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Pacemaker or Defibrillator Surgery Without Interruption of Direct Oral Anticoagulants: **BRUISE CONTROL - 2** (a randomized controlled trial of continued versus interrupted direct oral anti-coagulant at the time of surgery)

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D Birnie and V Essebag were co-principal investigators

Late-Breaking Clinical Trials Presentation
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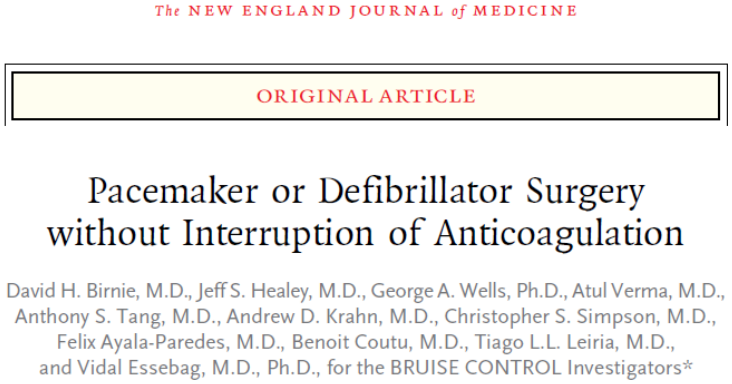
Background

- Oral anticoagulant use is common among patients requiring pacemaker or defibrillator surgery.
- BRUISE CONTROL trial demonstrated 80% fewer device pocket hematomas when surgery was performed without interruption of warfarin.[1]



Outcome	Heparin Bridging (N=338)	Continued Warfarin (N=343)	Relative Risk (95% CI)	P Value
Primary outcome				
Clinically significant hematoma — no. (%)	54 (16.0)	12 (3.5)	0.19 (0.10–0.36)	<0.001

[1] N Engl J Med 2013;368:2084-93.

- However, since the publication of BRUISE CONTROL the use of direct oral anticoagulants (DOACs) has grown substantially and they are now used in the majority of patients with AF

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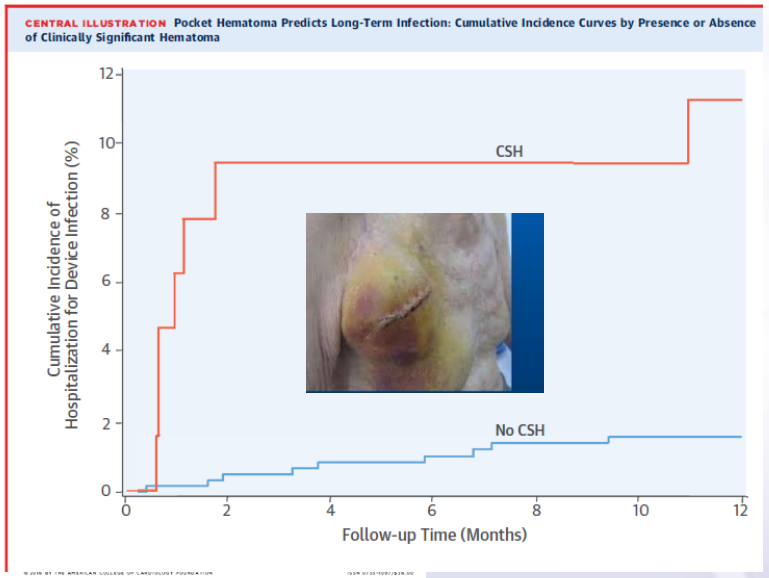
Background – balancing risks of thrombo-embolism and perioperative bleeding

- Experience from the major DOAC clinical trials found that brief, temporary interruptions for procedures or surgery are associated with approximately 3-fold increase in stroke embolism.[2,3]

- On the other hand, device pocket hematomas may have very significant sequelae for patients.
- They can necessitate prolonged cessation of anticoagulation which increases the risk of thromboembolism
- Very importantly they are associated with a markedly increased risk of serious device system infection.[4]



2. Healey J et al Circulation 2012;126:343-8.
3. Patel MR et al J Am Coll Cardiol 2013;61:651-8.
4. Essebag V et al J Am Coll Cardiol 2016; 67:1300-8.

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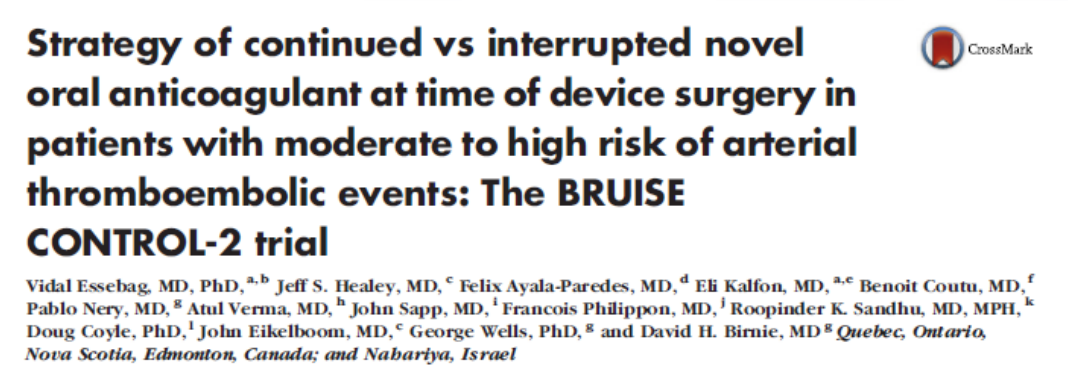
Methods

- Physician surveys have documented a lack of consensus on peri-operative management of DOACs
- Multicenter single-blind randomized controlled trial
- In brief, patients treated with dabigatran or rivaroxaban or apixaban and with a CHA_2DS_2-VASc score ≥2, were randomized to continued or interrupted DOAC.[5]



Strategy of continued vs interrupted novel oral anticoagulant at time of device surgery in patients with moderate to high risk of arterial thromboembolic events: The BRUISE CONTROL-2 trial

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5. Essebag V, et al. Am Heart J 2016;173:102-7.

Methods – Treatment groups

- **Continued DOAC**
  - Patients continued their DOAC throughout the surgical period, and took their morning dose prior to surgery.
- **Interrupted DOAC**
  - Patients on rivaroxaban or apixaban discontinued drug after taking their last dose 2 days before surgery.
  - Patients on dabigatran discontinued drug at a time interval dependent on their glomerular filtration rate.
  - All 3 drugs were resumed at the next regular dose timing ≥ 24 hours after end of surgery.

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Methods - Primary Outcome and Blinding

- The primary outcome was clinically significant hematoma (same definition as in BRUISE CONTROL) defined as a hematoma:
  - requiring re-operation and/or
  - resulting in prolongation of hospitalization and/or
  - requiring interruption of all anticoagulation for > 24 hours
- To permit investigator blinding, each center was required to identify two patient-care teams.
- The unblinded team had knowledge of treatment allocation and was responsible for device implantation and follow-up of only
- The blinded team had no knowledge of treatment allocation and was responsible for diagnosing, following, and making decisions about hematomas.

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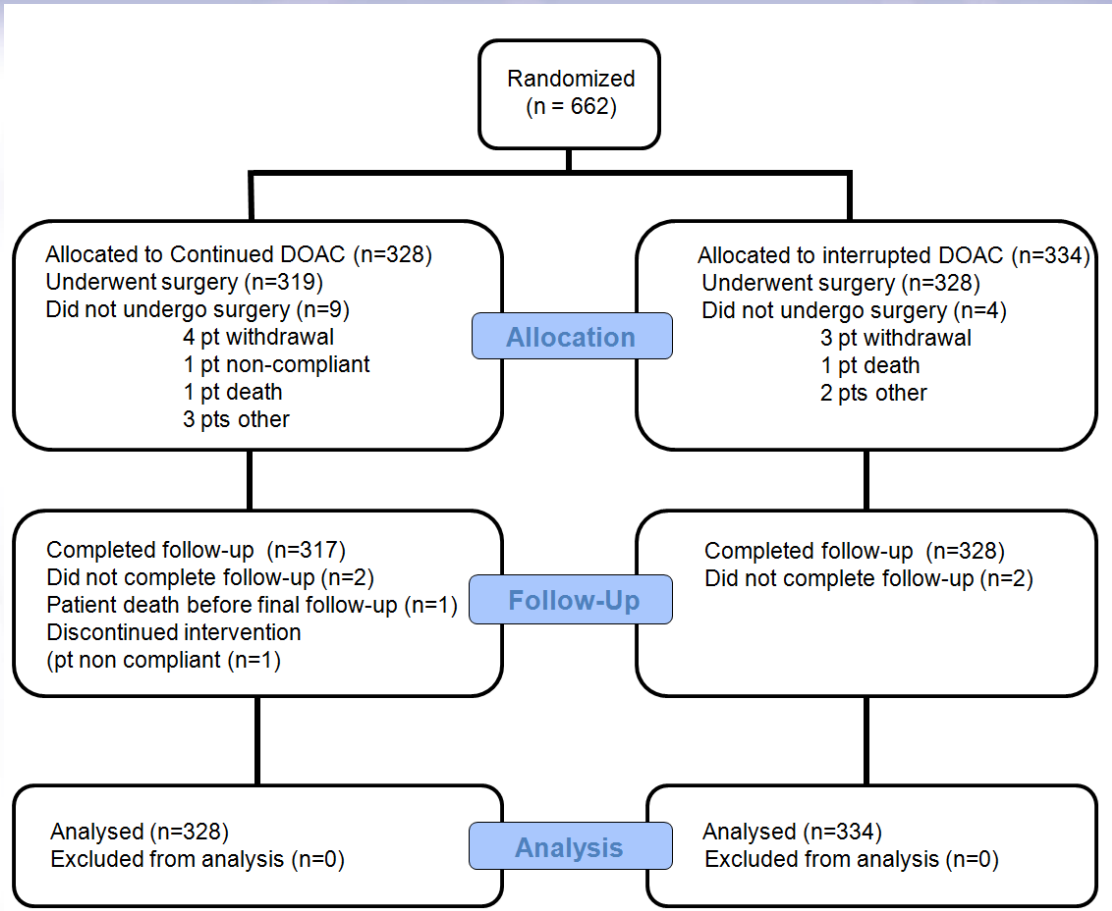
Methods - Sample size

- We hypothesized that performing device surgery without DOAC interruption would result in a reduced hematoma rate.
- We speculated that the rate of clinically significant hematoma with interrupted DOAC would be similar to that observed in the interrupted warfarin with heparin bridging arm of BRUISE CONTROL, specifically 16%.[1]
- Hence a sample size of 846 patients was calculated to have 80% power to detect a 40% relative risk reduction in the primary end point in the continued DOAC arm

[1] N Engl J Med 2013;368:2084-93.

Early Termination

- We enrolled patients at 15 centers in Canada and one in Israel.
- The data and safety monitoring board recommended study termination at the second pre-specified interim analysis
- We therefore report data on 662 patients enrolled between April 9, 2013 and June 1, 2017



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Results - Baseline Characteristics

Characteristic	Continued DOAC (N=328)	Interrupted DOAC (N=334)
Age – yr	74.1±8.9	73.4±8.9
Male sex – no. (%)	245 (74.7)	234 (70.1)
Body – mass index*	28.5±5.3	28.9± 5.4
Medical history – no. (%)		
Stroke	35 (10.7)	33 (9.9)
Transient ischemic attack	24 (7.3)	27 (8.1)
Peripheral embolus	8 (2.4)	8 (2.4)
Hypertension	245 (74.7)	249 (74.6)
Diabetes mellitus	103 (31.4)	119 (35.6)
Cardiomyopathy	170 (51.8)	161 (48.2)
Prior myocardial infarction	110 (33.5)	109 (32.6)
eGFR (ml/minute)	67.6±19.4	68.6±21.7
CHA_2DS_2-VASc score†	3.9±1.4	3.9±1.3
Direct oral anti-coagulant – no. (%)		
Dabigatran 110 mg twice daily**	62 (18.9)	61 (18.3)
Dabigatran 150 mg twice daily	34 (10.4)	46 (13.8)
Rivaroxaban 15mg once daily	28 (8.5)	27 (8.1)
Rivaroxaban 20 mg once daily	78 (23.8)	79 (23.7)
Apixaban 2.5mg twice daily	35 (10.7)	26 (7.8)
Apixaban 5mg twice daily	90 (27.4)	95 (28.4)

there was no significant differences in any variable

Results - DOAC Management

	Last pre-operative dose and surgery start		Surgery stop and first post-operative dose		Last pre-operative dose and first post-operative dose	
	Continued DOAC	Interrupted DOAC	Continued DOAC	Interrupted DOAC	Continued DOAC	Interrupted DOAC
Dabigatran with eGFR > 50ml/min	4 (3,7)	40 (38, 42)	7 (5,9)	31(27,33)	12 (11,14)	72 (67,72)
Dabigatran with eGFR 30-50 ml/min	4 (2,6)	64 (61,67)	8 (5,10)	30(28,34)	12 (11,19.5)	96 (95,96)
Rivaroxaban	16 (10,19)	41 (39,49)	8 (6,19)	31 (26,33)	24 (24,26)	72 (72,75)
Apixaban	5 (3,7)	39 (37,43)	7 (6,9)	32 (29,34)	13 (12,14)	72 (72,76)
All patients	6 (3,14)	40 (38,45)	8 (6,10)	31 (27,34)	14 (12,24)	72 (72,76)

P<0.001 for all comparisons between continued DOAC and interrupted DOAC

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Results - Operative Details

	Continued DOAC (N=319)	Interrupted DOAC (N=328)
New implant of a pacemaker – no.(%)		
Single	43 (25.2)	55 (31.1)
Dual	61 (35.7)	48 (27.1)
Cardiac resynchronization	7 (4.1)	12 (6.8)
New implant of a implantable cardioverter-defibrillator – no.(%)		
Single	30 (17.5)	27 (15.3)
Dual	17 (9.9)	20 (11.3)
Cardiac resynchronization	13 (7.6)	15 (8.5)
Device replacement or revision – no. (%)		
Pulse generator change only	113 (76.4)	116 (76.8)
Pulse generator change with additional *	29 (19.6)	32 (21.2)
Other	6 (4.1)	3 (2.0)
Details of surgery		
Duration of procedure - min		
median	39	38
Interquartile range	25-57	22 - 60
Venous-access guidance – no.(%)		
Peripheral venogram	69 (35.9)	77 (38.3)
Ultrasonography	7 (3.7)	10 (5.0)
Intrapocket administration of prohemostatic agent - no. (%)	21 (6.6)	10 (3.1)
Pressure dressing applied postoperatively – no.(%)	217 (68.0)	197 (60.1)
Sandbag applied postoperatively – no.(%)	17 (5.3)	18 (5.5)
Defibrillator threshold testing performed – no.(%)	12 (3.8)	13 (4.0)
Cardioversion performed – no.(%)	6 (1.9)	2 (0.6)
Specialty of physician performing surgery – no. (%)		
Electrophysiologist	296 (92.8)	312 (95.1)
Surgeon	17 (5.3)	12 (3.7)
Cardiologist	6 (1.9)	4 (1.2)
Fellow/Resident participation in the procedure – no.(%)	146 (45.8)	165 (50.3)

There were no significant between-group differences in any variables, except for intrapocket administration of prohemostatic agent and application of dressing postoperatively (both p=0.035).

Results – Primary Outcome

	Continued DOAC (N =328)	Interrupted DOAC (N=334)	P Value
Primary Outcome			
Clinically significant hematoma– no. (%)	7 (2.1)	7 (2.1)	0.973
Components of the Primary Outcome			
Hematoma prolonged hospitalization – no. (%)	1 (0.3)	2 (0.6)	1.000
Hematoma requiring interruption of anti-coagulation – no. (%)	7 (2.1)	7 (2.1)	0.973
Hematoma requiring re-operation – no. (%)	2 (0.6)	1 (0.3)	0.621

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Results – Secondary Outcomes

	Continued DOAC (N =328)	Interrupted DOAC (N=334)	P Value
Secondary Outcomes			
Non - clinically significant hematoma no. (%)	11 (3.4)	10 (3.0)	0.792
Any hematoma no. (%)	18 (5.5)	16 (4.8)	0.684
All-cause mortality – no. (%)	2 (0.6)	1 (0.3)	0.621
Pneumothorax – no. (%)	2 (0.6)	0	0.245
Hemothorax – no. (%)	0	0	-
Cardiac tamponade – no. (%)	1 (0.3)	1 (0.3)	1.000
Stroke – no. (%)	1 (0.3)	1 (0.3)	1.000

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Conclusions

- In our trial we found that either strategy (i.e. continuation or interruption of DOAC) is associated with similar, very low rates of device pocket hematoma.
- Operating with continued DOAC should not be considered specifically as a strategy to reduce hematoma rate.
- Continued DOAC may reduce the risk of thrombo-embolism, however, this study was not designed with power to answer this
- Either strategy may be reasonable depending on clinical scenario
- Scenarios where clinical judgment might favour operating with continued DOAC.
  - Surgeries where the situation suggests that waiting for the anticoagulant effect to dissipate might lead to unacceptable harm (e.g. patients with complete heart block and unstable temporary pacing),
  - Situations with high stroke risk (e.g. within days after an atrial fibrillation ablation or when concomitant cardioversion or defibrillation testing is planned), or for patients with a high CHA_2DS_2-VASc score to minimize the risk of stroke associated with interruption of anticoagulation.
- For other scenarios physicians and patients may prefer brief interruptions of DOAC.

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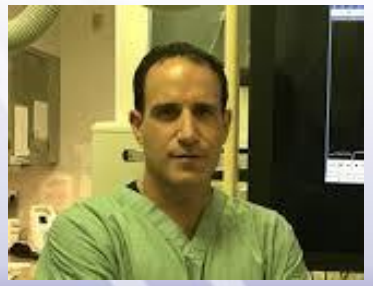

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Back-up

Secondary Outcomes - stroke

- There were two ischemic strokes, one in each arm.
- An 89-year-old female with a CHA_2DS_2-VASc score of 5 was randomized to continued DOAC. She underwent a single chamber pacemaker implantation and developed a clinically significant hematoma on the first post-operative day and her DOAC was held for 4 days. On post-operative day 3 she underwent hematoma evacuation and on post-operative day 5 she had an ischemic stroke confirmed by CT angiography.
- A 67-year-old female with a CHA_2DS_2-VASc score of 6 had an ischemic stroke two days after randomization to interrupted DOAC but before her DOAC was held.

Secondary Outcomes – tamponade/pericardial effusion

- There was one episode of delayed cardiac tamponade requiring pericardiocentesis in a 63-year-old lady in the continued DOAC arm.
- There was one pericardial effusion that was managed conservatively in a 72-year-old female randomized to interrupted DOAC.

Multi-variable Analysis

Variable	OR (95% CI)	P-value
Randomization (Continued vs. Interrupted)	1.025 (0.351,2.998)	0.964
Age	1.017 (0.954,1.085)	0.570
GFR	0.982 (0.953,1.011)	0.220
Any anti platelet	1.827 (0.556,5.998)	0.321
Intra-pocket administration	1.423 (0.171,11.818)	0.744
Pressure dressing	0.705 (0.237,2.099)	0.530

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Statistical Analysis

- Two interim analyses were planned when 33% and 66% of the patients had completed follow-up, with review by an independent data and safety monitoring board. The O'Brien-Fleming group sequential method was followed, with p-values of 0.0002 and 0.0119 for the first and second interim analyses.

Deaths

- There were 3 deaths; none of which were considered to be related to trial interventions.
- A 79-year-old male randomized to continued DOAC underwent an uneventful pacemaker pulse generator change and had an unwitnessed sudden death at home on post-op day 10. He was reported as well on the day prior to death and the cause of death was undetermined.
- A 73-year-old male randomized to continued DOAC was admitted to hospital 23 days after enrollment but prior to device surgery with sepsis and was diagnosed with Waldenstrom Macroglobulinemia and died 21 days later (without undergoing device surgery).
- A 76-year-old male randomized to the interrupted DOAC arm developed heart failure prior to a left ventricular lead repositioning. He did not stabilize sufficiently to undergo device surgery and died 13 days later.