CLINICAL TRIALS AND OBSERVATIONS

Management and clinical outcomes in patients treated with apixaban vs warfarin undergoing procedures

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Key Points

- Short-term preprocedure interruptions of either apixaban or warfarin are associated with a low rate of stroke or systemic embolism.
- Some patients taking apixaban or warfarin are able to undergo procedures safely without a preprocedure interruption of anticoagulation.

Using data from ARISTOTLE, we describe the periprocedural management of anticoagulation and rates of subsequent clinical outcomes among patients chronically anticoagulated with warfarin or apixaban. We recorded whether (and for how long) anticoagulant therapy was interrupted preprocedure, whether bridging therapy was used, and the proportion of patients who experienced important clinical outcomes during the 30 days postprocedure. Of 10 674 procedures performed during follow-up in 5924 patients, 9260 were included in this analysis. Anticoagulant treatment was not interrupted preprocedure 37.5% of the time. During the 30 days postprocedure, stroke or systemic embolism occurred after 16/4624 (0.35%) procedures among apixaban-treated patients and 26/4530 (0.57%) procedures among warfarin-treated patients (odds ratio [OR] 0.601; 95% confidence interval [CI] 0.322-1.120). Major bleeding occurred in 74/4560 (1.62%) procedures in the apixaban arm and 86/4454 (1.93%) in the warfarin arm (OR 0.846; 95% CI 0.614-1.166). The risk of death was similar with apixaban (54/4624 [1.17%]) and warfarin (49/4530 [1.08%]) (OR 1.082; 95% CI 0.733-1.598). Among patients in ARISTOTLE, the 30-day postprocedure stroke, death, and major bleeding rates were low and similar in apixaban- and warfarin-treated patients, regardless of whether anticoagulation was stopped beforehand. Our findings suggest that many patients on chronic anticoagulation can safely undergo procedures; some will not require a preprocedure interruption of anticoagulation. ARISTOTLE was registered at www.clinicaltrials.gov as #NCT00412984. (*Blood*. 2014;124(25):3692-3698)

Introduction

When patients taking an anticoagulant require a procedure, decisions about whether and when to interrupt antithrombotic therapy depend on the risks of postprocedural bleeding and the likelihood of periprocedural thrombotic events. Because the anticoagulant effect of warfarin and other vitamin K antagonists (VKA) dissipates slowly, these medications are often withheld several days prior to procedures associated with a moderate-to-high risk of bleeding. If a patient's risk for thromboembolism is considered high, pre- and postoperative bridging therapy with a short-acting, parenteral anticoagulant is often recommended.[1] However, relatively little high-quality evidence exists to define the population of VKA-treated patients who derive a net clinical benefit from bridging therapy.

In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, apixaban, an oral direct factor Xa inhibitor, was more effective than warfarin in the prevention of stroke or systemic embolism in patients with atrial fibrillation.[2] Similar to other target-specific oral anticoagulants (and in contrast to VKAs), apixaban has a rapid onset and offset of anticoagulant activity.[3] For patients who require procedures associated with bleeding risk, this pharmacodynamic profile seems attractive because, in theory, the drug can be stopped and restarted such that time without protection from thrombosis is short and bridging therapy is unnecessary. Indeed, data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial suggest that dabigatran, an oral direct thrombin inhibitor with a similarly short half-life, can be safely continued up to 48 hours preprocedure in many patients.[4] Thus, using data from patients taking either apixaban or warfarin who underwent a procedure in ARISTOTLE, we describe the management of anticoagulation as well as the procedures' characteristics and subsequent clinical outcomes.

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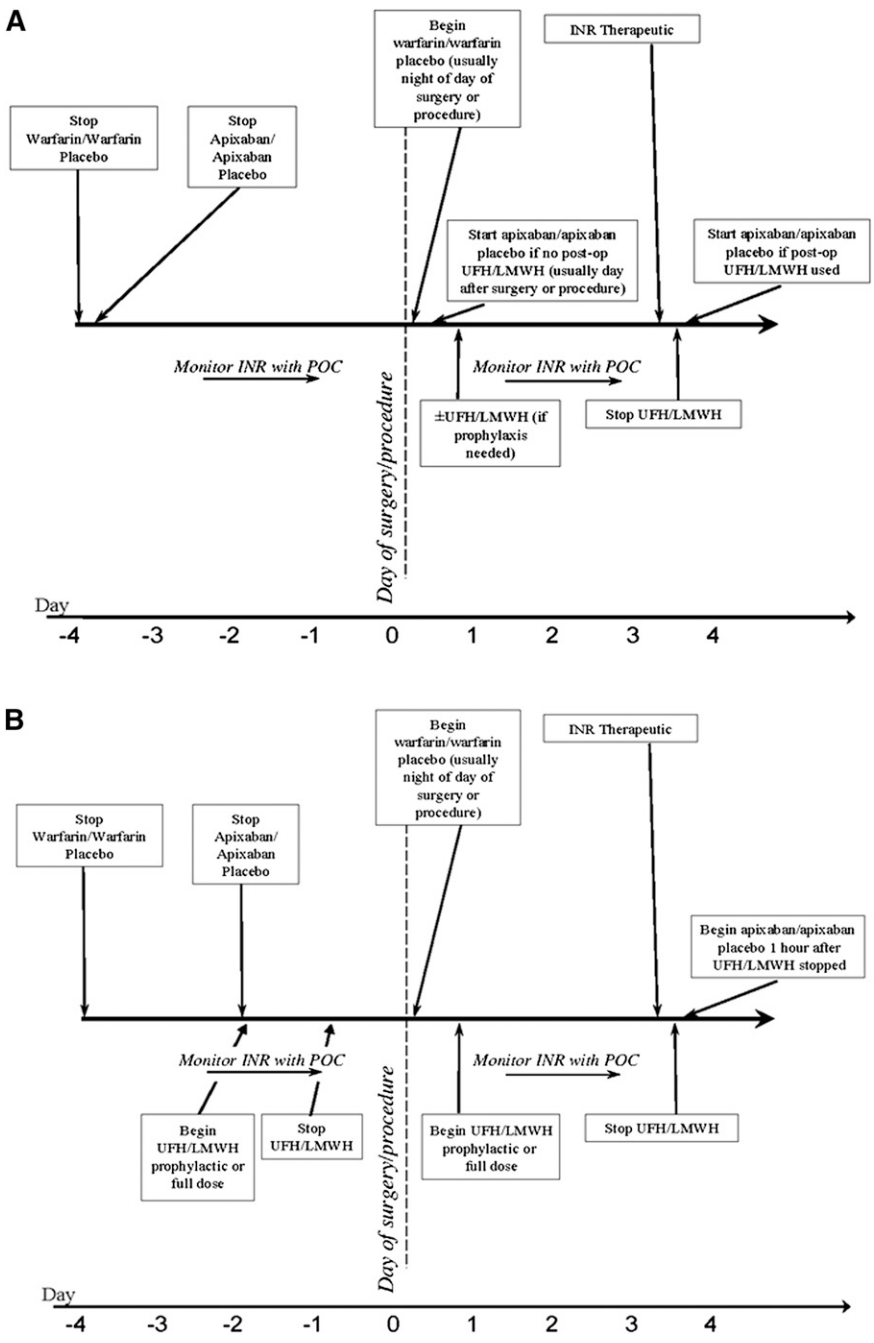

Figure 1. Periprocedural anticoagulation. (A) Bridging strategy suggested in the clinical trial protocol for low-risk patients. (B) Bridging strategy suggested in the clinical trial protocol for intermediate- and high-risk patients. INR, international normalized ratio; LMWH, low-molecular-weight heparin; POC, point of care; UFH, unfractionated heparin.

Methods

ARISTOTLE was a double-blind, double-dummy, randomized controlled trial of apixaban vs warfarin for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and at least 1 risk factor for stroke. Other details about the study design have been published elsewhere.[2,5] Institutional review board approval was obtained for the ARISTOTLE trial, and research was conducted in accordance with the Declaration of Helsinki.

Procedures

In this prespecified analysis, we identified all patients enrolled in ARISTOTLE who underwent a procedure for which anticoagulant therapy would, in some clinical situations, be interrupted.

Local investigators classified any procedure for which treatment was interrupted as emergent or nonemergent; for this analysis, we further classified procedures as major (requiring general anesthesia) or nonmajor. Only procedures performed on patients still taking blinded study medication (defined as having taken at least 1 dose ≤7 days prior to the procedure) were included in this analysis. When we describe the most frequent procedures, all procedures are included (even those from a day on which 2 or more procedures were performed). However, when we describe interruptions and event rates, procedures occurring on the same day are only counted once, as a single "procedure day," because the associated treatment decisions and follow-up for events cannot be separated.

For each patient, we recorded the following: whether and for how long anticoagulant therapy was interrupted prior to the procedure; whether bridging therapy with a parenteral anticoagulant was used; and whether the patient experienced stroke/systemic embolism, died, or had major bleeding

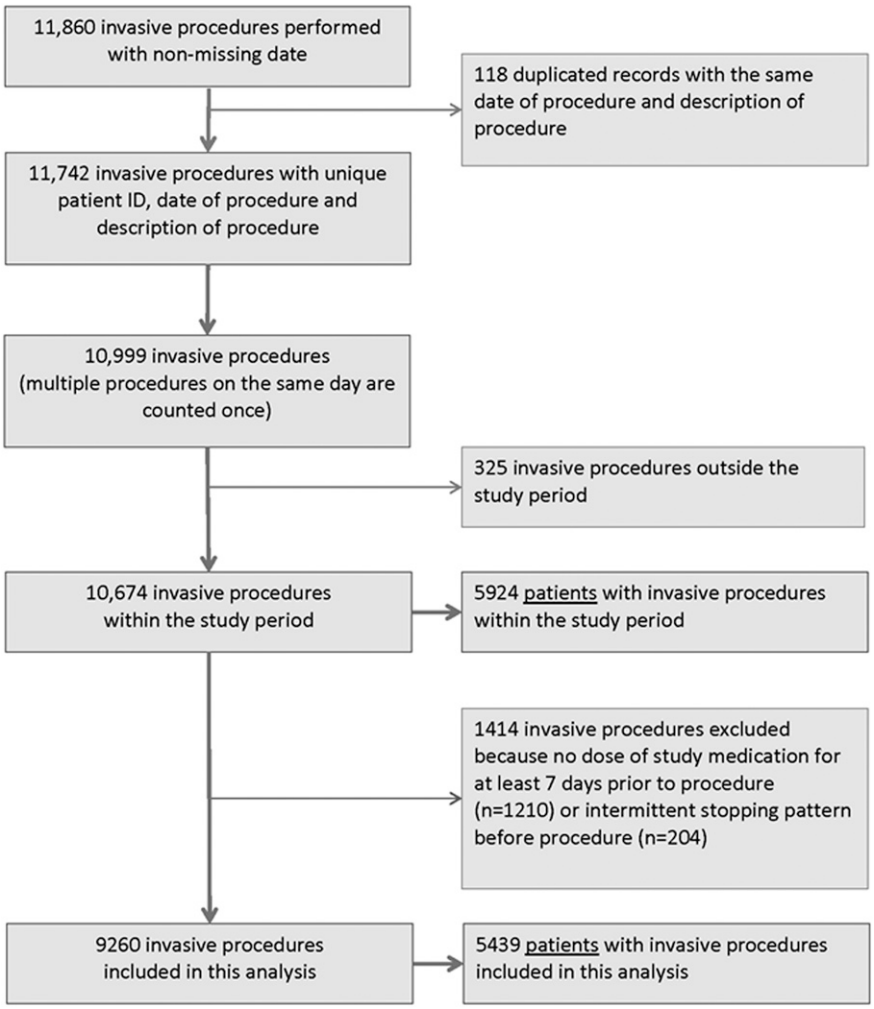

Figure 2. Diagram for inclusion of eligible patients and procedures.

(as defined by the International Society on Thrombosis and Hemostasis) during the 30 days after the procedure.

Based on the timing of the interruption of the study drug, each procedure was classified as either "no interruption" (if the study drug was not interrupted or interrupted on the same day of the procedure) or "any interruption" (if the study drug was stopped between 1 and 7 days before the procedure).

For nonemergent procedures, the study protocol provided guidance regarding the interruption of blinded study medication. In general, the protocol suggested that patients at low risk for thrombosis be managed without bridging (Figure 1A); heparin or low-molecular-weight heparin pre- and postoperatively was recommended for patients at intermediate-to-high risk of thrombosis (Figure 1B). However, the final decision about when (or if) study medication would be interrupted, whether (or how) bridging anticoagulation would be used, and when anticoagulant therapy would be restarted was left to local investigators.

Statistical analysis

Baseline characteristics for patients were summarized as frequencies and proportions for categorical variables and medians with 25th and 75th percentiles for continuous variables (except for $CHADS_2$ score, where mean and standard deviation were used). Comparisons between these groups were based on χ^2 and Wilcoxon tests.

Event rates during the 30 days following a procedure are summarized as frequencies and percentages and compared between randomized treatment using odds ratios (ORs) and 95% confidence intervals (CIs). ORs were derived using logistic generalized estimating equations, accounting for correlation between multiple procedures on the same patients by using a compound symmetric working correlation structure and robust variance. The interaction between randomized treatment and preprocedural interruption was tested by adding the randomized treatment and the interaction with interruption to the logistic models for each event. Adjusted ORs were derived adding the following variables to the model: age, $CHADS_2$ score, bridging therapy, major/nonmajor procedure, and emergency/nonemergency procedure.

All analyses were performed using SAS system version 9.22 (SAS Institute, Cary, NC).

Table 1. Most common procedures

Procedures	Frequency	%
Dental extraction/oral surgery	1435	14.6
Colonoscopy	978	9.9
Ophthalmic surgery	786	8.0
Upper endoscopy	743	7.6
Pacemaker insertion	344	3.5
Urinary tract cystoscopy	319	3.2
Percutaneous coronary intervention	271	2.8
Atrioventricular node ablation	94	1.0
Pulmonary vein isolation/ablation	78	0.8
Implantable cardioverter defibrillator	77	0.8

Proportions are calculated using a denominator n = 9839; some patients had >1 procedure performed on a given day.

Table 2. Baseline characteristics of patients, separated according to treatment assignment and whether study medication was interrupted preprocedure

Characteristic	Any interruption			No interruption			
	Overall (n = 3930)	Apixaban (n = 1960)	Warfarin (n = 1970)	Overall (n = 1509)	Apixaban (n = 741)	Warfarin (n = 768)	P*
Age, median (25th, 75th), y	71 (65, 77)	71 (65, 77)	71 (64, 77)	71 (65, 77)	72 (65, 77)	71 (65, 77)	.44
Female sex, no. (%)	1209 (30.8)	598 (30.5)	611 (31.0)	488 (32.3)	237 (32.0)	251 (32.7)	.26
Region, no. (%)							<.0001
North America	1623 (41.3)	798 (40.7)	825 (41.9)	525 (34.8)	262 (35.4)	263 (34.2)	
Latin America	579 (14.7)	286 (14.6)	293 (14.9)	163 (10.8)	74 (10.0)	89 (11.6)	
Europe	1319 (33.6)	661 (33.7)	658 (33.4)	615 (40.8)	304 (41.0)	311 (40.5)	
Asian Pacific	409 (10.4)	215 (11.0)	194 (9.8)	206 (13.7)	101 (13.6)	105 (13.7)	
Race, no. (%)							.003
White	3569 (90.8)	1765 (90.1)	1804 (91.6)	1322 (87.6)	653 (88.1)	669 (87.1)	
Black	43 (1.1)	28 (1.4)	15 (0.8)	16 (1.1)	6 (0.8)	10 (1.3)	
Asian	284 (7.2)	148 (7.6)	136 (6.9)	150 (9.9)	72 (9.7)	78 (10.2)	
Other	34 (0.9)	19 (1.0)	15 (0.8)	21 (1.4)	10 (1.3)	11 (1.4)	
Systolic blood pressure, median (25th, 75th), mm Hg	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	130 (120, 140)	.87
Weight, median (25th, 75th), kg	85 (73, 99)	85 (73, 99)	85 (74, 100)	83 (72, 96)	83 (72, 96)	83 (71, 96)	.0004
Prior myocardial infarction, no. (%)	614 (15.6)	316 (16.1)	298 (15.1)	244 (16.2)	117 (15.8)	127 (16.5)	.62
Prior clinically relevant or spontaneous bleeding, no. (%)	871 (22.2)	434 (22.1)	437 (22.2)	372 (24.7)	179 (24.2)	193 (25.1)	.05
History of fall within previous year, no. (%)	244 (6.8)	120 (6.7)	124 (6.9)	107 (7.7)	56 (8.1)	51 (7.2)	.26
Type of atrial fibrillation, no. (%)							.14
Paroxysmal	699 (17.8)	335 (17.1)	364 (18.5)	243 (16.1)	117 (15.8)	126 (16.4)	
Persistent or permanent	3229 (82.2)	1623 (82.9)	1606 (81.5)	1266 (83.9)	624 (84.2)	642 (83.6)	
Qualifying risk factors							
Age ≥75 y, no. (%)	1392 (35.4)	694 (35.4)	698 (35.4)	555 (36.8)	288 (38.9)	267 (34.8)	.60
Prior stroke, TIA or systemic embolism, no. (%)	701 (17.8)	344 (17.6)	357 (18.1)	322 (21.3)	150 (20.2)	172 (22.4)	.003
Heart failure or reduced LVEF, no. (%)	1131 (28.8)	565 (28.8)	566 (28.7)	480 (31.8)	226 (30.5)	254 (33.1)	.03
Diabetes, no. (%)	1079 (27.5)	527 (26.9)	552 (28.0)	402 (26.6)	214 (28.9)	188 (24.5)	.55
Hypertension requiring treatment, no. (%)	3471 (88.3)	1734 (88.5)	1737 (88.2)	1285 (85.2)	628 (84.8)	657 (85.5)	.002
$CHADS_2$, mean (SD)	2.1 (1.1)	2.1 (1.1)	2.1 (1.1)	2.2 (1.1)	2.2 (1.1)	2.2 (1.2)	.006
$CHADS_2$ score, no. (%)							.004
≤1	1363 (34.7)	682 (34.8)	681 (34.6)	509 (33.7)	251 (33.9)	258 (33.6)	
2	1437 (36.6)	724 (36.9)	713 (36.2)	500 (33.1)	242 (32.7)	258 (33.6)	
≥3	1130 (28.8)	554 (28.3)	576 (29.2)	500 (33.1)	248 (33.5)	252 (32.8)	
Medications at time of randomization, no. (%)							
ACE inhibitor or ARB	2763 (70.8)	1379 (70.9)	1384 (70.8)	1022 (68.3)	501 (67.9)	521 (68.6)	.07
Amiodarone	383 (9.8)	183 (9.4)	200 (10.2)	134 (9.0)	62 (8.4)	72 (9.5)	.33
β-Blocker	2556 (65.5)	1279 (65.8)	1277 (65.3)	926 (61.9)	446 (60.4)	480 (63.2)	.01
Aspirin	1302 (33.1)	669 (34.1)	633 (32.1)	467 (30.9)	226 (30.5)	241 (31.4)	.12
Clopidogrel	84 (2.1)	38 (1.9)	46 (2.3)	24 (1.6)	11 (1.5)	13 (1.7)	.20
Digoxin	1110 (28.5)	530 (27.2)	580 (29.7)	464 (31.0)	218 (29.5)	246 (32.4)	.07
Calcium blocker	1389 (35.6)	664 (34.1)	725 (37.1)	527 (35.2)	260 (35.2)	267 (35.2)	.78
Statin	1952 (50.0)	957 (49.2)	995 (50.9)	707 (47.2)	348 (47.2)	359 (47.3)	.06
Nonsteroidal anti-inflammatory agent	510 (13.1)	241 (12.4)	269 (13.8)	207 (13.8)	100 (13.6)	107 (14.1)	.46
Gastric antacid drugs	979 (25.1)	476 (24.5)	503 (25.7)	362 (24.2)	183 (24.8)	179 (23.6)	.49
Renal function, no. (%)							.11
Normal (80 mL/min)	1635 (41.6)	801 (40.9)	834 (42.3)	602 (39.9)	288 (38.9)	314 (40.9)	
Mild impairment (>50-80 mL/min)	1690 (43.0)	864 (44.1)	826 (41.9)	633 (41.9)	313 (42.2)	320 (41.7)	
Moderate impairment (>30-50 mL/min)	546 (13.9)	267 (13.6)	279 (14.2)	249 (16.5)	128 (17.3)	121 (15.8)	
Severe impairment (≤30 mL/min)	47 (1.2)	22 (1.1)	25 (1.3)	18 (1.2)	7 (0.9)	11 (1.4)	

ACE, angiotensin-converting enzyme; LVEF, left ventricular ejection fraction; SD, standard deviation; TIA, transient ischemic attack.
*P value compares overall any interruption vs overall no interruption.

Results

Procedure characteristics

Of the 18 201 patients enrolled in ARISTOTLE, 5924 (32.5%) underwent at least 1 eligible procedure and 5439 (88.3%) of those patients had a procedure that met the criteria to be included in this analysis (Figure 2). Of the 10 674 eligible procedures performed during the ARISTOTLE trial, 1414 were excluded from our analysis (204 because study medication was intermittently stopped and restarted during the 7 days prior, and 1210 because no doses of study medication were taken for at least 7 days prior). In general, the types of procedures excluded were similar to those included in the analysis. Only 266 (2.9%) of the 9260 procedures performed were classified by the investigator as emergent; 943 (10.2%) procedures were major, and 8317 (89.8%) procedures were considered nonmajor.

Table 3. Interruption patterns, according to treatment assignment, for the 9260 procedures that were included in the analysis

	Overall	Apixaban	Warfarin
Interruption			
No interruption*	3468 (37.5)	1775 (37.9)	1693 (37.0)
Any interruption	5792 (62.5)	2904 (62.1)	2888 (63.0)
Stop			
Did not stop	3155 (34.1)	1639 (35.0)	1516 (33.1)
Stopped the day of procedure	313 (3.4)	136 (2.9)	177 (3.9)
Stopped the day before procedure	365 (3.9)	230 (4.9)	135 (2.9)
Stopped 2 d before procedure	807 (8.7)	523 (11.2)	284 (6.2)
Stopped 3 d before procedure	1142 (12.3)	593 (12.7)	549 (12.0)
Stopped 4 d before procedure	1437 (15.5)	664 (14.2)	773 (16.9)
Stopped 5 d before procedure	1151 (12.4)	510 (10.9)	641 (14.0)
Stopped 6 d before procedure	495 (5.3)	217 (4.6)	278 (6.1)
Stopped 7 d before procedure	395 (4.3)	167 (3.6)	228 (5.0)

Values are frequency (%).
*Includes no interruption and stopped the day of procedure.

The most common (n ≥ 100 for each) procedures were dental extraction/oral surgery (14.6%), colonoscopy (9.9%), ophthalmic surgery (8.0%), upper endoscopy (7.6%), pacemaker insertion (3.5%), urinary tract cystoscopy (3.2%), and percutaneous coronary intervention (2.8%) (Table 1).

Patient characteristics

Overall, the patients included in this analysis were similar to the overall population enrolled in ARISTOTLE (mean age 71 years, 31% female, mean $CHADS_2$ score 2.1) (Table 2). Patients who interrupted study medication prior to their procedure had a higher mean $CHADS_2$ score (2.2 vs 2.1) and were more likely to have a history of stroke than those patients who continued study medication until the day of their procedure. Preprocedure interruption also varied according to region; compared with participants from Europe or Asia, patients enrolled in either North America or Latin America were more likely to withhold study medication at least 1 day prior to their procedure (Table 2).

Anticoagulation management

Anticoagulant treatment was not interrupted in 37.5% of procedures, and the proportion not interrupting therapy was similar between blinded treatment arms (37.9% for apixaban and 37.0% for warfarin). For the 62.5% of patients who did interrupt therapy preprocedure, the durations of preprocedure interruptions were comparable between the apixaban and warfarin arms (Table 3). Of all included patients and procedures, 11.7% received some form of bridging (parenteral) anticoagulation either before or after the procedure (548/4676 [11.7%] of apixaban-treated patients and 536/4578 [11.7%] of warfarin-treated patients). Preoperative vitamin K and fresh frozen plasma were administered infrequently (1.0% and 1.2% of procedures, respectively). Among patients who interrupted study drug (n = 5792), 38.1% were on study drug the day after the procedure, 57.8% were on study drug 2 days after the procedure, and 17.1% did not restart study drug within the 8 days after procedure. Of the 2465 patients taking aspirin, more than 90% continued aspirin preprocedure (irrespective of whether study medication was interrupted).

Clinical outcomes

During the 30 days after included procedures, stroke or systemic embolism occurred in 16/4624 (0.35%) apixaban-treated patients and in 26/4530 (0.57%) warfarin-treated patients (OR 0.601; 95% CI 0.322-1.120). Major bleeding within 30 days of the procedure occurred in 74/4560 (1.62%) procedures in the apixaban arm and 86/4454 (1.93%) procedures in the warfarin arm (OR 0.846; 95% CI 0.614-1.166). The risk of death within 30 days among procedures with apixaban (54/4624 [1.17%]) and procedures with warfarin (49/4530 [1.08%]) was similar (OR 1.082; 95% CI 0.733-1.598) (Table 4).

For several key end points, a test for interaction based on whether preprocedure study medication was interrupted is shown in Table 5. For the outcomes of death and major bleeding, preprocedure interruption of study drug appeared to modify the association with apixaban vs warfarin treatment, even after adjusting for age, $CHADS_2$ score, bridging, major/nonmajor procedures, and emergency/unknown procedures. A comparable proportion of patients within the apixaban treatment arm died within 30 days of the procedure, regardless of whether therapy was interrupted (1.0%) or not (1.4%). However, among the warfarin-treated patients, the 30-day all-cause mortality rate was 0.5% in patients with interruptions and 2.0% in patients with no interruptions prior to their procedure. For major bleeding, the 30-day rates within the apixaban arm were 1.65% (among interruptions) and 1.58% (among no interruptions), whereas within the warfarin arm the same rates were 1.26% (among interruptions) and 3.04% (among no interruptions).

Discussion

Our report of periprocedural event rates among apixaban-treated patients provides important information for patients who take apixaban and require a procedure. The timing of preprocedure anticoagulant treatment interruption was similar in patients on apixaban and warfarin. Our analysis of data from ARISTOTLE adds to the previously published evidence that some patients on chronic anticoagulation can undergo low-risk procedures without preprocedure interruption of their anticoagulant. For those who do interrupt therapy, our results suggest that the 30-day risk of postprocedure stroke or systemic embolism is low (<1%), consistent with previous studies of anticoagulation interruption.[4,6-9] Our observation that 1% to 2% of patients taking either warfarin or apixaban experienced postprocedural major bleeding within 30 days is similar to rates reported for nonbridged patients in other studies of anticoagulation interruption for procedures.[8] The finding that the rate of major (as well as the combination of major plus clinically relevant nonmajor) bleeding was not statistically different

Table 4. Thirty-day rates of major outcomes after procedures

Event	Apixaban Events*/ procedures (%) [n]†	Warfarin Events*/ procedures (%) [n]†	OR (95% CI)‡
Stroke/systemic embolism	16/4624 (0.35)	26/4530 (0.57)	0.601 (0.322-1.120)
Myocardial infarction	12/4624 (0.26)	18/4530 (0.40)	0.652 (0.312-1.356)
All-cause death	54/4624 (1.17)	49/4530 (1.08)	1.082 (0.733-1.598)
Major bleeding	74/4560 (1.62) [8]	86/4454 (1.93) [11]	0.846 (0.614-1.166)
Major/CRNM bleeding	133/4560 (2.92) [8]	154/4454 (3.46) [12]	0.854 (0.670-1.089)

CRNM, clinically relevant nonmajor.
*First unique event per procedure.
†[n] represents number of bleedings followed by death within 30 days.
‡OR (95% CI) for apixaban vs warfarin.

Table 5. Thirty-day rate of postprocedure events among those who interrupted or did not interrupt therapy prior to the procedure

Event	Interruption Events/procedures (%) [n]*	No interruption Events/procedures (%) [n]*	OR [interruption vs no interruption] (95% CI)	Interaction P†	Adjusted OR [interruption vs no interruption] (95% CI)‡	Interaction P†
Stroke/systemic embolism						
Overall	19/5741 (0.33)	23/3413 (0.67)	0.490 (0.267-0.901)		0.354 (0.168-0.747)	
Apixaban	9/2877 (0.31)	7/1747 (0.40)	0.781 (0.290-2.103)	.2352	0.651 (0.215-1.970)	.3121
Warfarin	10/2864 (0.35)	16/1666 (0.96)	0.362 (0.164-0.799)		0.245 (0.090-0.668)	
Myocardial infarction						
Overall	14/5741 (0.24)	16/3413 (0.47)	0.519 (0.253-1.066)		0.453 (0.212-0.972)	
Apixaban	6/2877 (0.21)	6/1747 (0.34)	0.606 (0.195-1.883)	.7213	0.549 (0.149-2.026)	.7003
Warfarin	8/2864 (0.28)	10/1666 (0.60)	0.464 (0.182-1.180)		0.387 (0.152-0.985)	
Death						
Overall	45/5741 (0.78)	58/3413 (1.70)	0.457 (0.309-0.676)		0.396 (0.260-0.603)	
Apixaban	30/2877 (1.04)	24/1747 (1.37)	0.754 (0.440-1.295)	.0078	0.671 (0.372-1.210)	.0153
Warfarin	15/2864 (0.52)	34/1666 (2.04)	0.253 (0.137-0.466)		0.201 (0.104-0.387)	
Major bleeding						
Overall	81/5566 (1.46)	79/3448 (2.29)	0.624 (0.458-0.850)		0.408 (0.288-0.578)	
Apixaban	46/2792 (1.65) [2]	28/1768 (1.58) [6]	1.023 (0.639-1.636)	.0041	0.787 (0.479-1.293)	.0086
Warfarin	35/2774 (1.26) [0]	51/1680 (3.04) [11]	0.406 (0.264-0.625)		0.223 (0.133-0.374)	
Major/CRNM bleeding						
Overall	133/5566 (2.39)	154/3448 (4.47)	0.517 (0.408-0.654)		0.384 (0.297-0.497)	
Apixaban	72/2792 (2.58) [2]	61/1768 (3.45) [6]	0.736 (0.520-1.042)	.0058	0.633 (0.440-0.910)	.0118
Warfarin	61/2774 (2.20) [0]	93 / 1680 (5.54) [12]	0.373 (0.270-0.517)		0.235 (0.162-0.342)	

*[n] represents number of bleedings followed by death within 30 days.
†Interaction between interruption and treatment
‡Adjusted for age, $CHADS_2$ score, bridging, major/nonmajor procedure, and emergency/nonemergency procedure.

between the 2 groups suggests that the lack of an antidote for apixaban does not result in more bleeding in this setting; however, the low number of patients undergoing major procedures limits the power of our analysis to detect a small difference, if one exists.

The double-blind design of ARISTOTLE almost certainly explains the similar rates of bridging anticoagulation (about 12%) in the 2 study groups. The pharmacologic properties of apixaban should eliminate the need for most periprocedural heparin/low-molecular-weight heparin, and periprocedural bridging therapy is not recommended in the prescribing information for apixaban. Had ARISTOTLE been an open-label study like RE-LY, bridging therapy may have been used less often among the apixaban-treated patients.

The interactions of preprocedure study medication interruption status with the effect of randomized treatment assignment on mortality and bleeding (Table 5) must be interpreted carefully. First, therapies and interruptions are not randomized at the time of procedure; therefore, although we adjusted for several variables, residual confounding is likely. Second, we were unable to find a biologically plausible explanation for the interaction on mortality, especially the lower rate of mortality on warfarin among patients who interrupted therapy. We did not observe an interaction for stroke, systemic embolism, or myocardial infarction. A similar discrepancy occurred for bleeding; however, fatal bleeding was too rare to explain the difference in mortality. It is possible that this interaction is due to the play of chance.

The main limitation of our analysis is that, in ARISTOTLE, periprocedural anticoagulation was neither randomized nor controlled. Because apixaban has a relatively short half-life, the ARISTOTLE study protocol suggested that patients at intermediate-to-high risk of thromboembolism stop apixaban/apixaban-placebo only 2 days before a procedure. Thus, it might seem surprising that in more than half (1558/3015) of the apixaban-treated patients who interrupted anticoagulation, therapy was stopped more than 3 days prior to their procedure. This observation is partly explained by recommendations in the protocol that, for patients at low risk of thromboembolism, both warfarin/warfarin-placebo and apixaban/apixaban-placebo be stopped 4 days prior to a procedure (Figure 1A). However, some investigators may have withheld both study medications for the same number of days even in higher risk patients, for the sake of simplicity. Given the variation in interruption duration, we cannot, with this analysis, make firm recommendations about the timing of periprocedural apixaban doses. That notwithstanding, our findings provide important information to practicing clinicians and suggest that the recommendations regarding periprocedural apixaban in the US prescribing information[10] are reasonable (ie, the suggestion that apixaban be stopped 24-48 hours prior to a procedure makes biological sense). However, the present analysis includes a relatively low proportion of patients who underwent major surgery, and additional data will be needed to better define the optimal periprocedural apixaban dosing for such patients.

Conclusion

In the ARISTOTLE trial, the risk of thromboembolism or major bleeding during the 30 days after procedures was low, and this risk was not significantly different according to whether a patient was assigned to warfarin or apixaban. The pharmacokinetic characteristics of apixaban suggest that periprocedural bridging (parenteral) anticoagulation should be unnecessary with this medication. However, the precise timing of interruption and resumption of apixaban will depend on the risks of bleeding and thrombosis in each individual situation.

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Authorship

Contribution: D.G. and R.D.L. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis; and L.T. and D.M.W. conducted the data analysis and contributed to the content and critical revision of the manuscript. All analyses were conducted at the Duke Clinical Research Institute, and the authors had full access to all data through the Duke Clinical Research Institute. The authors are fully responsible for the study design, data collection, analysis and interpretation of the data, and writing of the manuscript. The sponsor played no role in the decision to submit the manuscript for publication. All authors agreed to submit the manuscript for publication.

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