Supplementary Online Content

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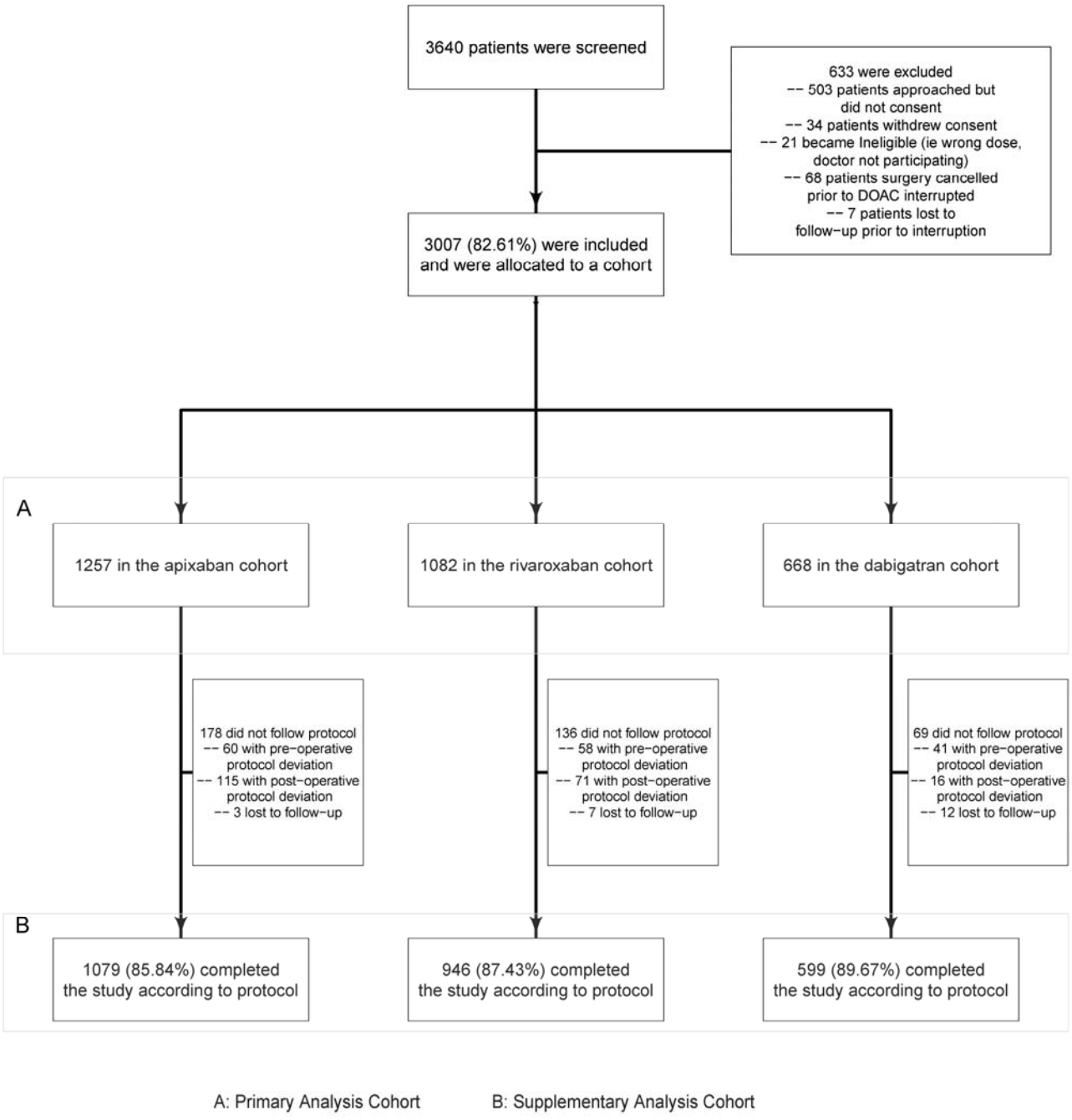
This supplementary material has been provided by the authors to give readers additional information about their work.

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



Legend: I A: ≥1 dose interrupted, B: Per protocol analysisTT, 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 pancreaticocholangiography
   - 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 Dickensen 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 ($<10\times10^9$/L platelets). Platelet poor plasma is separated into aliquots and stored at -70^{o}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)
above normal (>13.5 sec) - no. (%)	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)
above normal (>1.2) - no. (%)	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)
above normal (>35 sec) - no. (%)	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)
above normal (>30 sec) - no. (%)	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: carbemazapine, phenobarbital, phenytoin

Antifungals: fluconazole, itraconazole, posaconazole, voraconazole

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.