

Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant

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IMPORTANCE Patients with atrial fibrillation (AF) who use a direct oral anticoagulant (DOAC) and request elective surgery or procedure present a common clinical situation yet perioperative management is uncertain.

OBJECTIVE To investigate the safety of a standardized perioperative DOAC management strategy.

DESIGN, SETTING, AND PARTICIPANTS The Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) cohort study conducted at 23 clinical centers in Canada, the United States, and Europe enrolled and screened patients from August 1, 2014, through July 31, 2018. Participants (n = 3007) had AF; were 18 years of age or older; were long-term users of apixaban, dabigatran etexilate, or rivaroxaban; were scheduled for an elective surgery or procedure; and could adhere to the DOAC therapy interruption protocol.

INTERVENTIONS A simple standardized perioperative DOAC therapy interruption and resumption strategy based on DOAC pharmacokinetic properties, procedure-associated bleeding risk, and creatinine clearance levels. The DOAC regimens were omitted for 1 day before a low-bleeding-risk procedure and 2 days before a high-bleeding-risk procedure. The DOAC regimens were resumed 1 day after a low-bleeding-risk procedure and 2 to 3 days after a high-bleeding-risk procedure. Follow-up of patients occurred for 30 days after the operation.

MAIN OUTCOMES AND MEASURES Major bleeding and arterial thromboembolism (ischemic stroke, systemic embolism, and transient ischemic attack) and the proportion of patients with an undetectable or minimal residual anticoagulant level (<50 ng/mL) at the time of the procedure.

RESULTS The 3007 patients with AF (mean [SD] age of 72.5 [9.39] years; 1988 men [66.1%]) comprised 1257 (41.8%) in the apixaban cohort, 668 (22.2%) in the dabigatran cohort, and 1082 (36.0%) in the rivaroxaban cohort; 1007 patients (33.5%) had a high-bleeding-risk procedure. The 30-day postoperative rate of major bleeding was 1.35% (95% CI, 0%-2.00%) in the apixaban cohort, 0.90% (95% CI, 0%-1.73%) in the dabigatran cohort, and 1.85% (95% CI, 0%-2.65%) in the rivaroxaban cohort. The rate of arterial thromboembolism was 0.16% (95% CI, 0%-0.48%) in the apixaban cohort, 0.60% (95% CI, 0%-1.33%) in the dabigatran cohort, and 0.37% (95% CI, 0%-0.82%) in the rivaroxaban cohort. In patients with a high-bleeding-risk procedure, the rates of major bleeding were 2.96% (95% CI, 0%-4.68%) in the apixaban cohort and 2.95% (95% CI, 0%-4.76%) in the rivaroxaban cohort.

CONCLUSIONS AND RELEVANCE In this study, patients with AF who had DOAC therapy interruption for elective surgery or procedure, a perioperative management strategy without heparin bridging or coagulation function testing was associated with low rates of major bleeding and arterial thromboembolism.

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The perioperative management of patients who receive a direct oral anticoagulant (DOAC) for atrial fibrillation (AF) and require elective surgery or procedure is a common clinical scenario for which best practices are uncertain.¹ Each year, 1 in 6 patients with AF, or an estimated 6 million patients worldwide, will require perioperative anticoagulant management.^{2,3} When DOAC regimens became available for clinical use in AF, starting in 2010, no studies had been conducted to inform the timing of perioperative DOAC therapy interruption and resumption, whether heparin bridging should be given, and whether preoperative coagulation function testing was needed.⁴ Uncertainty about the perioperative management of DOACs may be associated with unsubstantiated practices and increased harm to patients. Thus, a DOAC therapy interruption interval that is too long may increase the risk for thromboembolism, whereas an interruption interval that is too short may increase the risk for bleeding which, in turn, delays anticoagulant resumption.⁵ Perioperative heparin bridging has been used in DOAC-treated patients,⁶ but this practice does not make pharmacologic sense given the short, 8- to 14-hour DOAC elimination half-lives,⁴ its association with increased bleeding, and its questionable efficacy.^{6,7} Preoperative coagulation testing has been suggested to identify patients with an excessive residual anticoagulant level in whom a procedure can be delayed or the DOAC reversed,⁸ but this suggestion is problematic because DOAC-specific coagulation tests are not widely available, reference ranges are lacking, and such testing may not be advantageous for patients.⁹

Most clinical studies investigating perioperative DOAC regimen management are retrospective subanalyses of randomized clinical trials that assessed DOAC regimens for stroke prevention in AF or are patient registries.^{3,10-13} One study that assessed standardized perioperative management included only patients who were taking dabigatran etexilate.¹⁴ The perioperative management of DOAC regimens varies widely in clinical practice,¹⁵ and practice guidelines provide weak and inconsistent management recommendations.¹⁶⁻²⁰

We designed the Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) study to assess the safety of a standardized perioperative management strategy for a DOAC regimen. We hypothesized that a simple management approach, which is based on DOAC-specific interruption and resumption intervals, forgoes perioperative heparin bridging, and does not require preoperative coagulation function testing, is safe to use for patient care. For each DOAC cohort that received DOAC-specific perioperative management, we defined safety as excluding 30-day perioperative rates of major bleeding of 2% and arterial thromboembolism of 1.5%, according to expected outcome rates (1% for major bleeding and 0.5% for arterial thromboembolism) observed with optimal perioperative management of warfarin sodium^{3,21} and with a proof-of-concept prospective study of standardized perioperative dabigatran management.¹⁴ We also postulated that this management would yield a high proportion of patients (>90%) with an undetectable or minimal residual anticoagulant level at the time of the procedure.

Key Points

Question Is a standardized perioperative management approach safe for patients with atrial fibrillation who use a direct oral anticoagulant and require elective surgery or procedure?

Findings In this cohort study of 3007 patients with atrial fibrillation using apixaban, dabigatran, or rivaroxaban, the direct oral anticoagulant treatment was stopped and resumed before and/or after elective surgery or procedure using standardized protocols without heparin bridging. The 30-day postoperative rates of major bleeding were less than 2%, and the rates of stroke were less than 1%.

Meaning In this study, in patients treated with a direct oral anticoagulant, a simple standardized perioperative management approach was associated with low rates of bleeding and stroke.

Methods

Study Design and Oversight

The PAUSE study design and data analysis plan were developed by the steering committee and are described elsewhere.²² The study was managed by the McMaster Centre for Transfusion Research, which was responsible for the study organization as well as data collection, validation, maintenance, and analysis. Study data were collected and managed using REDCap electronic data capture tools.²³ The institutional review board of each of the 23 participating clinical center in Canada, the United States, and Europe approved PAUSE, and all study participants provided written informed consent.

PAUSE is a prospective management study involving DOAC-treated patients with AF who required anticoagulant therapy interruption for elective surgery or procedure. Patients were separated into 3 cohorts on the basis of DOAC used (apixaban, dabigatran, or rivaroxaban) and received standardized perioperative management according to the DOAC. A randomized clinical trial design was considered to assess the proposed (experimental) management but was not adopted because no alternative strategy existed that would be suitable as a comparator (control) management. For example, a management approach that omits DOAC regimens for a longer (4- to 6-day) preoperative period, as suggested in other studies,¹⁶ would not make clinical sense as a comparator given the short DOAC elimination half-lives; moreover, the longer period without anticoagulation might expose patients to an increased thromboembolic risk. Similarly, adopting unspecified usual care as a comparator would also be unsuitable, as the usual care may be too heterogeneous to allow a meaningful comparison to the standardized, more uniform management used in this study.¹⁵ A cohort design is appropriate for assessing a management strategy when expected rates of clinical outcomes are low (0.5%-1% in PAUSE) and when there is sufficient statistical power to exclude clinically important higher outcome rates (1.5%-2% in PAUSE).^{23,24}

Patients

Consecutive patients with the following characteristics were assessed for study eligibility: adults (aged ≥18 years) with AF

Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol

DOAC	Surgical Procedure–Associated Bleeding Risk	Preoperative DOAC Interruption Schedule					Day of Surgical Procedure (No DOAC)	Postoperative DOAC Resumption Schedule			
		Day -5	Day -4	Day -3	Day -2	Day -1		Day +1	Day +2	Day +3	Day +4
Apixaban	High	→					Day of Surgical Procedure (No DOAC)		→		
	Low	→									
Dabigatran etexilate (CrCl ≥50 mL/min)	High	→							→		
	Low	→									
Dabigatran etexilate (CrCl <50 mL/min) ^a	High	→							→		
	Low	→									
Rivaroxaban	High	→							→		
	Low	→									

No DOAC was taken on certain days (shaded) and on the day of the elective surgery or procedure. The light blue arrows refer to an exception to the basic management, a subgroup of patients taking dabigatran with a creatinine clearance (CrCl) less than 50 mL/min. The orange arrows refer to patients having a high-bleed-risk surgical procedure. Dark blue arrows refer to patients having a

low-bleed-risk surgical procedure. The thickened orange part of arrows refer to flexibility in the timing of DOAC resumption after a procedure.

^a Cancer diagnosed within 3 months or has been treated within 6 months or metastatic.

who were long-term users of apixaban (5 mg or 2.5 mg twice daily), dabigatran etexilate (150 mg or 110 mg twice daily), or rivaroxaban (20 mg or 15 mg daily); were scheduled to have an elective surgery or procedure that required interruption of the anticoagulant regimen; and were able to adhere to the DOAC therapy interruption protocol at the time of enrollment. Patients were excluded if they fit 1 or more of the following criteria: creatinine clearance (CrCl) level less than 25 mL/min for apixaban users or CrCl level less than 30 mL/min for dabigatran or rivaroxaban users (to convert CrCl level to milliliters per second per meter squared, multiply by 0.0167),²⁵ cognitive impairment or psychiatric illness, did not consent to participate, previous study participation, or more than 1 procedure planned within 30 days. Before the procedure, patients were categorized as having a high- or low-bleeding-risk procedure according to a prespecified classification (eAppendix 1 in the Supplement)⁷; this classification informed the timing of DOAC therapy interruption and resumption.²² Our aim was that at least one-third of patients enrolled into each DOAC cohort would be classified as high bleeding risk.

Procedures

The perioperative management strategy for a DOAC regimen was designed with 2 broad aims: (1) to have the shortest duration of DOAC therapy interruption before and after the procedure so as to minimize the risks for bleeding and thromboembolism, and (2) to have a simple interruption and resumption protocol for each DOAC that would be easy to use by clinicians and easily understood by patients.

Patients were enrolled and managed using a standardized perioperative DOAC strategy based on DOAC pharmacokinetic properties (10- to 14-hour half-lives, and 1- to 3-hour peak action), the procedure-associated bleeding risk, and patient CrCl level (Figure).²² Before the procedure, DOAC regimens were omitted for 1 day before a low-bleeding-risk pro-

cedure (36- to 42-hour interval corresponding to approximately 3 DOAC half-lives) and were omitted 2 days before a high-bleeding-risk procedure (60- to 68-hour interval corresponding to approximately 5 DOAC half-lives). Patients using dabigatran with a CrCl level less than 50 mL/min had longer interruption intervals to account for renal dependence of dabigatran clearance.¹ Blood samples were taken from patients just before the procedure to measure their residual anticoagulant level, but these results were not available for clinical use. Plasma samples were frozen and stored at each clinical site and later analyzed in a centralized laboratory using standardized blood processing and assay methods (eAppendix 2 in the Supplement). After the operation, DOAC regimens were resumed 1 day (approximately 24 hours) after a low-bleeding-risk procedure and 2 to 3 days (48-72 hours) after a high-bleeding-risk procedure, provided that hemostasis was achieved. Patient thromboembolic risk, based on the CHADS₂ (congestive heart failure, hypertension, aged 75 years or older, diabetes, and previous stroke or transient ischemic attack) risk score, did not affect perioperative DOAC regimen management because this risk score is used in a perioperative setting to assess the need for heparin bridging, which was not performed in the present study.^{26,27} Patients at high risk for venous thromboembolism could receive a prophylactic dose of heparin after the operation until DOAC therapy resumption.

Clinical Outcomes and Residual Anticoagulant Level

Study clinical outcomes were assessed from the time the first DOAC dose was interrupted until 30 days after the operation. Patients had scheduled weekly telephone follow-up and additional clinic visits as needed to document clinical outcomes. The primary clinical outcomes were major bleeding and arterial thromboembolism (ischemic stroke, transient ischemic attack, and systemic embolism). The secondary clinical outcomes were clinically relevant nonmajor bleeding, minor

bleeding, death, myocardial infarction, deep vein thrombosis, pulmonary embolism, and catheter-associated venous or arterial thrombosis. Study outcomes were defined according to standardized criteria (eAppendix 3 in the [Supplement](#))^{28,29} and were independently adjudicated by a committee that was blinded to the DOAC cohort, procedure bleeding risk, and preoperative DOAC treatment levels.

The **residual anticoagulant** level just before the procedure was **measured by DOAC-specific anti-factor Xa assays for apixaban and rivaroxaban** as well as by the **dilute thrombin time for dabigatran**.³⁰ The residual anticoagulant level was also measured with nonspecific coagulation tests: prothrombin time, international normalized ratio, activated partial thromboplastin time, and thrombin time.³¹

Study Hypothesis and Sample Size Determination

We hypothesized that, for each DOAC cohort, the PAUSE management would be associated with a 1% rate of major bleeding (with the upper limit of the 1-sided 95% CI to exclude a 2% rate) and a 0.5% rate of arterial thromboembolism (with the upper limit of the 1-sided 95% CI to exclude a 1.5% rate). Thus, the null hypothesis was that the proposed protocol was unsafe; that is, the proportion of the major bleeding (or arterial thromboembolism) was 2% or higher (or $\geq 1.5\%$); an alternative hypothesis was that the protocol was safe; that is, the proportion was lower than 2% (or $< 1.5\%$). A 1-sided $P < .05$ was considered statistically significant, and a statistically significant result would mean that, with the 1-sided 95% CI, the true incidence of major bleeding was lower than 2% and arterial thromboembolism was lower than 1.5% for each DOAC cohort, rejecting the null hypothesis.

When PAUSE was designed in 2013, we were more confident about estimates, based on findings from available studies,^{3,21,32} of perioperative rates of major bleeding than arterial thromboembolism. Therefore, major bleeding was the primary determinant of sample size, and the sample size calculation was based on an expected rate of 1%. The required sample size was 987 patients per DOAC cohort, which provided 80% power at the .05 significance level (1-sided) to detect a proportion that was lower than 2% for major bleeding. With this sample size, there was also 80% power at the 5% significance level (1-sided) to detect a proportion that was lower than 1.5% for arterial thromboembolism, based on an expected rate of 0.5%.

The number of patients per DOAC cohort was increased by 10% (to 1097) to anticipate cancelled operations and patients lost to follow-up. We also postulated that the DOAC therapy interruption protocol would yield more than 90% of patients with a preoperative residual anticoagulant level less than 50 ng/mL, which was considered empirically as a level that would allow a procedure to proceed safely.

Statistical Analysis

For the primary clinical outcomes, a 1-sided test for 1 proportion with continuity correction was used to determine within each DOAC cohort at the patient level if the proportion of major bleeding was lower than 2% and if the proportion of arterial thromboembolism was lower than 1.5%.³³ The primary

analysis was conducted in the main study population of patients who had at least 1 DOAC dose interrupted. For each primary outcome within each DOAC cohort, we reported the proportion and associated 1-sided 95% CI as well as the P value from the 1-sided test for 1 proportion to check that the outcome rate was lower than the expected rate of 2% for major bleeding and 1.5% for arterial thromboembolism. For the secondary clinical outcomes, we assessed rates of mortality and other adverse events for patients within each DOAC cohort. We reported the proportions with 2-sided 95% CIs of the secondary outcomes for each cohort.

For the preoperative residual anticoagulant level outcome, we identified the proportion of patients with an anti-factor Xa level (for apixaban or rivaroxaban) or dilute thrombin time (for dabigatran) of less than 50 ng/mL (30–49.9 ng/mL and < 30 ng/mL) or 50 ng/mL or greater; this calculation was done separately for patients with a low-bleeding risk and patients with a high-bleeding-risk procedure because the bleeding risk determined the DOAC therapy interruption interval, which would affect the residual anticoagulant level. We also identified the median (interquartile range [IQR]) prothrombin time, international normalized ratio, activated partial thromboplastin time, and thrombin time as well as the proportion of patients with an elevated prothrombin time, international normalized ratio, activated partial thromboplastin time, and thrombin time.

Because the analyses of secondary clinical outcomes and coagulation test outcomes were descriptive, no statistical hypothesis testing was considered. In this analysis, we assessed rates of major bleeding in patients according to procedure-associated bleeding risk as perioperative management differed between patients considered at high and low risk for bleeding. We also assessed rates of primary outcomes in a population of patients within each cohort who adhered to the DOAC therapy interruption and resumption protocols.

Results

Patients

We screened 3640 patients from August 1, 2014, through July 31, 2018, from 23 clinical sites in Canada, the United States, and Europe (eAppendix 4 in the [Supplement](#)). Of these patients, 3007 (82.6%) were enrolled and were included in the primary analysis: 1257 (41.8%) in the apixaban cohort, 668 (22.2%) in the dabigatran cohort, and 1082 (36.0%) in the rivaroxaban cohort (eFigure in the [Supplement](#)). The baseline characteristics of the patients in each DOAC cohort are shown in [Table 1](#). Overall, patients had a mean (SD) age of 72.5 (9.39) years and were predominantly male (1988 [66.1%]). The types of procedures that patients underwent in each DOAC cohort are shown in eAppendix 5 in the [Supplement](#).

Perioperative Anticoagulant Management

[Table 2](#) shows the DOAC therapy interruption intervals for the apixaban, dabigatran (≥ 50 mL/min and < 50 mL/min subgroups), and rivaroxaban cohorts as well as the DOAC therapy resumption intervals for the apixaban, dabigatran, and riva-

Table 1. Baseline Patients Characteristics

Variable	No. (%)		
	Apixaban Cohort (n = 1257)	Dabigatran Cohort (n = 668)	Rivaroxaban Cohort (n = 1082)
Age, mean (SD), y	73.1 (9.15)	72.4 (9.9)	72.0 (9.3)
Male	805 (64.0)	458 (68.6)	725 (67.0)
BMI, mean (SD)	29.49 (6.2)	30.24 (6.8)	29.8 (6.5)
Race/ethnicity			
White	1204 (95.8)	654 (97.9)	1045 (96.6)
Non-white	43 (3.4)	12 (1.8)	25 (2.3)
Unknown	10 (0.8)	2 (0.3)	12 (1.1)
Risk stratification scores, mean (SD)			
CHADS ₂ ^a	2.1 (1.3)	2.2 (1.3)	2.0 (1.3)
CHADS ₂ -VA ₂ Sc ^b	3.5 (1.7)	3.5 (1.6)	3.3 (1.6)
Modified HAS-BLED ^c	2.0 (0.9)	1.9 (0.9)	1.8 (0.9)
Medical condition			
Congestive heart failure	243 (19.3)	111 (16.6)	140 (12.9)
Hypertension	933 (74.2)	504 (75.4)	784 (72.5)
Diabetes	337 (26.8)	185 (27.7)	273 (25.2)
Stroke	98 (7.8)	64 (9.6)	77 (7.1)
Transient ischemic attack	117 (9.3)	93 (13.9)	99 (9.1)
Coronary artery disease	232 (18.5)	113 (16.9)	177 (16.4)
Peripheral arterial disease	8 (0.6)	6 (0.9)	13 (1.2)
Bioprosthetic heart valve	35 (2.8)	10 (1.5)	20 (1.8)
Mitral valve disease	125 (9.9)	51 (7.6)	86 (7.9)
Venous thromboembolism	77 (6.1)	40 (6.0)	85 (7.9)
Active cancer ^d	105 (8.3)	57 (8.5)	107 (9.9)
Laboratory values, mean (SD)			
Hemoglobin, g/L	134.4 (17.8)	140.1 (50.0)	136.8 (31.6)
Platelets <100 × 10 ⁶ /L	8 (0.6)	2 (0.3)	3 (0.3)
Serum creatinine, μmol/L	94.1 (28.8)	87.7 (21.6)	90.3 (22.5)
Creatinine clearance, ml/min ^e	77.9 (32.0)	85.9 (35.7)	82.2 (32.8)
Medication use			
Lower-dose DOAC regimen ^f	252 (20.0)	248 (37.1)	181 (16.7)
Aspirin	156 (12.4)	98 (14.7)	99 (9.1)
P2Y ₁₂ inhibitor ^g	12 (0.9)	7 (1.0)	11 (1.0)
P-glycoprotein or cytochrome P450 3A4 inhibitor or inducer ^h	76 (6.0)	53 (7.9)	55 (5.1)
Elective surgery or procedure type			
High bleeding risk	406 (32.3)	228 (34.1)	373 (34.5)
Low bleeding risk	851 (67.7)	440 (65.9)	709 (65.5)
Anesthesia type			
General	410 (32.6)	193 (28.9)	384 (35.5)
Neuraxial	103 (8.2)	57 (8.5)	70 (6.5)
Other	689 (54.8)	369 (55.2)	584 (54.0)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DOAC, direct oral anticoagulant.

SI conversion factor: To convert creatinine clearance to milliliters per second per square meter, multiply by 0.0167.

^a CHADS₂ risk score range: 1-6; risks include congestive heart failure, hypertension, age 75 years or older, diabetes, and previous stroke or transient ischemic attack.

^b CHADS₂-VA₂Sc risk score range: 1-9; risks include congestive heart failure, hypertension, age 75 years or older or 65 years or older, diabetes, previous stroke or transient ischemic attack, female sex, and vascular disease.

^c HAS-BLED bleeding risk score range: 1-7; risks include hypertension, abnormal renal or liver function, previous stroke, previous bleed or bleed predisposition, labile international normalized ratio (omitted), age 65 years or older, and drug use that affects hemostasis or alcohol use (omitted).

^d Cancer diagnosed within 3 months or treated within 6 months or metastatic.

^e Based on Cockcroft-Gault formula.

^f Apixaban 2.5 mg twice daily, or dabigatran etexilate 110 mg twice daily, or rivaroxaban 15 mg daily.

^g Clopidogrel bisulfate, ticagrelor, prasugrel hydrochloride, or ticlopidine hydrochloride.

^h Drugs that can inhibit or induce DOAC activity (eAppendix 9 in the Supplement).

roxaban cohorts. Of the 3007 patients in the primary analysis cohort (≥1 dose interrupted), 159 (5.3%) deviated from the DOAC therapy interruption protocol, 202 (6.7%) deviated from the DOAC therapy resumption protocol, and 22 (0.7%) were lost to follow-up, leaving 2624 patients (87.3%) to be included in the per protocol analysis.

Study Outcomes

In the primary analysis cohort (Table 3), the 30-day postoperative rate of major bleeding was 1.35% (95% CI, 0%-2.00%)

in the apixaban cohort, 0.90% (95% CI, 0%-1.73%) in the dabigatran cohort, and 1.85% (95% CI, 0%-2.65%) in the rivaroxaban cohort. The rate of arterial thromboembolism was 0.16% (95% CI, 0%-0.48%) in the apixaban cohort, 0.60% (95% CI, 0%-1.33%) in the dabigatran cohort, and 0.37% (95% CI, 0%-0.82%) in the rivaroxaban cohort. All 43 major bleeding events occurred postoperatively at a median (IQR) of 2 (0-6) days; 9 of 10 arterial thromboembolic events occurred postoperatively at a median (IQR) of 2 (0-6) days. Rates of major bleeding according to procedure-associated bleeding risk are

Table 2. Preoperative and Postoperative Direct Oral Anticoagulant Interruption and Resumption

Cohort	Preoperative Management			Postoperative Management			Patient Receipt of Prophylactic-Dose LMWH, No. (%)
	DOAC Preoperative Omission, No. (IQR), d	Interruption Interval (IQR), h	Patient Adherence to Interruption Protocol, No. (%)	DOAC Postoperative Resumption, No. (IQR), d	Resumption Interval (IQR), h	Patient Adherence to Resumption Protocol, No. (%)	
Apixaban	Low bleeding risk (n = 851)	39.3 (37.4-41.5)	819 (96.24)	1 (1-1)	22.2 (19.3-31.9)	745 (87.5)	16 (1.9)
	High bleeding risk (n = 406)	63.8 (61-67)	378 (93.1)	3 (2-4)	67.8 (45.1-91.4)	399 (98.3)	133 (32.8)
	Dabigatran etexilate, CrCl $\geq$ 50 mL/min						
Dabigatran	Low bleeding risk (n = 386)	39.7 (38-41.9)	368 (95.34)	NA	NA	NA	NA
	High bleeding risk (n = 202)	63.2 (61.5-67.2)	187 (92.57)	NA	NA	NA	NA
	Dabigatran, CrCl < 50 mL/min						
Dabigatran (all patients) ^a	Low bleeding risk (n = 54)	64.4 (62-66)	50 (92.59)	NA	NA	NA	NA
	High bleeding risk (n = 26)	110.2 (108.3-112.7)	22 (84.62)	NA	NA	NA	NA
	Dabigatran (all patients) ^a						
Dabigatran	Low bleeding risk (n = 440)	NA	NA	1 (1-1)	23 (20.5-33.6)	425 (96.6)	7 (1.6)
	High bleeding risk (n = 228)	NA	NA	3 (2-3)	66.4 (45.1-81.4)	227 (99.6)	85 (37.3)
	Rivaroxaban						
Rivaroxaban	Low bleeding risk (n = 709)	48 (40.7-51)	674 (95.06)	1 (1-1)	25 (20.8-33.5)	641 (90.41)	8 (1.13)
	High bleeding risk (n = 373)	72 (65.6-75)	350 (93.83)	3 (2-4)	69.4 (46.4-94)	370 (99.2)	131 (35.1)

Abbreviations: CrCl, creatinine clearance; DOAC, direct oral anticoagulant; IQR, interquartile range; LMWH, low-molecular-weight heparin; NA, not applicable.

SI conversion factor: To convert creatinine clearance to milliliters per second per square meter, multiply by 0.0167.

^a Postoperative resumption of dabigatran was the same for patients with a CrCl 50 milliliters per minute or more and less than 50 milliliters per minute.

shown in Table 4; in the high-bleed-risk subgroups, the rate of major bleeding was 2.96% (95% CI, 0%-4.68%) in the apixaban cohort, 0.88 (95% CI, 0%-2.62%) in the dabigatran cohort, and 2.95% (95% CI, 0%-4.76%) in the rivaroxaban cohort.

In the secondary analysis of patients who adhered to the DOAC therapy interruption and resumption protocols, the 30-day postoperative rate of major bleeding was 1.2% (95% CI, 0%-1.89%) in the apixaban cohort, 1.0% (95% CI, 0%-1.93%) in the dabigatran cohort, and 1.69% (95% CI, 0%-2.53%) in the rivaroxaban cohort. The rate of arterial thromboembolism was 0.19% (95% CI, 0%-0.56%) in the apixaban cohort, 0.50% (95% CI, 0%-1.25%) in the dabigatran cohort, and 0.42% (95% CI, 0%-0.94%) in the rivaroxaban cohort (eAppendix 6 in the Supplement). Results according to clinical site are shown in eAppendix 7 in the Supplement.

Preoperative DOAC treatment levels were measured for 2541 patients (84.5%) (eAppendix 10 in the Supplement). The proportion of patients with a level less than 50 ng/mL was 90.5% in the apixaban cohort, 95.1% in the dabigatran cohort, and 96.8% in the rivaroxaban cohort. Among 1007 patients who had a high-bleeding-risk procedure, 832 (82.6%) had anticoagulant measurements, of whom the proportion with a residual anticoagulant level less than 50 ng/mL was 98.8%. The proportion of patients with a residual anticoagulant level of 30 to 49.9 ng/mL in the high-bleeding-risk procedure group was 4.8% in the apixaban cohort, 0.55% in the dabigatran cohort, and 14.0% in the rivaroxaban cohort. Results for the nonspecific coagulation tests are shown in eAppendix 8 in the Supplement.

Discussion

We found that in patients with AF who were receiving a DOAC (apixaban, dabigatran, or rivaroxaban) and required interruption of the anticoagulant regimen for elective surgery or procedure, a simple standardized perioperative management strategy that did not require the use of heparin bridging or preoperative coagulation function testing was associated with low rates of perioperative major bleeding (<2%) and arterial thromboembolism (<1%). Furthermore, a high proportion of patients (>90% overall; 98.8% of those at high bleeding risk) had a minimal or no residual anticoagulant level at the time of the procedure.

Based on the primary analysis cohort, our hypothesis that the PAUSE perioperative management strategy would exclude a 2% rate of major bleeding was supported in the dabigatran cohort (0.90%; 95% CI, 0%-1.73%) but not in the apixaban cohort (1.35%; 95% CI, 0%-2.0%) or rivaroxaban cohort (1.85%; 95% CI, 0%-2.65%), whereas our hypothesis that this management strategy would exclude a

Table 3. Primary Study Outcomes

Outcome	DOAC Cohort		
	Apixaban (n = 1257)	Dabigatran Etexilate (n = 668)	Rivaroxaban (n = 1082)
Primary			
Major bleeding ^a			
No. (%)	17 (1.35)	6 (0.90)	20 (1.85)
1-Sided 95% CI	0-2.00	0-1.73	0-2.65
P value	.051	.02	.36
Arterial thromboembolism ^{b,c}			
No. (%)	2 (0.16)	4 (0.60)	4 (0.37)
1-Sided 95% CI	0-0.48	0-1.33	0-0.82
P value	<.001	.03	.001
Secondary			
Death			
No. (%)	3 (0.24)	3 (0.45)	3 (0.28)
2-Sided 95% CI	0.08-0.70	0.15-1.31	0.09-0.81
Myocardial infarction			
No. (%)	1 (0.08)	0 (0)	0 (0)
2-Sided 95% CI	0.01-0.45	0-0.57	0-0.35
Deep vein thrombosis			
No. (%)	2 (0.16)	1 (0.15)	0 (0)
2-Sided 95% CI	0.04-0.58	0.03-0.84	0-0.35
Pulmonary embolism			
No. (%)	4 (0.32)	1 (0.15)	1 (0.09)
2-Sided 95% CI	0.12-0.82	0.03-0.84	0.02-0.52
Arterial catheter thrombosis ^d			
No. (%)	1 (0.08)	1 (0.15)	0 (0)
2-Sided 95% CI	0.01-0.45	0.03-0.84	0-0.35
Clinically relevant nonmajor bleeding			
No. (%)	21 (1.67)	13 (1.95)	26 (2.4)
2-Sided 95% CI	1.10-2.54	1.14-3.30	1.65-3.50
Minor bleeding			
No. (%)	54 (4.3)	38 (5.69)	62 (5.73)
2-Sided 95% CI	3.31-5.56	4.17-7.71	4.5-7.28

Abbreviation: DOAC, direct oral anticoagulant.

^a P value of the 1-sided test for 1 proportion to check that the proportion of major bleeding per DOAC was less than 2%.

^b P value of the 1-sided test for 1 proportion to check that the proportion of arterial thromboembolism per DOAC was less than 1.5%.

^c All episodes of arterial thromboembolism were ischemic stroke.

^d No episodes of catheter-related venous thrombosis were reported.

Table 4. Incidence of Major Bleeding by Elective Surgery or Procedure-Associated Bleeding Risk

Procedure-Associated Bleeding Risk	Apixaban Cohort (n = 1257)	Dabigatran Etexilate Cohort (n = 668)	Rivaroxaban Cohort (n = 1082)
Low bleeding risk			
No. (%)	851 (67.7)	440 (65.9)	709 (65.5)
30-d Postoperative rate of major bleeding, % (95% CI)	0.59 (0-1.20)	0.91 (0-2.01)	1.27 (0-2.17)
High bleeding risk			
No. (%)	406 (32.3)	228 (34.1)	373 (34.5)
30-d Postoperative rate of major bleeding, % (95% CI)	2.96 (0-4.68)	0.88 (0-2.62)	2.95 (0-4.76)

1.5% rate of arterial thromboembolism was supported in all 3 cohorts. In the per protocol analysis, excluding a 2% rate of major bleeding was supported in the dabigatran cohort (1.0%; 95% CI, 0%-1.93%) and the apixaban cohort (1.2%; 95% CI, 0%-1.89%) but not in the rivaroxaban cohort (1.69%; 95% CI, 0%-2.53%); excluding a rate of arterial thromboembolism of 1.5% was supported in all 3 cohorts.

Our exploratory postulation that a high proportion of patients (>90%) would have a residual anticoagulant level less

than 50 ng/mL at the time of the operation was supported in all 3 DOAC cohorts. In addition, we found that, among patients with a high-bleeding-risk procedure (which included any patient with neuraxial anesthesia) in whom there was concern of bleeding complications associated with an excessive residual anticoagulant level,^{16,18,19} almost all patients (98.8%) had a residual anticoagulant level less than 50 ng/mL. Moreover, the proportion of such patients with a residual anticoagulant level less than 30 mg/mL, which some experts con-

sider an optimal preoperative anticoagulant level,¹³ was high in the apixaban cohort (93.1%) and dabigatran cohort (98.9%). Among patients in the rivaroxaban cohort with a high-bleeding-risk procedure, a lower proportion (85.4%) had a residual anticoagulant level less than 30 ng/mL, an observation that requires further study. When the findings were assessed according to procedure-associated high- and low-bleeding risk, rates of major bleeding appeared to be higher among patients with a high-bleeding-risk procedure in the apixaban and rivaroxaban cohorts. This finding may reflect an intrinsically higher rate of bleeding expected with major procedures. Further study is needed to assess the PAUSE perioperative DOAC regimen management in patients with high-bleeding-risk procedures.

Most other studies that assessed perioperative DOAC regimen management are not comparable to this study because their management was not standardized, perioperative heparin bridging was allowed, and fewer patients (10%-20%) with high bleeding risk were studied.^{3,10-14} In these studies, perioperative rates of major bleeding, for example, varied and were as high as 6%.³ Two pertinent studies that assessed standardized perioperative anticoagulant management without heparin bridging had similar adverse outcome rates to those in this study. In a cohort study of 541 patients receiving dabigatran who had standardized perioperative interruption and resumption of their treatment, the 30-day postoperative rate of major bleeding was 1.8% and the arterial thromboembolism rate was 0.2%.¹⁴ In the BRIDGE trial, which evaluated a bridging strategy in patients with AF who had perioperative warfarin treatment interruption, patients who were not bridged had a 30-day postoperative rate of major bleeding of 1.3% and arterial thromboembolism rate of 0.4%,⁷ and those who underwent a high-bleeding-risk procedure had a rate of major bleeding of 3.2%.³⁴

Limitations and Strengths

This study has limitations. First, although a cohort study design may introduce patient selection bias, this was unlikely because a high proportion (83%) of screened patients participated in this study, and their risk factor profile, as measured by the CHA₂DS₂VASc risk score, was comparable to that of patients with AF included in population-based studies.³⁵ Second, although few patients (n = 230) received neuraxial anesthesia, in whom there was a concern about bleeding risk during

the operation associated with an excessive residual anticoagulant level, the management of such patients was the same as all patients undergoing a high-bleeding-risk procedure (n = 1007). Accordingly, the high proportion (98.8%) of patients with minimal to no residual anticoagulant level in this group would be applicable to those with neuraxial anesthesia. Third, the dabigatran cohort did not reach the expected sample size, owing to the decrease in dabigatran use compared with other DOAC regimens during the study, but the number of patients accrued was sufficient to address the study hypotheses in this cohort. Fourth, patients using edoxaban tosylate were not included as the drug was not available for clinical use when the PAUSE study started, and the results are not generalizable to this DOAC. Fifth, the 50 ng/mL cut point used in this study to define a clinically important residual preoperative DOAC level was not established, and further study is needed to assess a correlation between preoperative DOAC treatment levels and bleeding. Sixth, most patients included were white, and additional studies are needed in nonwhite populations. Seventh, patients with venous thromboembolism, who represent a different study population,³⁶ were not included.

A strength of this study is the generalizability of the results to patients assessed in clinical practice, as a high proportion of screened patients were enrolled (83%) and few were lost to follow-up (<1%). Another strength is the clinical applicability of the DOAC regimen management we assessed, as most patients adhered to the perioperative DOAC therapy interruption (95%) and resumption (93%) management protocol. The simple strategy of omitting DOAC regimens for 1 day before and after a low-bleeding-risk procedure and 2 days before and after a high-bleeding-risk procedure (except for patients using dabigatran with a CrCl <50 mL/min) is, therefore, likely to be easily adoptable in clinical practice.

Conclusions

In this study, patients with AF who had DOAC therapy interruption for elective surgery or procedure, a simple standardized perioperative management strategy without heparin bridging or measurement of coagulation function was associated with low rates of major bleeding and arterial thromboembolism.

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Supplementary Online Content

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eFigure. Screening of Patients, Enrollment into DOAC Cohort, and Study Completion

eAppendix 1. Classification of Surgery/Procedure as High or Low Bleeding Risk

eAppendix 2. Blood Processing Methods and Coagulation Assays Used

eAppendix 3. Clinical Outcome Definitions

eAppendix 4. List of Clinical Sites, Site Investigators, and Patients Recruited per Site

eAppendix 5. Types of Surgery/Procedures Patients Underwent

eAppendix 6. Study Outcomes in Patients Adhering to DOAC Interruption and

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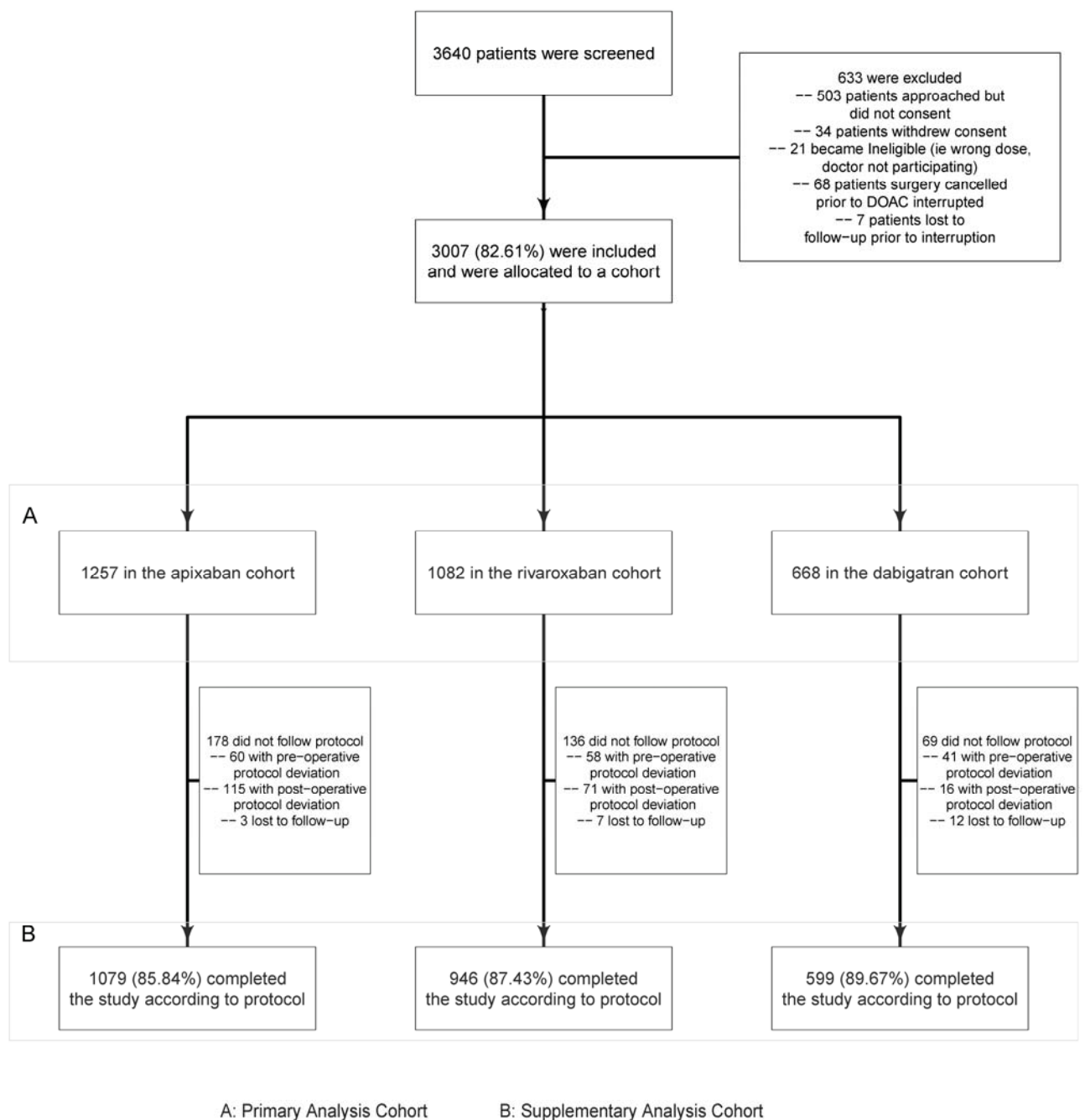
eAppendix 9. Drugs That Can Inhibit or Induce DOAC Activity

eAppendix 10. Anticoagulant Level at Time of Surgical Procedure Based on Direct Oral

Anticoagulant–Specific Coagulation Tests

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Screening of Patients, Enrollment into DOAC Cohort, and Study Completion



Legend: I A: ≥ 1 dose interrupted, B: Per protocol analysis TT, intention-to-treat; PP, per protocol.

eAppendix 1. Classification of Surgery/Procedure as High or Low Bleeding Risk

High Bleed Risk Surgery/Procedures

- 1) any surgery requiring **neuraxial anesthesia**
 - neuraxial anesthesia/injection
 - epidural anesthesia/injection
- 2) major intracranial or neuraxial surgery
 - brain cancer resection
 - laminectomy or neuraxial tumour resection
 - intracranial (subdural, epidural) bleed evacuation
- 3) major thoracic surgery
 - lobectomy, pneumonectomy
 - esophagectomy
- 4) major cardiac surgery
 - coronary artery bypass
 - valve replacement or repair
- 5) major vascular surgery
 - aortic aneurysm repair
 - aortobifemoral bypass, popliteal bypass
 - carotid endarterectomy
- 6) major **abdominopelvic** surgery
 - hepatobiliary cancer resection
 - pancreatic cancer or pseudocyst resection
 - **colorectal** and gastric cancer resection
 - diverticular disease resection
 - inflammatory bowel disease resection
 - renal cancer resection
 - bladder cancer resection
 - endometrial cancer resection
 - ovarian cancer resection
 - radical prostatectomy
- 7) major orthopedic surgery
 - **hip arthroplasty** or **hip fracture** repair
 - **knee** arthroplasty or tibial osteotomy
 - shoulder arthroplasty
 - metatarsal osteotomy
- 8) other major cancer or reconstructive surgery
 - head and neck cancer surgery
 - reconstructive facial, abdominal, limb surgery

Low Bleeding Risk Surgery/Procedures

- 1) gastrointestinal procedures
 - colonoscopy
 - gastroscopy
 - sigmoidoscopy
 - endoscopic retrograde pancreaticholangiography
 - capsule endoscopy

- push enteroscopy
- Barrett's esophagus ablation
- 2) cardiac procedures
 - permanent pacemaker implantation or battery change
 - internal cardiac defibrillator implantation or battery change
 - arterioventricular node ablation
 - coronary artery angiography (radial approach)
- 3) dental procedures
 - tooth extraction (up to two extractions)
 - endodontic (root canal) procedure
- 4) skin procedures
 - skin biopsy
- 5) eye procedures
 - phacoemulsification (cataract)

eAppendix 2. Blood Processing Methods and Coagulation Assays Used

The pre-procedure blood sample was collected into a Vacutainer tube (Becton Dickinson Canada, Mississauga, ON) containing sodium citrate (0.105M, 3.2%); it is centrifuged for 15 minutes at 1500G, plasma is transferred and double-spun at 1500 G for 5 minutes to ensure platelet poor plasma ($<10 \times 10^9/L$ platelets). Platelet poor plasma is separated into aliquots and stored at -70°C at each participating clinical site temporarily. Plasma sample kits were prepared and shipped to sites by the Clinical Research Laboratory and Biobank, Hamilton General Hospital, shipped back periodically and stored in liquid nitrogen until analyzed. Samples were analyzed at the Hamilton Regional Laboratory Medicine Program's Special Coagulation Laboratory by medical laboratory technologists who are blinded to the patient characteristics.

The following coagulation function tests and assays were used: prothrombin time (PT) (Siemens Thromborel S, Marburg, De); activated partial thromboplastin time (aPTT) (Siemens Dade Actin FS, Marburg, De); thrombin time (TT) (Sigma-Aldrich, Oakville, Can); dilute thrombin time (dTT) (Hemoclot®, Hyphen BioMed, Neuville-sur-Oise, Fr); and anti-factor Xa levels (Hyphen BioMed, Neuville-sur-Oise, Fr). All testing was performed on a STAr-Evolution analyzer (Diagnostica Stago, Asnières-sur-Seine, Fr). The reference intervals for these assays are as follows: PT=11-15 seconds; INR=0.8-1.2; aPTT=22-35 seconds; TT=20-30 seconds. There is no therapeutic range for dTT and anti-factor Xa levels but the lower limit that is reported is <20 ng/mL for the dTT and for the rivaroxaban and apixaban anti-factor Xa levels.

eAppendix 3. Clinical Outcome Definitions

Primary Clinical Outcomes

The first primary outcome is major bleeding, defined by any one of the following criteria:

- i) Fatal bleeding
- ii) Symptomatic and retroperitoneal, intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, or intra-articular;
- iii) Extrasurgical site bleeding causing a drop in hemoglobin ≥ 20 g/L (1.24 mmol/L)
- iv) Extrasurgical site bleeding leading to transfusion ≥ 2 units whole blood or red cells within 48 hours of the bleed;
- v) surgical bleed that leads to intervention (e.g., re-operation) or has one of: interferes with mobilization, leads to delayed wound healing, or leads to deep wound infection;
- vi) Surgical site bleeding requiring intervention (re-operation) resulting in prolonged care or stay
- vii) Surgical site bleeding that is unexpected or prolonged
- viii) Surgical site bleeding sufficiently large to cause hemodynamic instability associated with drop in hemoglobin ≥ 20 g/L (1.24 mmol/L) within 48 hour of seeking medical help
- ix) Surgical site bleeding sufficiently large to cause hemodynamic instability associated with transfusion ≥ 2 units whole blood or red cells within 48 hours of the bleed;

The second primary outcome is arterial thromboembolism, comprising:

- i) ischemic stroke, defined as any new focal neurologic deficit that persists for >24 hours or any new focal neurologic deficit of any duration, that occurs with evidence of acute infarction on computed tomography (CT) or magnetic resonance imaging (MRI) of the brain;
- ii) systemic embolism, defined as symptomatic embolism to upper or lower extremity or abdominal organ, confirmed intra-operatively or by objective imaging studies (e.g., CT angiography);
- iii) transient ischemic attack, defined as symptomatic focal neurologic deficit (lasting typically <1 hour and not for >24 hours), that occurs with no evidence of acute infarction on CT or MRI of brain.

Secondary Clinical Outcomes

The secondary clinical outcomes comprise: i) clinically relevant non-major bleeding, defined as bleeding not satisfying criteria for major bleeding that requires a medical assessment (e.g., unscheduled visit to the doctor's office or to an emergency department) and/or treatment/intervention such as DOAC interruption; ii) minor bleeding, defined as bleeding not satisfying criteria for major or clinically relevant non-major bleeding; iii) death due to any cause; iv) venous thromboembolism, defined by symptomatic deep vein thrombosis or pulmonary embolism that is confirmed by objective imaging studies (e.g., ultrasound, CT pulmonary angiogram); and v) acute coronary syndrome, defined by symptomatic myocardial ischemia that is confirmed by objective criteria (electrocardiographic and/or elevated cardiac troponins).

eAppendix 4. List of Clinical Sites, Site Investigators, and Patients Recruited per Site

Clinical Site	Site Investigator	Number of Patients Enrolled
St Joseph's Healthcare Hamilton, Hamilton, ON, Canada	Frederick Spencer	424
Hamilton General Hospital, Hamilton, ON, Canada	Sam Schulman	953
Juravinski Hospital, Hamilton, ON, Canada	Peter Gross	101
McMaster University Medical Centre, Hamilton, ON, Canada	Shannon Bates	16
University of Alberta, Edmonton, AB, Canada	Cynthia Wu	22
The Ottawa Hospital, Ottawa, ON, Canada	Marc Carrier	314
Queen Elizabeth II Hospital, Halifax, NS, Canada	Sudeep Shivakumar	100
St. Mary's, Montreal, PQ, Canada	Susan Solymoss	46
Hôpital Montfort, Ottawa, ON, Canada	Gregoire Le Gal	209
Montreal General Hospital, Montreal, PQ, Canada	Susan Solymoss	71
Health Science Centre, Winnipeg, MB, Canada	Stephen Kowalski	47
Centre hospitalier Universitaire de Sherbrooke, PQ, Canada	Genevieve Le Templier	57
Vancouver General Hospital, Vancouver, BC, Canada	Agnes Lee	89
Peter Lougheed Centre, Calgary, AB, Canada	Elizabeth MacKay	23
Toronto General Hospital, Toronto, ON, Canada	Erik Yeo	81
Hôpital Maisonneuve-Rosemont, Montreal, PQ, Canada	Jeannine Kassis	48
Jewish General Hospital, Montreal, PQ, Canada	Mark Blostein	44
Henry Ford Health System, Detroit, MI, USA	Vinay Shah	33
NorthShore University Health Systems, Evanston, IL, USA	Alfonso Tafur	192
Universitaire Ziekenhuizen, Leuven, Belgium	Thomas Vanassche	107
Kaiser Permanente Colorado, Denver, CO, US	Nathan Clark	20
Academic Medical Centre, University of Amsterdam, The Netherlands	Michiel Coppens	4
University of Thessaly, Larissa, Greece	Eleni Arnaoutoglou	6

eAppendix 5. Types of Surgery/Procedures Patients Underwent

Surgery/Procedure	Apixaban	Dabigatran	Rivaroxaban
	Cohort	Cohort	Cohort
	n=1257	n=668	n=1082
Cardiothoracic	528 (42%)	204 (30.5%)	387 (35.8%)
Gastrointestinal	250 (19.9%)	149 (22.3%)	228 (21.1%)
Orthopedic	135 (10.7%)	103 (15.4%)	105 (9.7%)
Urologic	103 (8.2%)	72 (10.8%)	103 (9.5%)
General Surgery	93 (7.4%)	45 (6.7%)	83 (7.7%)
Ear-Nose-Throat	39 (3.1%)	23 (3.4%)	49 (4.5%)
Gynecological	27 (2.1%)	18 (2.7%)	35 (3.2%)
Interventional Radiology	26 (2.1%)	16 (2.4%)	23 (2.1%)
Dermatological	20 (1.6%)	15 (2.2%)	22 (2.0%)
Neurosurgical	16 (1.3%)	10 (1.5%)	21 (1.9%)
Vascular	12 (0.95%)	7 (1.0%)	10 (0.92%)
Ophthalmological	8 (0.64%)	4 (0.6%)	10 (0.92%)
Dental	0 (0%)	2 (0.3%)	6 (0.55%)
Other	0 (0%)	0 (0%)	0 (0%)

eAppendix 6. Study Outcomes in Patients Adhering to DOAC Interruption and Resumption Protocols*

Outcome	DOAC Cohort		
	Apixaban	Dabigatran	Rivaroxaban
	n=1079	n=599	n=946
Primary - number, % (1-sided 95% CI)			
Major bleeding†	13, 1.2 (0-1.89); p=0.031	6, 1.0 (0-1.93); p=0.04	16, 1.69 (0-2.53); p=0.249
Arterial thromboembolism‡§	2, 0.19 (0-0.56); p<0.001	3, 0.50 (0-1.25); p=0.022	4, 0.42 (0-0.94); p=0.003
Secondary - number, % (2-sided 95% CI)			
Death	2, 0.19 (0.05-0.67)	2, 0.33 (0.09-1.21)	3, 0.32 (0.11-0.93)
Myocardial infarction	1, 0.09 (0.02-0.52)	0, 0 (0-0.64)	0, 0 (0-0.4)
Deep-vein thrombosis	2, 0.19 (0.0 - 0.67)	1, 0.17 (0.03-0.94)	0, 0 (0-0.4)
Pulmonary embolism	3, 0.28 (0.09-0.81)	1, 0.17 (0.03-0.94)	1, 0.11 (0.02-0.6)
Arterial catheter thrombosis¶	1, 0.09 (0.02-0.52)	1, 0.17 (0.03-0.94)	0, 0 (0-0.4)
Clinically relevant non-major bleeding	20, 1.85 (1.2-2.85)	11, 1.84 (1.03-3.26)	25, 2.64 (1.8-3.87)
Minor bleeding	50, 4.63 (3.53-6.06)	33, 5.51 (3.95-7.64)	56, 5.92 (4.59-7.61)

Legend:

*Analysis done in patients in whom no DOAC was taken on interruption days pre-surgery/procedure and no DOAC taken on day of surgery/procedure.

†p-value of the 1-sided test for one proportion to test the proportion of major bleeding per DOAC is <2%

‡p-value of the 1-sided test for one proportion to test the proportion of ATE per DOAC is <1.5%

§All events were ischemic stroke.

¶No episodes of catheter-related venous thrombosis were reported.

eAppendix 7. Primary Outcome Rates According to Clinical Site

Clinical Site	Number of patients enrolled	Number (%) of patients with major bleed	Number (%) of patients with ATE
St Joseph's Healthcare Hamilton, Hamilton, ON, Canada	424	1 (0.24%)	3 (0.71%)
Hamilton General Hospital, Hamilton, ON, Canada	953	7 (0.73%)	4 (0.42%)
Juravinski Hospital, Hamilton, ON, Canada	101	2 (1.98%)	0 (0%)
McMaster University Medical Centre, Hamilton, ON, Canada	16	0 (0%)	0 (0%)
University of Alberta, Edmonton, AB, Canada	22	2 (9.09%)	0 (0%)
The Ottawa Hospital, Ottawa, ON, Canada	314	5 (1.59%)	0 (0%)
Queen Elizabeth II Hospital, Halifax, NS, Canada	100	3 (3%)	0 (0%)
St. Mary's, Montreal, PQ, Canada	46	0 (0%)	0 (0%)
Hôpital Montfort, Ottawa, ON, Canada	209	0 (0%)	0 (0%)
Montreal General Hospital, Montreal, PQ, Canada	71	0 (0%)	0 (0%)
Health Science Centre, Winnipeg, MB, Canada	47	3 (6.38%)	0 (0%)
Centre hospitalier Universitaire de Sherbrooke, PQ, Canada	57	1 (1.75%)	0 (0%)
Vancouver General Hospital, Vancouver, BC, Canada	89	4 (4.49%)	0 (0%)
Peter Lougheed Centre, Calgary, AB, Canada	23	1 (4.35%)	0 (0%)
Toronto General Hospital, Toronto, ON, Canada	81	1 (1.23%)	1 (1.23%)
Hôpital Maisonneuve-Rosemont, Montreal, PQ, Canada	48	2 (4.17%)	0 (0%)
Jewish General Hospital, Montreal, PQ, Canada	44	1 (2.27%)	0 (0%)
Henry Ford Health System, Detroit, MI, USA	33	2 (6.06%)	1 (3.03%)
NorthShore University Health Systems, Evanston, IL, USA	192	2 (1.04%)	1 (0.52%)
Universitaire Ziekenhuizen, Leuven, Belgium	107	6 (5.61%)	0 (0%)
Kaiser Permanente Colorado, Denver, CO, USA	20	0 (0%)	0 (0%)
Academic Medical Centre, University of Amsterdam, The Netherlands	4	0 (0%)	0 (0%)
University of Thessaly, Larissa, Greece	6	0 (0%)	0 (0%)

eAppendix 8. Anticoagulant Level at Time of Surgery/Procedure based on Non-specific Coagulation Tests

Measurement of Anticoagulant Level	DOAC Cohort					
	Apixaban		Dabigatran		Rivaroxaban	
	Low bleed risk	High bleed risk	Low bleed risk	High bleed risk	Low bleed risk	High bleed risk
	n=851	n=406	n=440	n=228	n=709	n=373
Samples collected – no. (%)	772 (90.7)	357 (87.9)	367 (83.4)	196 (85.7)	627 (88.4)	338 (90.6)
Samples with residual DOAC values – no. (%)	751 (88.2)	335 (82.5)	352 (80.0)	183 (80.5)	606 (85.5)	314 (84.2)
Non-specific coagulation tests*						
PT, median (IQR)	13.4 (12.6-14.6)	13.5 (12.6-14.5)	13.9 (12.7-15.5)	13.7 (12.9-14.2)	13.6 (12.9-14.7)	13.5 (12.9-14.2)
<i>above normal (>13.5 sec) - no. (%)</i>	150 (20.0)	61 (18.2)	31 (8.8)	21 (11.5)	81 (13.4)	36 (11.5)
INR, median (IQR)	1 (1-1.1)	1 (1-1.1)	1 (1-1.1)	1 (1-1.1)	1 (1-1.1)	1 (1-1.1)
<i>above normal (>1.2) - no. (%)</i>	45 (6.0)	13 (3.9)	20 (5.7)	2 (1.1)	32 (5.3)	8 (2.5)
aPTT, median (IQR)	29 (27-31)	28 (27-30)	32 (29-35.8)	30 (28-32)	27 (25-30)	27 (25-29)
<i>above normal (>35 sec) - no. (%)</i>	95 (12.65)	26 (7.8)	88 (25.0)	12 (6.6)	57 (9.4)	14 (4.46)
TT, median (IQR)	24 (23-25)	24 (23-25)	35 (28-48)	27 (25-31)	24 (21-26)	24 (20-26)
<i>above normal (>30 sec) - no. (%)</i>	13 (1.7)	7 (2.1)	224 (63.6)	48 (26.2)	40 (6.6)	5 (1.6)

Legend:

*Results expressed as median (inter-quartile range) and proportions of patients within each category expressed as number (percent); PT, prothrombin time; INR, international normalised ratio; aPTT, activated partial thromboplastin time; TT, thrombin time; IQR, inter-quartile range.

eAppendix 9. Drugs That Can Inhibit or Induce DOAC Activity

Antiarrhythmics: amiodarone, digoxin, diltiazem, dronedarone, quinidine, verapamil

Antibiotics: azithromycin, clarithromycin, rifampicin

Anticonvulsants: carbamazepine, phenobarbital, phenytoin

Antifungals: fluconazole, itraconazole, posaconazole, voriconazole

HIV protease inhibitors: ritonavir

Other: naproxen, St. John's wort

eAppendix 10. Anticoagulant Level at Time of Surgical Procedure Based on Direct Oral Anticoagulant–Specific Coagulation Tests

Measurement of Anticoagulant Level	DOAC Cohort, No. (%)					
	Apixaban		Dabigatran		Rivaroxaban	
	Low Bleeding Risk (n = 851)	High Bleeding Risk (n = 406)	Low Bleeding Risk (n = 440)	High Bleeding Risk (n = 228)	Low Bleeding Risk (n = 709)	High Bleeding Risk (n = 373)
Samples collected	772 (90.7)	357 (87.9)	367 (83.4)	196 (85.7)	627 (88.4)	338 (90.6)
Samples with residual DOAC values	751 (88.2)	335 (82.5)	352 (80.0)	183 (80.5)	606 (85.5)	314 (84.2)
DOAC-Specific Coagulation Tests						
Anti–Factor Xa Level (Apixaban and Rivaroxaban) or Dilute Thrombin Time (Dabigatran), ng/mL						
≥50	96 (12.9)	7 (2.09)	25 (7.1)	1 (0.55)	27 (4.5)	2 (0.64)
30-49.9	134 (17.8)	16 (4.8)	35 (9.9)	1 (0.55)	133 (21.9)	44 (14.0)
<30	521 (69.4)	312 (93.1)	292 (82.9)	181 (98.9)	446 (73.6)	268 (85.3)

Abbreviation: DOAC, direct oral anticoagulant.