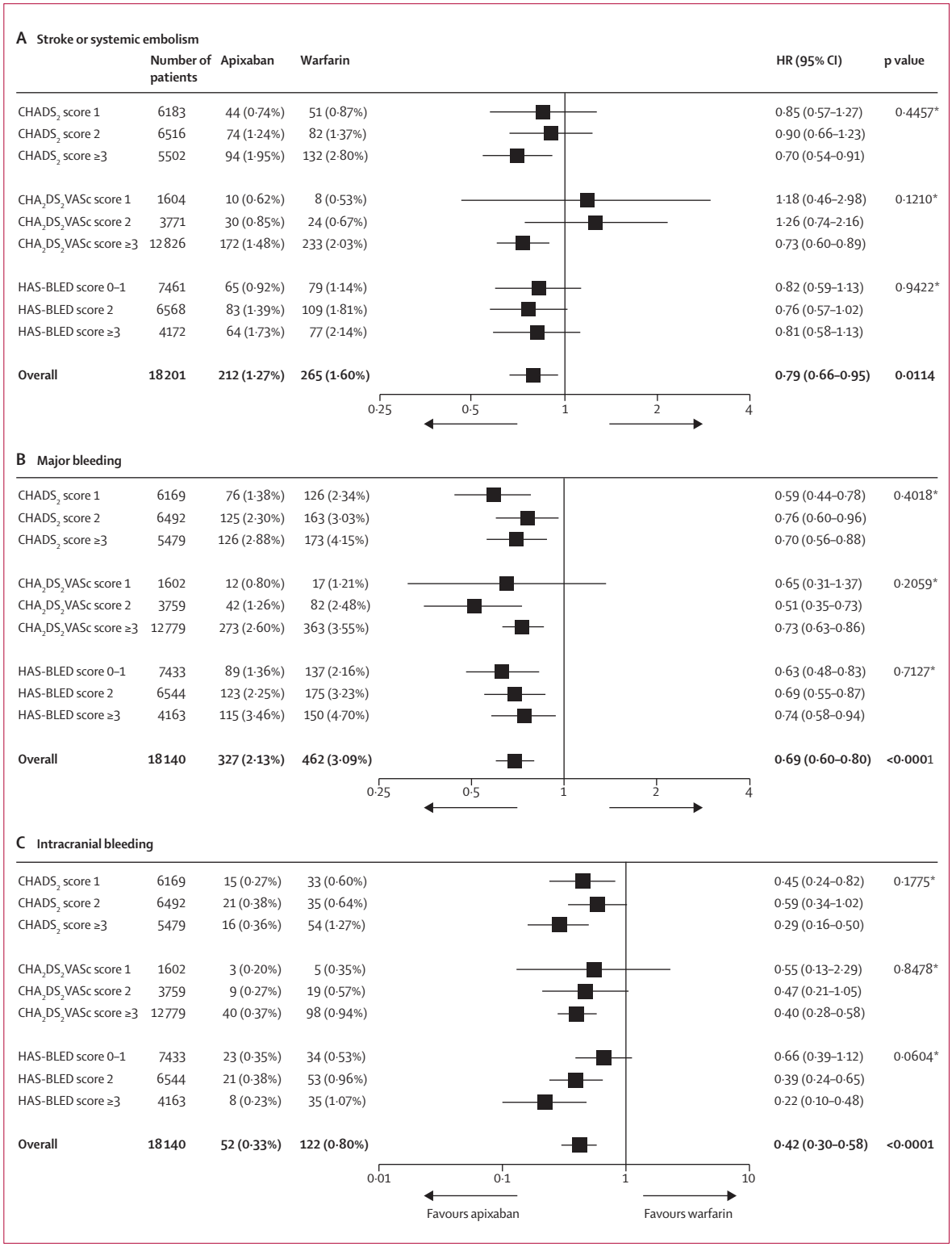

Figure 2: **Clinical outcomes according to different risk scores**
(A) Stroke or systemic embolism; (B) major bleeding; and (C) intracranial bleeding according to $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED score categories.
*p for interaction.

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	Number of events (% per person-year)		HR (95% CI)	p value	p for interaction
	Apixaban	Warfarin			
Stroke or systemic embolism	212 (1·27%)	265 (1·60%)	0·79 (0·66–0·95)	0·0114	0·4457
1	44 (0·74%)	51 (0·87%)	0·85 (0·57–1·27)	..	
2	74 (1·24%)	82 (1·37%)	0·90 (0·66–1·23)	..	
≥3	94 (1·95%)	132 (2·80%)	0·70 (0·54–0·91)	..	
Stroke or systemic embolism during treatment*	138 (0·96%)	200 (1·39%)	0·69 (0·56–0·86)	0·0009	0·1162
1	25 (0·49%)	36 (0·69%)	0·70 (0·42–1·17)	..	
2	54 (1·05%)	59 (1·13%)	0·93 (0·64–1·35)	..	
≥3	59 (1·45%)	105 (2·62%)	0·56 (0·40–0·76)	..	
Ischaemic stroke	140 (1·54%)	136 (1·50%)	1·02 (0·81–1·29)	0·8732	0·4651
1	29 (0·49%)	22 (0·37%)	1·30 (0·75–2·26)	..	
2	48 (0·80%)	44 (0·73%)	1·09 (0·73–1·65)	..	
≥3	63 (1·31%)	70 (1·48%)	0·88 (0·63–1·24)	..	
Ischaemic or uncertain type of stroke	162 (0·97%)	175 (1·05%)	0·92 (0·74–1·13)	0·4220	0·3958
1	31 (0·52%)	27 (0·46%)	1·13 (0·68–1·90)	..	
2	57 (0·95%)	56 (0·93%)	1·02 (0·70–1·47)	..	
≥3	74 (1·53%)	92 (1·95%)	0·79 (0·58–1·07)	..	
Myocardial infarction	90 (0·53%)	102 (0·61%)	0·88 (0·66–1·17)	0·3720	0·3400
1	24 (0·40%)	25 (0·42%)	0·95 (0·54–1·66)	..	
2	35 (0·58%)	32 (0·53%)	1·09 (0·68–1·76)	..	
≥3	31 (0·64%)	45 (0·94%)	0·68 (0·43–1·07)	..	
All-cause mortality	603 (3·52%)	669 (3·94%)	0·89 (0·80–1·00)	0·0465	0·7658
1	138 (2·28%)	142 (2·37%)	0·96 (0·76–1·22)	..	
2	216 (3·53%)	243 (3·98%)	0·89 (0·74–1·06)	..	
≥3	249 (5·03%)	284 (5·81%)	0·87 (0·73–1·03)	..	
Stroke, systemic embolism, or all-cause mortality	752 (4·49%)	837 (5·04%)	0·89 (0·81–0·98)	0·0192	0·6779
1	171 (2·80%)	179 (3·04%)	0·94 (0·77–1·16)	..	
2	265 (4·42%)	292 (4·87%)	0·91 (0·77–1·07)	..	
≥3	316 (6·56%)	366 (7·75%)	0·85 (0·73–0·99)	..	
ISTH major bleeding	327 (2·13%)	462 (3·09%)	0·69 (0·60–0·80)	<0·0001	0·4018
1	76 (1·38%)	126 (2·34%)	0·59 (0·44–0·78)	..	
2	125 (2·30%)	163 (3·03%)	0·76 (0·60–0·96)	..	
≥3	126 (2·88%)	173 (4·15%)	0·70 (0·56–0·88)	..	
Intracranial bleeding	52 (0·33%)	122 (0·80%)	0·42 (0·30–0·58)	<0·0001	0·1775
1	15 (0·27%)	33 (0·60%)	0·45 (0·24–0·82)	..	
2	21 (0·38%)	35 (0·64%)	0·59 (0·34–1·02)	..	
≥3	16 (0·36%)	54 (1·27%)	0·29 (0·16–0·50)	..	
Any bleeding	2356 (18·1%)	3060 (25·8%)	0·71 (0·68–0·75)	<0·0001	0·6810
1	748 (15·8%)	959 (22·2%)	0·73 (0·66–0·80)	..	
2	859 (18·6%)	1111 (26·1%)	0·72 (0·66–0·79)	..	
≥3	749 (20·3%)	990 (30·4%)	0·69 (0·63–0·76)	..	
Net clinical events†	1009 (6·13%)	1168 (7·20%)	0·85 (0·78–0·92)	0·0002	0·7443
1	227 (3·86%)	270 (4·67%)	0·83 (0·69–0·99)	..	
2	369 (6·28%)	414 (7·07%)	0·89 (0·77–1·02)	..	
≥3	413 (8·77%)	484 (10·6%)	0·83 (0·73–0·95)	..	

Data are number of events (% per person-year) unless otherwise specified. Person-year is defined as the sum of days from randomisation or start of study drug to first event across all patients, divided by 365·25. % per person-year is defined as the number of patients who had an event divided by person-year multiplied by 100. All analyses of bleeding endpoints were of data from the treated population (n=18 140). We did not report numerators/denominators because they do not add up to the event rate (event rate=%/[person-year]). HR=hazard ratio. ISTH=International Society on Thrombosis and Haemostasis. *From first dose until 2 days after last dose of study drug. †Stroke, systemic embolism, ISTH major bleeding, or all-cause mortality.

Table 3: **Endpoints by $CHADS_2$ score**

	Number of events (% per person-year)		HR (95% CI)	p value	p for interaction
	Apixaban	Warfarin			
Stroke or systemic embolism	212 (1·27%)	265 (1·60%)	0·79 (0·66–0·95)	0·0114	0·1210
1	10 (0·62%)	8 (0·53%)	1·18 (0·46–2·98)	..	
2	30 (0·85%)	24 (0·67%)	1·26 (0·74–2·16)	..	
≥3	172 (1·48%)	233 (2·03%)	0·73 (0·60–0·89)	..	
Stroke or systemic embolism during treatment*	138 (0·96%)	200 (1·39%)	0·69 (0·56–0·86)	0·0009	0·3568
1	5 (0·36%)	5 (0·37%)	0·96 (0·28–3·30)	..	
2	20 (0·65%)	20 (0·63%)	1·02 (0·55–1·89)	..	
≥3	113 (1·15%)	175 (1·77%)	0·65 (0·51–0·82)	..	
Myocardial infarction	90 (0·53%)	102 (0·61%)	0·88 (0·66–1·17)	0·3720	0·8520
1	3 (0·19%)	2 (0·13%)	1·40 (0·23–8·38)	..	
2	11 (0·31%)	14 (0·39%)	0·81 (0·37–1·78)	..	
≥3	76 (0·65%)	86 (0·74%)	0·87 (0·64–1·19)	..	
All-cause mortality	603 (3·52%)	669 (3·94%)	0·89 (0·80–1·00)	0·0465	0·8769
1	29 (1·78%)	33 (2·17%)	0·82 (0·50–1·35)	..	
2	84 (2·33%)	89 (2·43%)	0·95 (0·70–1·27)	..	
≥3	490 (4·12%)	547 (4·63%)	0·89 (0·79–1·01)	..	
Stroke, systemic embolism, or all-cause mortality	752 (4·49%)	837 (5·04%)	0·89 (0·81–0·98)	0·0192	0·6823
1	37 (2·31%)	38 (2·53%)	0·91 (0·58–1·44)	..	
2	105 (2·97%)	107 (2·97%)	0·99 (0·75–1·29)	..	
≥3	610 (5·25%)	692 (6·02%)	0·87 (0·78–0·97)	..	
ISTH major bleeding	327 (2·13%)	462 (3·09%)	0·69 (0·60–0·80)	<0·0001	0·2059
1	12 (0·80%)	17 (1·21%)	0·65 (0·31–1·37)	..	
2	42 (1·26%)	82 (2·48%)	0·51 (0·35–0·73)	..	
≥3	273 (2·60%)	363 (3·55%)	0·73 (0·63–0·86)	..	
Intracranial bleeding	52 (0·33%)	122 (0·80%)	0·42 (0·30–0·58)	<0·0001	0·8478
1	3 (0·20%)	5 (0·35%)	0·55 (0·13–2·29)	..	
2	9 (0·27%)	19 (0·57%)	0·47 (0·21–1·05)	..	
≥3	40 (0·37%)	98 (0·94%)	0·40 (0·28–0·58)	..	
Any bleeding	2356 (18·1%)	3060 (25·8%)	0·71 (0·68–0·75)	<0·0001	0·0998
1	176 (13·4%)	182 (15·4%)	0·88 (0·72–1·08)	..	
2	404 (13·9%)	569 (21·0%)	0·68 (0·59–0·77)	..	
≥3	1776 (20·2%)	2309 (29·0%)	0·71 (0·67–0·76)	..	
Net clinical events†	1009 (6·13%)	1168 (7·20%)	0·85 (0·78–0·92)	0·0002	0·7697
1	48 (3·20%)	50 (3·56%)	0·90 (0·61–1·34)	..	
2	135 (4·07%)	171 (5·18%)	0·78 (0·63–0·98)	..	
≥3	826 (7·91%)	947 (9·32%)	0·85 (0·78–0·94)	..	

Data are number of events (% per person-year). Person-year is defined as the sum of days from randomisation or start of study drug to first event across all patients, divided by 365·25. % per person-year is defined as the number of patients who had an event divided by person-year multiplied by 100. All analyses of bleeding endpoints were of data from the treated population (n=18 140). We did not report numerators/denominators because they do not add up to the event rate (event rate=%/[person-year]). HR=hazard ratio. ISTH=International Society on Thrombosis and Haemostasis. *From first dose until 2 days after last dose of study drug. †Stroke, systemic embolism, ISTH major bleeding, or all-cause mortality.

Table 4: **Endpoints by CHA_2DS_2VASc score**

higher $CHADS_2$ scores (67·7% for $CHADS_2$ score of 1, 65·8% for $CHADS_2$ score of 2, and 64·8% for $CHADS_2$ score of ≥3; p<0·0001), and higher in patients with higher HAS-BLED score categories (63·5% for HAS-BLED 0–1, 67·0% for HAS-BLED 2, and 68·5% for HAS-BLED ≥3; p<0·0001).

Excluding patients who died, more patients with higher $CHADS_2$ scores prematurely and permanently stopped taking the study drug than did those with lower $CHADS_2$ scores (1217 [20·2%] of 6013 patients with a $CHADS_2$ score of 1, 1417 [22·8%] of 6223 patients with a $CHADS_2$ score of 2, and 1412 [27·1%] of 5207 patients with a $CHADS_2$ score of ≥3); however, fewer patients assigned to apixaban discontinued treatment than did those assigned to warfarin across all $CHADS_2$ score categories, particularly in patients with $CHADS_2$ scores of 3 or higher (p for interaction=0·0200). Premature and permanent study drug discontinuation also increased with CHA_2DS_2VASc score (277 [17·7%] of 1566 patients with CHA_2DS_2VASc 1, 692 [18·9%] of 3654 patients with CHA_2DS_2VASc 2, and 3077 [25·2%] of 12 223 patients with CHA_2DS_2VASc ≥3 discontinued study drug) and HAS-BLED score (1532 [21·5%] of 7143 patients with HAS-BLED 1, 1498 [23·8%] of 6281 patients with HAS-BLED 2, and 1016 [25·3%] of 4019 patients with HAS-BLED ≥3 discontinued study drug). Early discontinuation in patients receiving apixaban was equal to that in patients given warfarin across all CHA_2DS_2VASc (p for interaction=0·2642) and HAS-BLED score categories (p for interaction=0·5706). Figure 2 shows the numbers of patients with stroke or systemic embolism and ISTH major bleeding by $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED score categories.

Irrespective of $CHADS_2$ score, patients assigned apixaban had significantly lower rates of stroke or systemic embolism, mortality, ISTH major bleeding, intracranial bleeding, and any bleeding than did those assigned warfarin (table 3), with no evidence of statistical heterogeneity. The benefits of apixaban compared with warfarin for all endpoints (including events during treatment only) across CHA_2DS_2VASc categories (table 4) were similar to those seen across $CHADS_2$ score categories. No difference was recorded for myocardial infarction.

Irrespective of HAS-BLED score, patients assigned to apixaban had lower rates of stroke or systemic embolism, mortality, ISTH major bleeding, TIMI major or minor bleeding, GUSTO severe or moderate bleeding, and any bleeding, including events during treatment only, than did those assigned to warfarin (table 5). The reduction in intracranial bleeding with apixaban compared with warfarin was greater in patients with a HAS-BLED score of 3 or higher (hazard ratio [HR] 0·22; 95% CI 0·10–0·48) than was the reduction seen in those with a HAS-BLED score of 0–1 (HR 0·66; 95% CI 0·39–1·12), but not significantly so (p for interaction=0·0604; figure 1).

Finally, irrespective of $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED score, patients who received apixaban had less net clinical events, with lower rates of the composite of stroke, systemic embolism, ISTH major bleeding, and all-cause mortality, than did patients who received warfarin. These results were driven mainly by reductions in bleeding.

Discussion

The advantages of apixaban compared with warfarin with respect to stroke or systemic embolism, major bleeding, and mortality were similar across patients, irrespective of their risk for stroke and bleeding assessed by $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED scores. We reported a reduced rate of intracranial bleeding in patients who received apixaban in all $CHADS_2$, CHA_2DS_2VASc, and HAS-BLED categories, and the reduction in intracranial bleeding with apixaban tended to be greater in patients with the highest HAS-BLED score (≥3) than in those with a score of 0–1 or 2.

Many stroke risk stratification schemes for patients with atrial fibrillation are available in clinical practice, but all have a suboptimum predictive value for thromboembolic events.[15–21] Although the $CHADS_2$ score is the most often used and best validated score of this type, its ability to discriminate patients at risk of stroke is poor, particularly for those at low risk. Nevertheless, these risk scores help to guide decisions on the usefulness of anticoagulant treatment in patients with atrial fibrillation. In accordance with previous findings,[22] our study showed that high $CHADS_2$ scores identify patients at high risk of stroke as well as those at high risk of bleeding during treatment with warfarin or apixaban. Additionally, we showed that patients at high risk of stroke according to $CHADS_2$ score are at high risk of bleeding as assessed by the HAS-BLED score. This correlation between risk factors for stroke and bleeding might be responsible, in part, for the warfarin treatment paradox, in which patients at higher risk for stroke are less likely to be given oral anticoagulation because they have an increased risk of bleeding.[23–31]

Several of the factors associated with an increased risk of stroke (ie, advanced age, hypertension, and previous stroke) are also associated with a raised risk of bleeding.[32] Several bleeding risk scores have been proposed; however, only a few have been derived from and validated in patients with atrial fibrillation.[33] Guidelines have recommended the HAS-BLED score as a potential additional method to help guide decisions about anticoagulant treatment[3,16]—a score of 3 or higher suggests a high risk of bleeding that merits some caution or regular clinical review of the patient.[3] In our analyses, we showed that a higher HAS-BLED score was associated with increased bleeding risk during treatment with both apixaban and warfarin and that apixaban was better than warfarin at reducing bleeding across all HAS-BLED score categories. In fact, the greatest reduction in intracranial bleeding in patients who received apixaban was seen in patients with a HAS-BLED score of 3 or more. These findings might help physicians to make better choices about oral anticoagulation in patients with atrial fibrillation, since bleeding, particularly intracranial bleeding, is a major factor against the use of anticoagulants.

The outcome during warfarin treatment is related to the TTR with INR 2·0–3·0.[34,35] Low TTR has been associated with the presence of comorbidities and high $CHADS_2$ score, contributing to the increased bleeding and stroke event rates reported in these patients.[36,37] Surprisingly, we noted that TTR was slightly higher in patients with HAS-BLED scores of 3 or higher. This finding could be attributed to labile INR and a history of bleeding in these patients, which are both variables that are not part of the $CHADS_2$ score. Thus, a potential explanation for these

	Number of events (% per person-year)		HR (95% CI)	p value	p for interaction
	Apixaban	Warfarin			
Stroke or systemic embolism	212 (1·27%)	265 (1·60%)	0·79 (0·66–0·95)	0·0114	0·9422
0–1	65 (0·92%)	79 (1·14%)	0·82 (0·59–1·13)	..	
2	83 (1·39%)	109 (1·81%)	0·76 (0·57–1·02)	..	
≥3	64 (1·73%)	77 (2·14%)	0·81 (0·58–1·13)	..	
Stroke or systemic embolism during treatment*	138 (0·96%)	200 (1·39%)	0·69 (0·56–0·86)	0·0009	0·4642
0–1	49 (0·81%)	58 (0·95%)	0·85 (0·58–1·24)	..	
2	50 (0·98%)	81 (1·54%)	0·64 (0·45–0·90)	..	
≥3	39 (1·24%)	61 (1·97%)	0·63 (0·42–0·95)	..	
Ischaemic stroke	140 (1·54%)	136 (1·50%)	1·02 (0·81–1·29)	0·8732	0·9898
0–1	42 (0·59%)	41 (0·59%)	1·02 (0·66–1·56)	..	
2	48 (0·80%)	48 (0·80%)	1·00 (0·67–1·50)	..	
≥3	50 (1·35%)	47 (1·30%)	1·04 (0·70–1·55)	..	
Ischaemic or uncertain type of stroke	162 (0·97%)	175 (1·05%)	0·92 (0·74–1·13)	0·4220	0·8532
0–1	46 (0·65%)	53 (0·76%)	0·86 (0·58–1·28)	..	
2	59 (0·98%)	66 (1·09%)	0·90 (0·63–1·28)	..	
≥3	57 (1·54%)	56 (1·55%)	1·00 (0·69–1·44)	..	
Myocardial infarction	90 (0·53%)	102 (0·61%)	0·88 (0·66–1·17)	0·3720	0·3291
0–1	16 (0·23%)	27 (0·39%)	0·58 (0·31–1·08)	..	
2	38 (0·63%)	41 (0·68%)	0·93 (0·60–1·45)	..	
≥3	36 (0·97%)	34 (0·93%)	1·04 (0·65–1·66)	..	
All-cause mortality	603 (3·52%)	669 (3·94%)	0·89 (0·80–1·00)	0·0465	0·2619
0–1	220 (3·05%)	242 (3·40%)	0·90 (0·75–1·08)	..	
2	242 (3·96%)	249 (4·03%)	0·98 (0·82–1·17)	..	
≥3	141 (3·72%)	178 (4·80%)	0·77 (0·62–0·96)	..	
Stroke, systemic embolism, or all-cause mortality	752 (4·49%)	837 (5·04%)	0·89 (0·81–0·98)	0·0192	0·1723
0–1	265 (3·75%)	298 (4·28)	0·88 (0·74–1·04)	..	
2	301 (5·02%)	306 (5·08)	0·99 (0·84–1·16)	..	
≥3	186 (5·03%)	233 (6·46)	0·78 (0·64–0·94)	..	
ISTH major bleeding	327 (2·13%)	462 (3·09)	0·69 (0·60–0·80)	<0·0001	0·7127
0–1	89 (1·36%)	137 (2·16)	0·63 (0·48–0·83)		
2	123 (2·25%)	175 (3·23)	0·69 (0·55–0·87)		
≥3	115 (3·46%)	150 (4·70)	0·74 (0·58–0·94)		
Intracranial bleeding	52 (0·33%)	122 (0·80)	0·42 (0·30–0·58)	<0·0001	0·0604
0–1	23 (0·35%)	34 (0·53)	0·66 (0·39–1·12)	..	
2	21 (0·38%)	53 (0·96)	0·39 (0·24–0·65)	..	
≥3	8 (0·23%)	35 (1·07)	0·22 (0·10–0·48)	..	
TIMI major or minor bleeding	239 (1·55%)	370 (2·46)	0·63 (0·54–0·75)	<0·0001	0·2949
0–1	63 (0·96%)	118 (1·85)	0·52 (0·38–0·70)	..	
2	91 (1·66%)	138 (2·54)	0·65 (0·50–0·85)	..	
≥3	85 (2·54%)	114 (3·54)	0·72 (0·54–0·95)	..	

(Continues on next page)

	Number of events (% per person-year)		HR (95% CI)	p value	p for interaction
	Apixaban	Warfarin			
(Continued from previous page)					
GUSTO severe or moderate bleeding	199 (1·29%)	328 (2·18%)	0·60 (0·50–0·71)	<0·0001	0·8909
0–1	57 (0·87%)	93 (1·46%)	0·60 (0·43–0·83)	..	
2	74 (1·34%)	130 (2·39%)	0·56 (0·42–0·75)	..	
≥3	68 (2·02%)	105 (3·25%)	0·62 (0·46–0·85)	..	
Any bleeding	2356 (18·1%)	3060 (25·8%)	0·71 (0·68–0·75)	<0·0001	0·9246
0–1	751 (12·9%)	996 (18·8%)	0·70 (0·64–0·77)	..	
2	868 (18·9%)	1140 (26·8%)	0·71 (0·65–0·78)	..	
≥3	737 (28·1%)	924 (40·0%)	0·72 (0·66–0·80)	..	
Net clinical events†	1009 (6·13%)	1168 (7·20%)	0·85 (0·78–0·92)	0·0002	0·8885
0–1	333 (4·77%)	392 (5·72%)	0·84 (0·72–0·97)	..	
2	388 (6·58%)	441 (7·50%)	0·87 (0·76–1·00)	..	
≥3	288 (8·05%)	335 (9·59%)	0·84 (0·72–0·98)	..	

Data are number of events (% per person-year). Person-year is defined as the sum of days from randomisation or start of study drug to first event across all patients, divided by 365·25. % per person-year is defined as the number of patients who had an event divided by person-year multiplied by 100. All analyses that include bleeding endpoints were performed on the treated population (n=18 140). We did not report numerators/denominators because they do not add up to the event rate (event rate=%/[person-year]). GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries. HR=hazard ratio. MI=myocardial infarction. TIMI=Thrombolysis in Myocardial Infarction. *From first dose until 2 days after last dose of study drug. †Stroke, systemic embolism, ISTH major bleeding, or all-cause mortality.

Table 5: **Endpoints by HAS-BLED score**

***Panel:* Research in context**

Systematic review

We searched PubMed for reports published before May, 2012, in all languages using the terms "apixaban", "warfarin", "atrial fibrillation", "stroke and bleeding risk scores", and "clinical trial". Only one study—the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial[7,14]—compared apixaban with warfarin in patients with atrial fibrillation.

Interpretation

This was the first study to show that the benefits of apixaban with respect to stroke and bleeding when compared with warfarin are consistent across patients with a range of risks for stroke and bleeding, and similar findings have been seen with other new oral anticoagulants. Individual patient risk assessment might therefore be less relevant when used to tailor apixaban treatment than it is for warfarin.

results might be more careful dosing of warfarin in patients with previous bleeding and labile INRs, who are at higher risk of bleeding.

The CHA_2DS_2VASc score has been proposed as a more sensitive measure of stroke risk than the $CHADS_2$ score, with the main advantage being more effective stratification of patients at low risk for stroke.[12] In our study, apixaban resulted in a significant reduction in stroke or systemic embolism and mortality, with no evidence of a differential effect by risk of stroke across the full range of CHA_2DS_2VASc scores. Patients with both a $CHADS_2$ score of 0 and a CHA_2DS_2VASc score of 0 or 1 are not thought to need treatment with oral anticoagulation; therefore, patients who scored 0 were not included in ARISTOTLE. Aspirin is recommended and frequently used as an alternative for thromboembolism prophylaxis in these lower-risk patients with atrial fibrillation.[2] However, apixaban is more effective at stroke prevention, is better tolerated than is aspirin, and has a similar risk of major bleeding to low-dose aspirin in patients with atrial fibrillation and a $CHADS_2$ score of 1 or higher who are not suitable for oral anticoagulation.[8] Since patients with $CHADS_2$ or CHA_2DS_2VASc scores of 0 were not included in either ARISTOTLE[7,14] or AVERROES (Apixaban versus Acetylsalicylic Acid to Prevent Strokes) trials,[8] the benefit–risk profile of apixaban in these lower-risk patients can only be established by new prospective randomised trials.

Risk scores have been put forward as ways to guide the choice of antithrombotic therapy in patients with atrial fibrillation.[17] Therefore, evidence showing that the efficacy and safety of new anticoagulants, such as apixaban, are consistent across patients' risk scores for stroke and bleeding is important because it shows that scores might be less relevant for patients on apixaban. The analysis of the RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial, which examined two doses of dabigatran (an oral factor IIa inhibitor) versus warfarin in relation to $CHADS_2$ score, suggested that the higher dose of dabigatran (150 mg twice daily) reduced stroke or systemic embolism to a greater extent than did warfarin, whereas the lower dose (110 mg twice daily) caused less bleeding than did warfarin, and, as in our study, the result did not differ according to $CHADS_2$ score.[22] Because apixaban causes substantially less bleeding, including intracranial bleeding, than does warfarin, and has similar rates of serious bleeding to aspirin, and because its effects do not differ in patients according to $CHADS_2$, CHA_2DS_2VASc, or HAS-BLED score, these risk scoring systems might be less relevant when used to tailor apixaban treatment to individual patients (at least for those with a $CHADS_2$ score of 1 of higher) than they are for warfarin (panel). However, the absolute incremental benefit with apixaban versus warfarin is larger in higher-risk patients, and therefore cost-effectiveness might be variable across different risk profiles. Thus, further improvement in the methods for risk stratification of both stroke and bleeding should help to advance personalised treatment with novel oral anticoagulants in patients with atrial fibrillation, particularly those at low risk.

Our study has several limitations. First, the ARISTOTLE trial was not designed or powered to detect interactions between study drug and risk-score subgroups. Second, the $CHADS_2$ and CHA_2DS_2VASc scores were first developed in patients who had never taken warfarin before, whereas HAS-BLED was developed in a group who had received warfarin. Our study contained

7800 (43%) warfarin-naive patients and 10 401 (57%) warfarin-experienced patients. Third, for HAS-BLED score, we calculated labile INR on the basis of the only available INR value in warfarin-experienced patients at baseline, and this approach was different from how labile INR was first defined (TTR <60%).[13] Therefore, our results might have overestimated the number of patients with labile INR, increasing the overall HAS-BLED scores of our population. Finally, our results were derived from a large clinical trial population that differs from an unselected clinical patient population.

In summary, further improvement in risk stratification for both stroke and bleeding is needed, particularly for patients with atrial fibrillation at low risk for these events.

Contributors

RDL conceived the study, had full access to all the data, and takes responsibility for the integrity of the data and the accuracy of the data analysis. RDL, SMA-K, PM, LW, CBG, and JHA designed the study; RDL, LW, CBG, JHA, and HY obtained the data; RDL, LW, CBG, JHA, and HY analysed the data; and all authors interpreted the data. RDL drafted the manuscript, and all authors critically revised it.

Conflicts of interest

RDL has received a research grant from Bristol-Myers Squibb and consulting fees from Pfizer and Boehringer Ingelheim. SMA-K has received research funding from Bristol-Myers/Squibb to co-chair the clinical events committee for the ARISTOTLE trial. LW has received research grants from AstraZeneca, Merck/Schering-Plough, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, and GlaxoSmithKline; has been a consultant for Merck/Schering-Plough, Regado Biosciences, Evolva, Portola, CSL Behring, Athera Biotechnologies, Boehringer-Ingelheim, AstraZeneca, GlaxoSmithKline, and Bristol-Myers Squibb/Pfizer; has received lecture fees from AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, Schering-Plough; and has received honoraria from Boehringer Ingelheim, AstraZeneca, Bristol-Myers Squibb/Pfizer, GlaxoSmithKline, and Schering-Plough/Merck. JA has received consultant fees from Bristol-Myers Squibb, Pfizer, Janssen Pharmaceuticals, Boehringer-Ingelheim, and Daiichi Sankyo. MCB was part of the Steering Committee for the ARISTOTLE trial, of which Bristol-Myers Squibb paid for national coordination activities. RDC has received consultant and speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi Sankyo, and Lilly; and research grants from AstraZeneca and Boehringer Ingelheim. PD has received consulting fees and honoraria from Bristol-Myers Squibb/Pfizer. JDE has received consulting or advisory board fees from AstraZeneca and Bristol-Myers Squibb; received data safety monitoring board fees from Novartis, Johnson & Johnson, Brigham and Women's Hospital, Schering-Plough Research Institute; and served on the adjudication committee for the Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial (National Institutes of Health). JAE has received a consulting fee and travel support from Bristol-Myers Squibb/Pfizer for the ARISTOTLE trial. BJG is a member of data safety monitoring boards for Baxter Healthcare Corporation, Ortho-McNeil Janssen Scientific Affairs, Amorcyte, Abbott Laboratories, GE Healthcare, St Jude Medical, Medispec, Merck & Co, and Boston Scientific. CBG has received grants from Bristol-Myers Squibb, Pfizer, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, the Medtronic Foundation, Merck, Sanofi-Aventis, Astellas, and the Medicines Company; consulting fees from AstraZeneca, Boehringer Ingelhelm, Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-LaRoche, Novartis, Otsuka Pharmacautical, Sanofi-Aventis, Lilly, Pfizer, and the Medicines Company; and support for travel from Hoffmann-La Roche, Novartis, and Pfizer. SHH has received consulting fees from Sanofi-Aventis, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Bayer, and Cardiome; and lecture fees from Sanofi-Aventis, St Jude Medical, Medtronic, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer. JH has received research support from Bristol-Myers Squibb. EMH has served as a consultant to Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Johnson & Johnson, and Pfizer. JJVM's employer, Glasgow University, was paid by the study sponsors for his time spent as a member of the Executive Committee of ARISTOTLE, and his travel and accommodation related to ARISTOTLE Executive or Steering Committee meetings was paid by the study sponsors. PM is a full-time employee of Bristol-Myers Squibb and owns stock in the company as part of salary and compensation. JHA has received research grants from Bristol-Myers Squibb, Merck/Schering-Plough, and Regado Biosciences; travel support from Bristol-Myers Squibb; and consulting fees from Bristol-Myers Squibb, Pfizer, Merck/Schering-Plough, AstraZeneca, Boehringer-Ingelheim, Ortho-McNeail-Janssen Pharmaceuticals, PolyMedix, Regado Biosciences, Bayer, and Daiichi-Sankyo. HY, CE, and DV declare that they have no conflicts of interest.

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