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ORIGINAL ARTICLE
Atrial fibrillation

Clinical outcomes of patients with diabetes and atrial fibrillation treated with apixaban: results from the ARISTOTLE trial

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Aims We compared clinical outcomes in patients with AF with and without diabetes in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial.

Methods and results The main efficacy endpoints were SSE and mortality; safety endpoints were major and major/clinically relevant non-major bleeding. A total of 4547/18 201 (24.9%) patients had diabetes who were younger (69 vs. 70 years), more had coronary artery disease (39 vs. 31%), and higher mean $CHADS_2$ (2.9 vs. 1.9) and HAS-BLED scores (1.9 vs. 1.7) (all $P < 0.0001$) than patients without diabetes. Patients with diabetes receiving apixaban had lower rates of SSE [hazard ratio (HR) 0.75, 95% confidence interval (CI) 0.53–1.05), all-cause mortality (HR 0.83, 95% CI 0.67–1.02), cardiovascular mortality (HR 0.89, 95% CI 0.66–1.20), intra-cranial haemorrhage (HR 0.49, 95% CI 0.25–0.95), and a similar rate of myocardial infarction (HR 1.02, 95% CI 0.62–1.67) compared with warfarin. For major bleeding, a quantitative interaction was seen (P-interaction = 0.003) with a greater reduction in major bleeding in patients without diabetes even after multivariable adjustment. Other measures of bleeding showed a consistent reduction with apixaban compared with warfarin without a significant interaction based on diabetes status.

Conclusion Apixaban has similar benefits on reducing stroke, decreasing mortality, and causing less intra-cranial bleeding than warfarin in patients with and without diabetes.

Keywords Diabetes • Atrial fibrillation • Clinical outcomes • Oral anti-coagulant

Introduction

Diabetes and atrial fibrillation are both highly prevalent and global public health issues.[1] Importantly, patients with diabetes are at increased risk for stroke when atrial fibrillation is present, and diabetes is thus part of stroke risk prediction tools.[2] Recently, newer oral anti-coagulation agents have been shown to be efficacious and safe for the prevention of stroke in patients with atrial fibrillation.[3–6] Given that patients with diabetes are at increased risk for stroke, they have been included in the major trials and constitute 23,[4] 25,[3] 36,[6] or 40%[5] of the enrolled population in four recent large trials. In addition to being at increased risk for stroke, patients with diabetes are at risk for other cardiovascular events and thus the focus on overall vascular protection. For patients with diabetes, quality of care is reflected, in part, by the appropriate use of statins, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), and control of blood pressure as key metrics for vascular protection.[7]

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, there was a

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significant reduction in stroke and systemic embolism, all-cause mortality, and bleeding in favour of apixaban compared with warfarin for patients with atrial fibrillation and at least one additional risk factor for stroke. We investigated the impact of diabetes on outcomes and the effect of apixaban compared with warfarin in patients with atrial fibrillation with and without diabetes in the ARISTOTLE trial.

Methods

The ARISTOTLE trial (NCT00412984) design and results have been published.[3,8] 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 three 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 (INR), 2.0–3.0] in patients with atrial fibrillation at risk of stroke.

Patient population

To be eligible to participate in the ARISTOTLE trial, patients had to have atrial fibrillation or atrial flutter and at least one additional risk factor for stroke: symptomatic heart failure within 3 months or left ventricular ejection fraction ≤40%; hypertension requiring pharmacological treatment; age ≥75 years; diabetes mellitus; or prior stroke, transient ischaemic attack, or systemic embolism. Other inclusion and exclusion criteria have been published.[3] For the purpose of the trial, diabetes was defined by the site investigator according to local guidelines.

Trial design and outcome measures

The primary efficacy endpoint in ARISTOTLE was stroke (ischaemic or haemorrhagic) or systemic embolism. The primary safety outcome was International Society of Thrombosis and Haemostasis (ISTH) major bleeding. Major bleeding was defined as acute or subacute clinically overt bleeding accompanied by one or more of the following: (i) decrease in the haemoglobin level of ≥2 g/dL, (ii) transfusion of ≥2 U of packed red blood cells, and/or (iii) bleeding that is fatal or occurs in at least one of the following critical sites: intra-cranial, intra-spinal, intra-ocular, pericardial, intra-articular, intra-muscular with compartment syndrome, or retroperitoneal. A clinical events committee adjudicated all primary and secondary (all-cause death, myocardial infarction) outcomes according to pre-specified criteria, but site of bleed was classified by site. For patients assigned to receive warfarin, the median (25th, 75th percentiles) time-in-therapeutic-range was calculated, using the linear interpolation method, for patients with and without diabetes.[9]

Ethics committee approval was obtained for all investigational sites, and all patients provided written informed consent.

Statistical analyses

We examined the baseline characteristics of patients by their diabetes status. Continuous variables are presented as medians and 25th and 75th percentiles, with between-group comparisons, tested by non-parametric (Wilcoxon) tests. $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores are presented as mean and standard deviation and compared using *t*-tests. Categorical variables are presented as counts and percentages and compared by χ^2 tests or Fisher's exact tests, where appropriate.

Analyses of primary and secondary efficacy endpoints included all randomized patients (intention-to-treat) and included all events from randomization until the efficacy cut-off date. Bleeding analyses were 'on treatment' including all randomized patients who received at least one dose of the study drug and included all events from receipt of the study drug until 2 days after the last dose of the study drug. Event rates per 100 patient-years of follow-up are reported. Hazard ratios [95% confidence intervals (CI)] comparing apixaban with warfarin were derived from the Cox proportional hazards models. Treatment effects were compared according to diabetes status, by adding interactions to the model. For statistically significant interactions ($P < 0.05$), exploratory analyses were carried out to identify characteristics associated with diabetes status that might be causing the statistically significant interaction. For this purpose, we identified variables that were associated with either diabetes or the endpoint and included them as adjustment covariates in a multivariable model, along with the two-way interactions with randomized treatment.

All analyses were performed using SAS software, version 9.3 (SAS Institute Inc., Cary, NC, USA). A two-sided *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Of the 18 201 patients in ARISTOTLE, 4547 (24.9%) had diabetes. Patients with diabetes were younger (69 vs. 70 years), more had a history of coronary artery disease (39 vs. 31%), renal dysfunction (60 vs. 52%), and higher mean $CHADS_2$ (2.9 vs. 1.9) and HAS-BLED scores (1.9 vs. 1.7) (all $P < 0.0001$) than patients without diabetes. Other detailed history, risk scores, physical examination, and laboratory investigation results are in *Table 1*.

Random blood glucose values were available on 16 439 patients at baseline. Median blood glucose was 101 mg/dL (25th, 75th: 92, 114) for patients without diabetes and 141 mg/dL (112, 186) for patients with diabetes. Overall, 3492 (76.8%) patients with diabetes were on a diabetes-related medication, including metformin (50.1%), sulfonylureas (19.3%), insulin (18.1%), sitagliptin (2.8%), thiazolidinedione (5.8%), or other hypoglycaemic medication (20.7%). There were no differences in diabetes treatment between the apixaban or warfarin groups.

Concerning INR, median time in therapeutic range was similar for patients with diabetes [65.2% (52.5, 75.8)] and for patients without diabetes [66.2% (52.4–76.7)]. Patients with diabetes had higher discontinuation rates of study drug compared with patients without diabetes (27.9 vs. 25.8%, $P = 0.0043$). After excluding discontinuations due to death, 23.1% of patients with diabetes discontinued apixaban compared with 24.7% of patients on warfarin ($P = 0.2167$).

Quality of care

At baseline, a total of 55.2% ($n = 2485$) of patients with diabetes received a statin. After 1 year of follow-up, 56.2% ($n = 2355$) of patients with diabetes were taking a statin; of the 1844 patients not taking a statin at the beginning of the trial, 130 (7.5%) began taking a statin. Median baseline systolic and diastolic blood pressure was 130/80 mmHg in patients with diabetes, with 28.9% ($n = 1047$) achieving <130/80 mmHg at baseline. Of the 1047 patients at target blood pressure at baseline, 608 (58.1%) remained at target and 439 (41.9%) were above this threshold at 1 year. Of the 2661 patients not at target at baseline, 1950 (73.3%) remained above target blood pressure, and 711 (26.7%) were at target blood pressure at 1 year. Thus, a total of 1319 patients (35.5% of patients with diabetes) were at the blood pressure target at 1 year. In terms of renin–angiotensin blockade, 77.4% ($n = 3481$) were on either an ACE inhibitor or an ARB at baseline; by 1 year this was 76.6% ($n = 3212$). Of the 941

Table 1 Baseline characteristics

	Diabetes			No diabetes			*P*-Value*
	Overall (*N* = 4547)	Apixaban (*N* = 2284)	Warfarin (*N* = 2263)	Overall (*N* = 13654)	Apixaban (*N* = 6836)	Warfarin (*N* = 6818)	
Age, median (25th, 75th), years	69 (63, 75)	69 (63, 75)	69 (62, 75)	70 (63, 76)	70 (63, 76)	70 (63, 76)	<0.0001
Female sex, no. (%)	1589 (34.9)	813 (35.6)	776 (34.3)	4827 (35.4)	2421 (35.4)	2406 (35.3)	0.6195
Region, no. (%)							
North America	1423 (31.3)	726 (31.8)	697 (30.8)	3051 (22.3)	1523 (22.3)	1528 (22.4)	<0.0001
Latin America	702 (15.4)	348 (15.2)	354 (15.6)	2766 (20.3)	1395 (20.4)	1371 (20.1)	
Europe	1701 (37.4)	832 (36.4)	869 (38.4)	5642 (41.3)	2840 (41.5)	2802 (41.1)	
Asia Pacific	721 (15.9)	378 (16.5)	343 (15.2)	2195 (16.1)	1078 (15.8)	1117 (16.4)	
Systolic blood pressure, median (25th, 75th), mmHg	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	0.2399
Diastolic blood pressure, median (25th, 75th), mmHg	80 (70, 85)	80 (70, 85)	80 (70, 85)	80 (71, 88)	80 (71, 87)	80 (71, 88)	<0.0001
Weight, median (25th, 75th), kg	88 (74, 103)	86 (74, 102)	89 (74, 104)	80 (69, 93)	80 (69, 93)	80 (69, 93)	<0.0001
Prior stroke, TIA, or systemic embolism, no. (%)	930 (20.5)	455 (19.9)	475 (21.0)	2608 (19.1)	1293 (18.9)	1315 (19.3)	0.0459
Hypertension, no. (%)	4085 (89.8)	2028 (88.8)	2057 (90.9)	11831 (86.6)	5934 (86.8)	5897 (86.5)	<0.0001
Heart failure or reduced LVEF, no. (%)	1624 (35.7)	832 (36.4)	792 (35.0)	4827 (35.4)	2403 (35.2)	2424 (35.6)	0.6571
Coronary artery disease, no. (%)	1766 (38.9)	873 (38.3)	893 (39.5)	4276 (31.3)	2174 (31.8)	2102 (30.9)	<0.0001
Peripheral artery disease, no. (%)	325 (7.2)	160 (7.1)	165 (7.4)	559 (4.1)	282 (4.2)	277 (4.1)	<0.0001
Type of atrial fibrillation, no. (%)							
Paroxysmal	659 (14.5)	321 (14.1)	338 (14.9)	2127 (15.6)	1053 (15.4)	1074 (15.8)	0.0788
Persistent or permanent	3887 (85.5)	1963 (85.9)	1924 (85.1)	11525 (84.4)	5781 (84.6)	5744 (84.2)	
$CHADS_2$, mean (SD)	2.9 (1.09)	2.8 (1.07)	2.9 (1.10)	1.9 (0.99)	1.9 (0.99)	1.9 (1.00)	<0.0001
$CHADS_2$ score, no. (%)							
≤1	197 (4.3)	99 (4.3)	98 (4.3)	5986 (43.8)	3001 (43.9)	2985 (43.8)	<0.0001
2	1826 (40.2)	928 (40.6)	898 (39.7)	4690 (34.3)	2334 (34.1)	2356 (34.6)	
≥3	2524 (55.5)	1257 (55.0)	1267 (56.0)	2978 (21.8)	1501 (22.0)	1477 (21.7)	
CHA_2DS_2-VASc, mean (SD)	4.2 (1.50)	4.2 (1.50)	4.2 (1.51)	3.1 (1.41)	3.2 (1.42)	3.1 (1.40)	<0.0001
CHA_2DS_2-VASc score, no (%)							
0–2	550 (12.1)	274 (12.0)	276 (12.2)	4825 (35.3)	2419 (35.4)	2406 (35.3)	<0.0001
3–5	3118 (68.6)	1581 (69.2)	1537 (67.9)	7974 (58.4)	3997 (58.5)	3977 (58.3)	
>5	879 (19.3)	429 (18.8)	450 (19.9)	855 (6.3)	420 (6.1)	435 (6.4)	
HAS-BLED, mean (SD)	1.9 (1.06)	1.8 (1.04)	1.9 (1.07)	1.7 (1.05)	1.8 (1.05)	1.7 (1.05)	<0.0001
HAS-BLED score, no. (%)							
0–1	1750 (38.5)	884 (38.7)	866 (38.3)	5711 (41.8)	2857 (41.8)	2854 (41.9)	<0.0001
2	1618 (35.6)	817 (35.8)	801 (35.4)	4950 (36.3)	2465 (36.1)	2485 (36.4)	
≥3	1179 (25.9)	583 (25.5)	596 (26.3)	2993 (21.9)	1514 (22.1)	1479 (21.7)	
Prior use of VKA for >30 days, no. (%)	2717 (59.8)	1364 (59.7)	1353 (59.8)	7684 (56.3)	3844 (56.2)	3840 (56.3)	<0.0001
Medications at time of randomization, no. (%)							
ACE inhibitor or ARB	3481 (77.4)	1748 (77.3)	1733 (77.4)	9351 (69.7)	4716 (70.4)	4635 (69.1)	<0.0001
Amiodarone	448 (10.0)	234 (10.3)	214 (9.6)	1603 (12.0)	775 (11.6)	828 (12.3)	0.0003
β-Blocker	2947 (65.5)	1498 (66.2)	1449 (64.7)	8535 (63.7)	4299 (64.2)	4236 (63.2)	0.0269
Aspirin	1550 (34.1)	785 (34.4)	765 (33.8)	4082 (29.9)	2074 (30.3)	2008 (29.5)	<0.0001
Clopidogrel	98 (2.2)	50 (2.2)	48 (2.1)	240 (1.8)	120 (1.8)	120 (1.8)	0.0855
Digoxin	1578 (35.1)	798 (35.3)	780 (34.9)	4250 (31.7)	2118 (31.6)	2132 (31.8)	<0.0001
Calcium channel blocker	1665 (37.0)	821 (36.3)	844 (37.7)	3902 (29.1)	1923 (28.7)	1979 (29.5)	<0.0001
Statin	2485 (55.2)	1257 (55.6)	1228 (54.9)	4988 (37.2)	2493 (37.2)	2495 (37.2)	<0.0001
Non-steroidal anti-inflammatory agent	445 (9.9)	210 (9.3)	235 (10.5)	1075 (8.0)	542 (8.1)	533 (7.9)	<0.0001
Gastric antacid drugs	974 (21.6)	479 (21.2)	495 (22.1)	2376 (17.7)	1204 (18.0)	1172 (17.5)	<0.0001
Renal function, no. (%)							
Normal (>80 mL/min)	2157 (47.6)	1059 (46.6)	1098 (48.6)	5361 (39.5)	2702 (39.7)	2659 (39.2)	<0.0001

Continued

Table 1 *Continued*

	Diabetes			No diabetes			*P*-Value*
	Overall (*N* = 4547)	Apixaban (*N* = 2284)	Warfarin (*N* = 2263)	Overall (*N* = 13654)	Apixaban (*N* = 6836)	Warfarin (*N* = 6818)	
Mild impairment (>50–80 mL/min)	1738 (38.3)	888 (39.1)	850 (37.6)	5849 (43.0)	2929 (43.0)	2920 (43.0)	
Moderate impairment (>30–50 mL/min)	578 (12.8)	298 (13.1)	280 (12.4)	2169 (16.0)	1067 (15.7)	1102 (16.2)	
Severe impairment (≤30 mL/min)	60 (1.3)	29 (1.3)	31 (1.4)	210 (1.5)	108 (1.6)	102 (1.5)	

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; LVEF, left ventricular ejection fraction; TIA, transient ischaemic attack; VKA, vitamin K antagonist.
**P*-value comparing diabetic vs. non-diabetics patients (ignoring randomized treatment).

Table 2 Association between randomized treatment and efficacy and safety endpoint by diabetic status

	Diabetes			No diabetes			*P*-value*
	Apixaban rate (*n*)	Warfarin rate (*n*)	HR (95% CI)	Apixaban rate (*n*)	Warfarin rate (*n*)	HR (95% CI)	
Efficacy endpoints							
Stroke or systemic embolism	1.39 (57)	1.86 (75)	0.746 (0.529–1.053)	1.23 (155)	1.51 (190)	0.809 (0.654–1.000)	0.7064
Death from any cause	3.90 (164)	4.71 (196)	0.827 (0.672–1.017)	3.40 (439)	3.69 (473)	0.922 (0.810–1.050)	0.3844
Cardiovascular death	1.88 (79)	2.12 (88)	0.888 (0.655–1.203)	1.77 (229)	1.99 (256)	0.889 (0.744–1.062)	0.9995
Myocardial infarction	0.78 (32)	0.76 (31)	1.019 (0.622–1.670)	0.46 (58)	0.56 (71)	0.812 (0.574–1.149)	0.4588
Intra-cranial haemorrhage	0.34 (13)	0.70 (26)	0.489 (0.251–0.951)	0.33 (39)	0.84 (96)	0.398 (0.275–0.578)	0.5998
Safety endpoints							
ISTH major bleeding	3.01 (112)	3.13 (114)	0.961 (0.740–1.247)	1.85 (215)	3.08 (348)	0.603 (0.509–0.715)	0.0034
ISTH CRNM bleeding	2.12 (79)	2.49 (90)	0.855 (0.632–1.156)	2.07 (239)	3.16 (354)	0.658 (0.558–0.775)	0.1392
ISTH major or CRNM bleeding	5.03 (184)	5.53 (197)	0.912 (0.746–1.115)	3.76 (429)	6.17 (680)	0.612 (0.542–0.690)	0.0009
TIMI major bleeding	1.22 (46)	1.66 (61)	0.736 (0.502–1.079)	0.87 (102)	1.71 (195)	0.511 (0.402–0.650)	0.1119
TIMI major or minor bleeding	2.16 (81)	2.40 (88)	0.901 (0.666–1.218)	1.36 (158)	2.48 (282)	0.547 (0.450–0.664)	0.0064
GUSTO severe bleeding	0.61 (23)	0.95 (35)	0.642 (0.379–1.086)	0.49 (57)	1.19 (137)	0.408 (0.299–0.555)	0.1444
GUSTO severe or moderate bleeding	1.89 (71)	2.43 (89)	0.776 (0.568–1.061)	1.10 (128)	2.09 (239)	0.524 (0.423–0.650)	0.0420
Any bleeding	20.03 (635)	28.22 (801)	0.727 (0.655–0.807)	17.45 (1721)	25.07 (2259)	0.710 (0.667–0.756)	0.7103

CI, confidence interval; CRNM, clinically relevant non-major; GUSTO, global use of strategies to open occluded arteries; HR, hazard ratio; ISTH, International Society of Thrombosis and Haemostasis; TIMI, thrombolysis in myocardial infarction.
**P*-value for the randomized treatment by diabetes status interaction. Rates are events per 100 patient-years.

patients not on an ACE or ARB at the beginning of the trial, 101 patients (10.7%) were initiated on an ACE or ARB. In patients with diabetes with either peripheral artery disease or coronary artery disease, 81.1% (n = 1642) were on an ACE inhibitor or ARB at baseline; by 1 year this was 80.4% (n = 1505).

Efficacy outcomes for patients with diabetes

Patients with diabetes receiving apixaban had lower rates of stroke or systemic embolism (HR 0.746, 95% CI 0.529–1.053), all-cause mortality (HR 0.827, 95% CI 0.672–1.017), and cardiovascular mortality (HR 0.888, 95% CI 0.655–1.203) compared with patients receiving warfarin (*Table 2* and *Figure 1*). Rates of myocardial infarction were low and similar for patients receiving apixaban or warfarin. No treatment interaction for patients with or without diabetes was seen for any of the efficacy endpoints.

Intra-cranial haemorrhage in patients with diabetes

Apixaban was associated with a substantial reduction in intra-cranial haemorrhage in both patients with and without diabetes (HR 0.489 with diabetes, HR 0.398 without diabetes, both favouring apixaban vs. warfarin, *P* interaction = 0.5998) (*Table 2* and *Figure 2A*).

Bleeding outcomes according to diabetes status

ISTH major bleeding was less common with apixaban than warfarin in the overall ARISTOTLE population. For patients with diabetes,

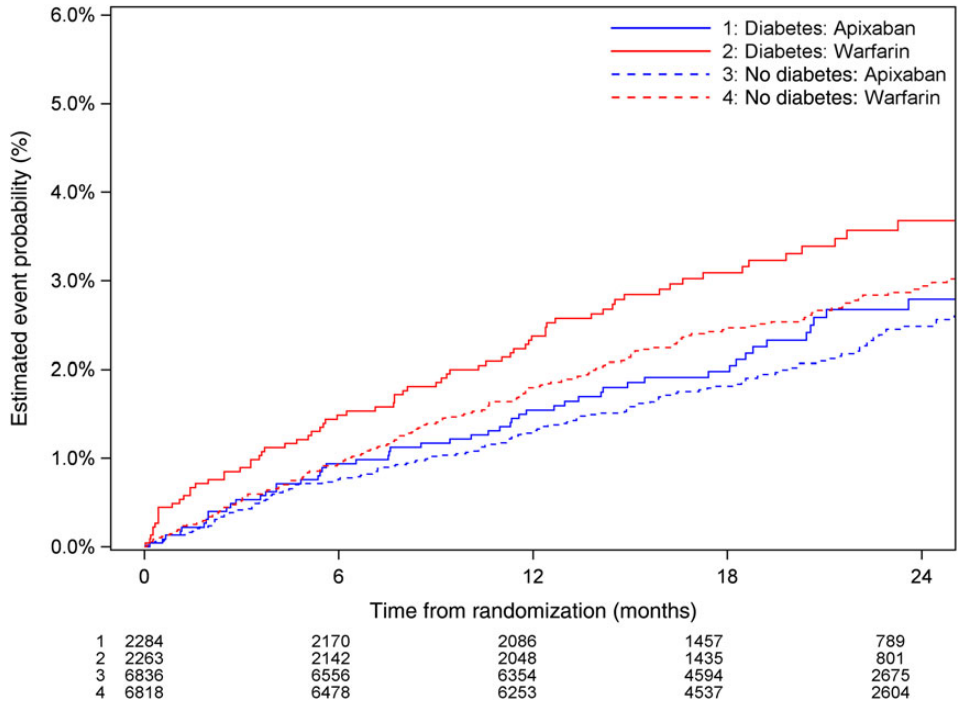

Figure 1 Kaplan–Meier curves of unadjusted outcomes of the primary endpoint (stroke or systemic embolism) by diabetes status.

this reduction was non-significant (apixaban rate 3.01 bleeds/100 patient-years; warfarin rate 3.13 bleeds/100 patient-years; HR 0.961, 95% CI 0.740–1.247). For patients without diabetes, there was a significant reduction in ISTH major bleeding with apixaban (1.85 bleeds/100 patient-years) compared with warfarin (3.08 bleeds/100 patient-years; HR 0.603, 95% CI 0.509–0.715). This difference in the benefits of apixaban compared with warfarin between patients with and without diabetes was statistically significant (interaction $P = 0.0034$) (*Table 2* and *Figure 2B*). Similar results were seen for ISTH major or clinically relevant non-major (CRNM) bleeding (interaction $P = 0.0009$) (*Table 2* and *Figure 2C*). For other measures of bleeding, however, there were consistent reductions with apixaban compared with warfarin for thrombolysis in myocardial infarction (TIMI) major bleeding (interaction $P = 0.1119$), global use of strategies to open occluded arteries (GUSTO) severe bleeding (interaction $P = 0.1444$), ISTH CRNM bleeding (interaction $P = 0.1392$), or for any bleeding (interaction $P = 0.7103$) (*Table 2* and *Figure 2D*).

To further explore the statistically significant interaction with major bleeding, a previously validated multivariable model of factors associated with ISTH major bleeding (age, sex, region of enrolment, coronary artery disease, prior myocardial infarction, history of bleeding, anaemia status, $CHADS_2$ score, and renal function) and variables that differed between patients with and without diabetes (weight, peripheral artery disease, prior use of vitamin K antagonists and the following medications at randomization: aspirin, amiodarone, calcium channel blockers, statins, non-steroidal anti-inflammatory agents, and antacids) were added to the interaction model for adjustment, along with their two-way interactions with treatment. The interaction between diabetes and the effect of randomized treatment on ISTH major bleeding remained statistically significant even after adjustment ($P = 0.0052$). None of the candidate variables mentioned above or other interactions explained the significant interaction between diabetes and randomized treatment on ISTH major bleeding. Three-way interactions between the effect of randomized treatment on ISTH major bleeding and diabetes were also tested for the following baseline variables: renal function, anti-thrombotics, statins, and acid-suppressing drugs. None of the three-way interactions were statistically significant.

Location of bleeding by diabetes status is shown in *Table 3*. Of note, patients with diabetes had higher rates of digestive tract bleeding (HR 1.502, 95% CI 1.156–1.953; $P = 0.0023$) and intra-ocular bleeding (HR 1.902, 95% CI 1.056– 3.424; $P = 0.0322$) than patients without diabetes.

Discussion

In the ARISTOTLE trial, apixaban consistently reduced stroke or systemic embolism, all-cause mortality, and intra-cranial haemorrhage when compared with warfarin in patients with and without diabetes. In the overall ARISTOTLE cohort, apixaban caused less major bleeding than warfarin; however, a significant quantitative interaction was observed between diabetes status and apixaban vs. warfarin on bleeding, demonstrating that compared with warfarin, apixaban caused even less major bleeding among patients without diabetes when compared with patients with diabetes.

Across all definitions of bleeding, patients on apixaban had (numerically) lower rates of bleeding than patients on warfarin, regardless of diabetes status, but an interaction, with less reduction in bleeding, was noted for the primary safety endpoint of ISTH major

bleeding. Similar results were not seen in a trial of apixaban vs. aspirin in atrial fibrillation, in trials of apixaban in venous thromboembolism prevention and treatment,[10,11] or with other target-specific oral anti-coagulants vs. warfarin in atrial fibrillation.[4–6] Additional modelling with two- and three-way interactions did not yield further insight. There is no good mechanistic hypotheses to explain this interaction, and thus an explanation may be the play of chance, especially with 23 subgroups analyzed.[12] Of note, although patients

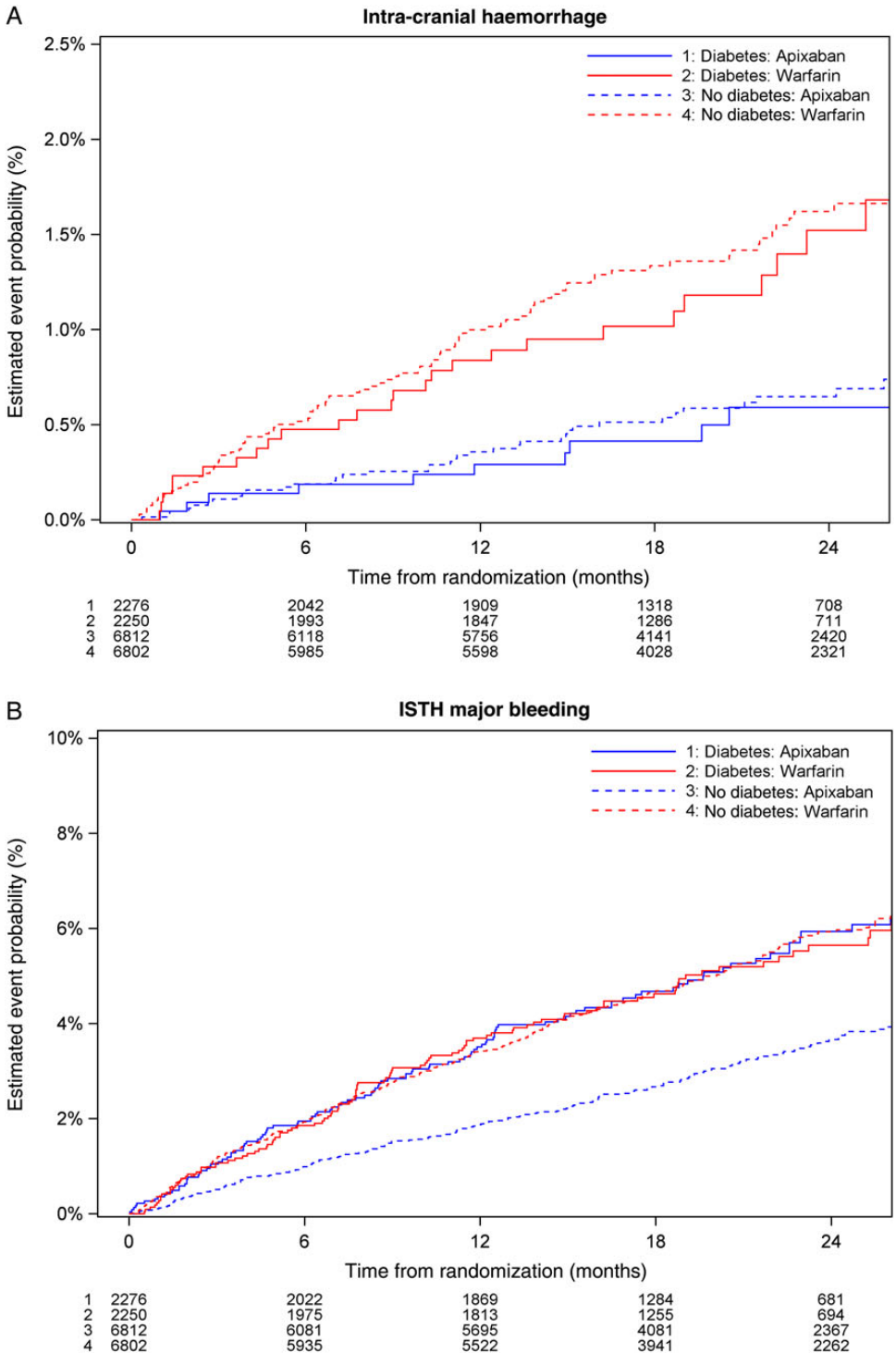

Figure 2 Kaplan–Meier curves of unadjusted outcomes of (*A*) intra-cranial haemorrhage, (*B*) ISTH major bleeding, (*C*) ISTH major or CRNM bleeding, and (*D*) any bleeding by diabetes status.

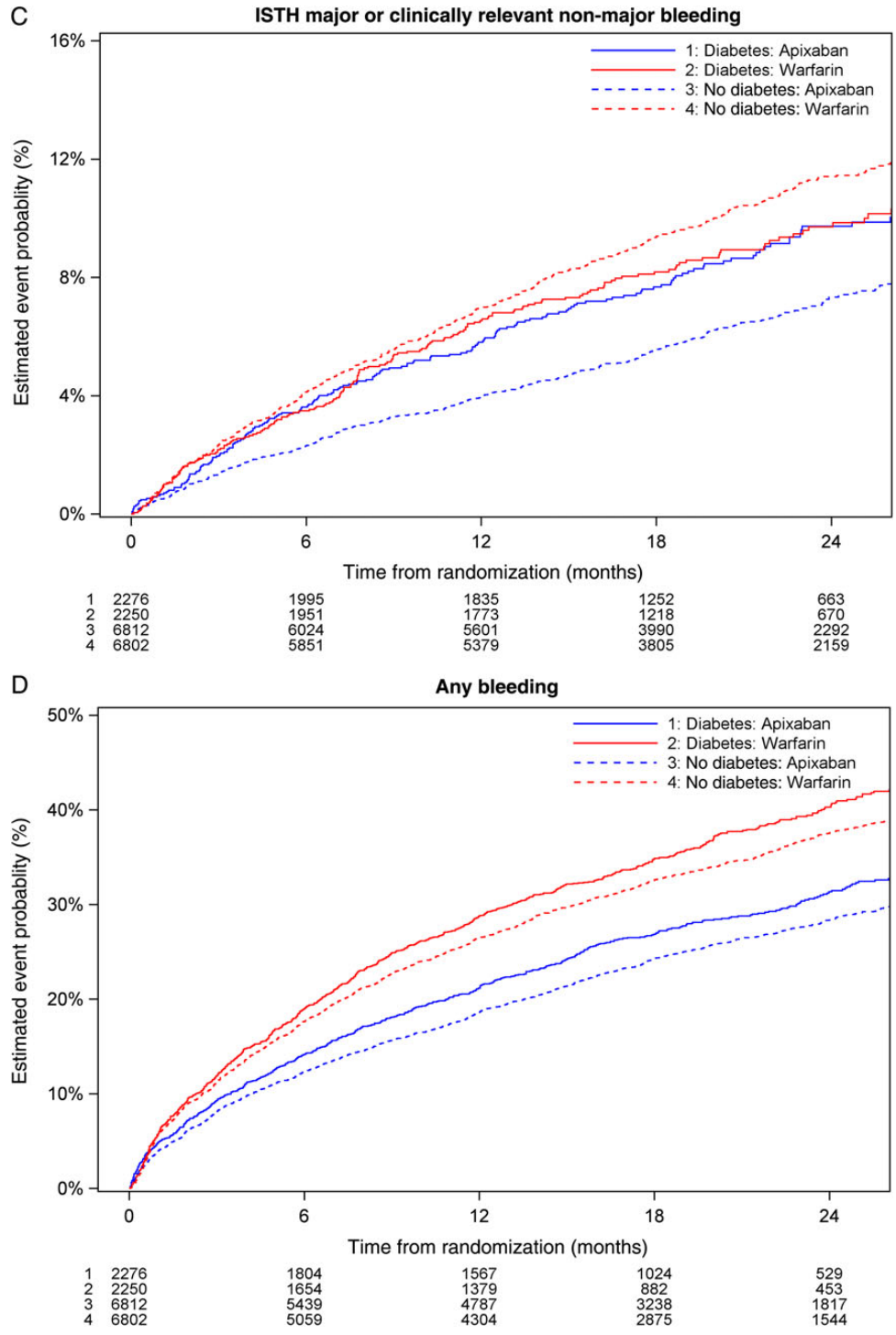

Figure 2 Continued.

with diabetes had higher mean $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores and higher rates of concomitant vascular disease and aspirin use, they had similar rates of bleeding in the warfarin arm when compared with patients without diabetes. Finally, as the benefit in stroke prevention, mortality and reduction of intra-cranial haemorrhage with apixaban vs. warfarin was consistent in patients with and without diabetes; apixaban remains a preferred treatment for patients with diabetes despite the smaller reduction in the rate of bleeding than in patients without diabetes.[13,14]

With respect to location of bleeding in patients with or without diabetes on apixaban or warfarin, no specific signal was seen. Of the 15 different locations of bleeds as reported by the site investigator,

Table 3 Location-specific bleeding outcomes in diabetic and non-diabetic patients

Bleeding location	Overall rate (*n*)	Diabetes rate (*n*)	No diabetes rate (*n*)	Diabetes vs. no diabetes HR (95% CI)	*P*-value
Intra-cranial	0.57 (174)	0.52 (39)	0.58 (135)	0.890 (0.624–1.272)	0.5235
Intra-articular	0.05 (16)	0.04 (3)	0.06 (13)	0.718 (0.204–2.518)	0.6043
Digestive tract	0.83 (254)	1.11 (83)	0.74 (171)	1.502 (1.156–1.953)	0.0023
Gastrointestinal (upper)	0.49 (151)	0.60 (45)	0.46 (106)	1.308 (0.923–1.855)	0.1308
Gastrointestinal (lower)	0.24 (75)	0.35 (26)	0.21 (49)	1.660 (1.032–2.672)	0.0367
Haemorrhoidal	0.02 (7)	0.04 (3)	0.02 (4)	2.275 (0.509–10.164)	0.2819
Rectal	0.08 (26)	0.15 (11)	0.06 (15)	2.257 (1.037–4.915)	0.0403
Haemoptysis	0.01 (4)	0.01 (1)	0.01 (3)	1.004 (0.104–9.649)	0.9975
Haemothorax	0.02 (5)	0.03 (2)	0.01 (3)	2.026 (0.339–12.128)	0.4392
Intra-muscular	0.01 (2)	0.01 (1)	0.00 (1)	3.027 (0.189–48.391)	0.4336
Bruising/ecchymosis	0.04 (11)	0.01 (1)	0.04 (10)	0.306 (0.039–2.388)	0.2586
Epistaxis	0.07 (23)	0.07 (5)	0.08 (18)	0.880 (0.327–2.371)	0.8007
Retroperitoneal	0.02 (7)	0.03 (2)	0.02 (5)	1.279 (0.248–6.596)	0.7689
Intra-spinal	0.01 (4)	0.03 (2)	0.01 (2)	3.039 (0.428–21.578)	0.2663
Vaginal	0.02 (7)	0.03 (2)	0.02 (5)	1.211 (0.235–6.243)	0.8188
Haematoma	0.25 (78)	0.28 (21)	0.25 (57)	1.141 (0.692–1.881)	0.6063
Haematuria	0.14 (42)	0.13 (10)	0.14 (32)	0.960 (0.472–1.953)	0.9109
Intra-ocular	0.15 (47)	0.24 (18)	0.12 (29)	1.902 (1.056–3.424)	0.0322
Other	0.46 (141)	0.63 (47)	0.41 (94)	1.553 (1.094–2.204)	0.0138

Rates are events per 100 patient-years.
CI, confidence interval; HR, hazard ratio.

patients with diabetes had higher rates of bleeding in two locations (intra-ocular, gastrointestinal tract), consistent with previous studies of patients with diabetes undergoing anti-coagulation for atrial fibrillation. However, caution should be exercised in interpreting these results given the infrequent nature of these events.

In terms of quality of care within a clinical trial, we have previously identified that even at sites engaged in clinical research with patient volunteers focused on their own health, ancillary care still has room to improve.[15] As an example, while 77% of patients were on an ACE inhibitor or ARB, 10.7% of patients not on an ACE inhibitor or ARB at baseline were initiated on this class of drug during the first year of ARISTOTLE. Further efforts within clinical trials and clinical practice to reach optimal quality of care are needed.

Limitations

This analysis has several limitations. First, although we used appropriate adjustment models for confounders and testing for statistical interaction terms, unmeasured confounders may exist. Secondly, due to multiple statistical testing, it is possible that nominally statistically significant results may be a play of chance. Thirdly, diabetes was defined by the site investigator using definitions appropriate for their locale, and no single definition was used for entry into the overall trial. Finally, although patients with diabetes form a large subgroup within ARISTOTLE, there may be limited power to detect a difference in some of our analyses.

Conclusions

In patients with atrial fibrillation, apixaban consistently reduces stroke or systemic embolism, all-cause mortality, and intra-cranial haemorrhage compared with warfarin in patients with and without diabetes. Although it is most likely a chance finding, there was an indication of less reduction in bleeding with apixaban compared with warfarin in patients with diabetes than without diabetes. As the main benefits in efficacy, safety, and tolerability with apixaban were consistent in patients with and without diabetes, apixaban should remain a preferred treatment for stroke prevention in patients with diabetes and atrial fibrillation requiring oral anti-coagulation.

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