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CLINICAL RESEARCH
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Continued vs. interrupted direct oral anticoagulants at the time of device surgery, in patients with moderate to high risk of arterial thrombo-embolic events (BRUISE CONTROL-2)

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Aims Guidelines recommend warfarin continuation rather than heparin bridging for pacemaker and defibrillator surgery, after the BRUISE CONTROL trial demonstrated an 80% reduction in device pocket haematoma with this approach. However, direct oral anticoagulants (DOACs) are now used to treat the majority of patients with atrial fibrillation. We sought to understand the best strategy to manage the DOACs at the time of device surgery and specifically hypothesized that performing device surgery without DOAC interruption would result in a reduced haematoma rate.

Methods and results We randomly assigned patients with atrial fibrillation and CHA_2DS_2-VASc score ≥2, to continued vs. interrupted DOAC (dabigatran, rivaroxaban, or apixaban). The primary outcome was blindly evaluated, clinically significant device pocket haematoma: resulting in re-operation, interruption of anticoagulation, or prolonging hospital stay. In the continued arm, the median time between pre- and post-operative DOAC doses was 12 h; in the interrupted arm the median time was 72 h. Clinically significant haematoma occurred in of 7 of 328 (2.1%; 95% CI 0.9–4.3) patients in the continued DOAC arm and 7 of 334 (2.1%; 95% CI 0.9–4.3) patients in the interrupted DOAC arm ($P = 0.97$). Complications were uncommon, and included one stroke and one symptomatic pericardial effusion in each arm.

Conclusions These results suggest that, dependent on the clinical scenario, either management strategy (continued DOAC or interrupted DOAC) might be reasonable, at least for patients similar to those enrolled in our trial.

Keywords Pacemaker • Implantable defibrillator • Perioperative • Anticoagulation

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Introduction

Oral anticoagulant use is common among patients requiring pacemaker or defibrillator surgery.[1,2] The BRUISE CONTROL trial demonstrated 80% fewer device pocket haematomas when surgery was performed without interruption of warfarin, compared to warfarin-treated patients who had their anticoagulation interrupted and received heparin bridging.[3] 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 atrial fibrillation.[4–7] For example in 2015, DOACs accounted for 56% and 80% of all new anticoagulant prescriptions in UK[5] and in Stockholm,[7] respectively.

Compared to warfarin, DOACs have a short half-life and most do not have a clinically available direct reversing agent. The results of BRUISE CONTROL,[3] and other trials of perioperative management of warfarin,[8] cannot be extrapolated to patients receiving DOACs. Thus, there is uncertainty about how DOACs should be managed perioperatively around device surgery to balance the risks of thromboembolism and perioperative bleeding. Experience from the major DOAC clinical trials found that brief, temporary interruptions for procedures or surgery are associated with an approximately three-fold increase in stroke/systemic embolism.[9,10] On the other hand, device pocket haematomas may have very significant sequelae for patients. They can necessitate prolonged cessation of anticoagulation[3] which increases the risk of thromboembolism and are associated with a markedly increased risk of serious device system infection.[11,12] Current guidelines recommend interruption of DOACs for device surgery, without heparin bridging.[13] Physician surveys[14,15] have documented a lack of consensus on perioperative management of DOACs.

Methods

Study design

BRUISE CONTROL-2 (NCT: 01675076), was conducted at 15 hospitals in Canada and 1 in Israel. The study complied with the Declaration of Helsinki. The protocol was approved by the research ethics board at each of the participating centres. The detailed study design and protocol have been published previously.[16]

Patients

Eligible patients were aged ≥ 18 and planned for elective device (pacemaker or defibrillator) surgery with non-rheumatic atrial fibrillation and CHA_2DS_2-VASc score ≥ 2, treated with dabigatran or rivaroxaban or apixaban. All patients gave written consent.

Randomization and blinding

Eligible and consenting patients were randomized in a 1:1 ratio to continued DOAC or interrupted DOAC. Randomization was performed using web-based electronic randomization (Dacima, Montreal); was stratified by clinical centre and DOAC; and used randomly selected block sizes of between 4 and 6. To permit investigator blinding, each centre was required to identify two patient-care teams. Each team consisted of research co-ordinator(s) and physician(s). The blinded team had no knowledge of treatment allocation and was responsible for reviewing patients' wounds and for diagnosing, following, and making all decisions about management of haematomas including directing interruption of anticoagulation and need for evacuation.

Study procedures

The trial was initially conducted with dabigatran only, as this was the only DOAC with post-marketing approval. As additional DOACs became approved, the protocol was expanded on 16 January 2015 to include patients on apixaban and rivaroxaban, and the perioperative management of dabigatran was simplified. In both arms of the expanded protocol, patients remained on their usual prescribed type and dose of DOAC. In the continued arm, all patients continued their DOAC throughout the surgical period, and took their morning dose prior to surgery. In the interrupted arm, 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.[9] All three drugs were resumed at the next regular dose timing ≥24 h after end of surgery. Aspirin was continued in all patients with an indication for concomitant aspirin and DOAC therapy; other antiplatelet drugs were managed at physician's discretion.

Patients were seen daily by the blinded study team throughout their inpatient stay and at their first routine post-operative outpatient visit (1–2 weeks after surgery). Patients also had a telephone follow-up on Day 3 or 4.

Outcome measures

The primary outcome was clinically significant haematoma, defined as a haematoma that required re-operation and/or resulted in prolongation of hospitalization and/or required interruption of oral anticoagulation.[3]

Statistical analysis

We hypothesized that performing device surgery without DOAC interruption would result in a reduced haematoma rate. At the time, we designed the study there were no data on the rates of clinically significant haematoma in DOAC treated patients. We speculated that the rate of clinically significant haematoma with interrupted DOAC would be similar to that observed in the interrupted warfarin with heparin bridging arm of BRUISE CONTROL, specifically 16%.[3] Hence a sample size of 846 patients was calculated to have 80% power to detect a 40% relative risk reduction in the primary endpoint in the continued DOAC arm, using a two-sided alpha of 0.05. Two interim analyses were planned when 33% and 66% of the patients had completed follow-up.

Primary and secondary outcomes were compared between treatment arms using the χ^2 test. A multivariable logistic regression model was performed to determine predictors of the primary outcome. Pre-specified subgroup analyses included comparison of patients taking any antiplatelet agent or not; and having *de novo* implants compared to subsequent surgeries. All outcomes were analysed by intention-to-treat and included all randomized patients. Analyses were conducted using SAS software, version 9.4 (SAS Institute). A data and safety monitoring board oversaw the study.

Results

Data on 590 patients were reviewed by the data and safety monitoring board at the second pre-specified interim analysis on 18 May 2017 at which time they recommended study termination because of futility. There were no pre-specified stopping rules for futility but the DSMB calculated that with the planned sample size the conditional power was 1.2% and the futility index was 0.988. The sample size was

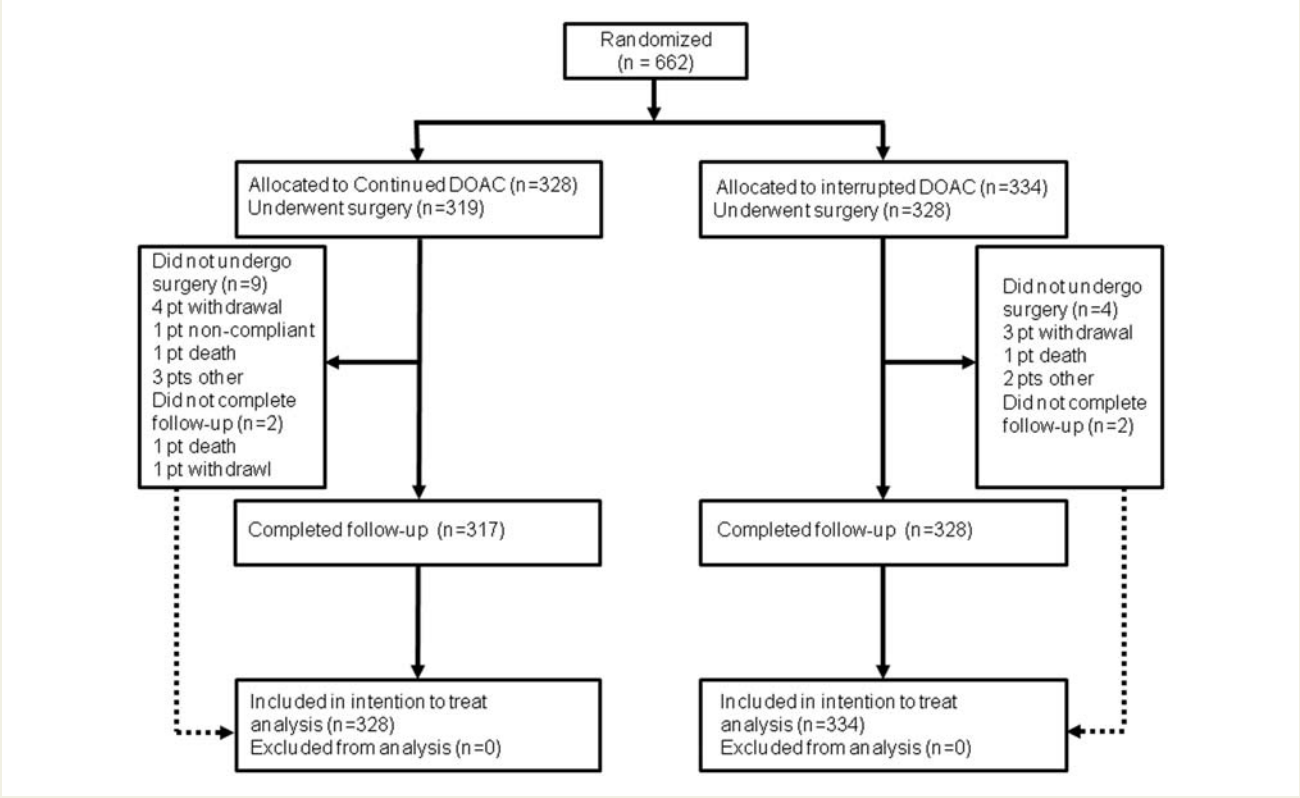


Figure 1 Trial randomization and follow-up.

recalculated based on combined event rates and found to be >7000 patients. The steering committee met on 1 June 2017 and agreed with trial termination. We therefore report data on 662 patients enrolled between 9 April 2013 and 1 June 2017. Details of trial enrolment and follow-up are shown in *Figure 1*.

The baseline clinical characteristics of the patients were similar in the two arms (*Table 1*). Perioperative DOAC management is summarized in *Table 2*. Operative details were similar in the groups with two exceptions (*Table 3*). Intra-pocket pro-haemostatic agent was used in 21 of 319 (6.6%) patients in the continued DOAC arm compared to 10 of 328 (3.1%, $P = 0.035$) in the interrupted arm. A pressure dressing was applied post-operatively in 217 of 319 (68.0%) of patients in the continued DOAC arm compared to 197 of 328 (60.1%, $P = 0.035$) in the interrupted arm.

The primary outcome, clinically significant haematoma, occurred in of 7 of 328 (2.1%; 95% CI 0.9–4.3) patients in the continued DOAC arm and 7 of 334 (2.1%; 95% CI 0.9–4.3) patients in the interrupted DOAC arm ($P = 0.97$). Non-clinically significant haematomas occurred in 11 of 328 (3.4%) and 10 of 334 (3.0%), respectively, $P = 0.79$.

To examine the influence of the imbalance in the two operative details (intra-pocket pro-haemostatic agent and pressure dressing use), we performed a logistic regression analysis (pre-specified in protocol) and two sensitivity analyses (not pre-specified). In the logistic regression analysis, age, glomerular filtration rate, use of antiplatelet agent, DOAC subtype, intra-pocket pro-haemostatic agent, and pressure dressing use were not significantly associated with clinically significant haematoma. In the sensitivity analyses, we analysed the occurrence of the primary endpoint after excluding patients who received intra-pocket pro-haemostatic agent in one analysis and excluding patients who received a post-procedure pressure dressing in the other analysis; there was no difference in the primary endpoint between the two groups.

Secondary outcomes are shown in Supplementary material online, *Table S1*. There were no significant differences. An adverse event occurred in 24 of 328 (7.3%) and 19 of 334 (5.7%), respectively, $P = 0.40$. There were three deaths; none of which were considered to be related to trial interventions. There was one stroke and one symptomatic pericardial effusion in each arm. Additional patient level detail of the deaths, strokes, and episodes of cardiac tamponade are given in the Supplementary material online. Results for the primary outcome were consistent in the two pre-specified subgroups analyses.

Discussion

In this large randomized trial, we evaluated the safety of performing pacemaker or defibrillator surgery without interrupting DOAC medication. We found that either strategy (i.e. continuation or interruption) is associated with similar low rates of device pocket haematoma. We also found that performing device procedures with continued DOAC was not associated with any major perioperative bleeding events. These results suggest that, dependent on the clinical

Table 1 Baseline characteristics of the intention-to-treat population

Characteristic	Continued DOAC (*n* = 328)	Interrupted DOAC (*n* = 334)
Age (years)	74.1 (8.9)	73.4 (8.9)
Male sex	245 (74.7%)	234 (70.1%)
Body mass index[a]	28.5 (5.3)	28.9 (5.4)
Medical history		
Stroke	35 (10.7%)	33 (9.9%)
Transient ischaemic 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/min)	67.6 (19.4)	68.6 (21.7)
CHA_2DS_2-VASc score	3.9 (1.4)	3.9 (1.3)
Direct oral anticoagulant		
Dabigatran 110 mg twice daily[b]	62 (18.9%)	61 (18.3%)
Dabigatran 150 mg twice daily	34 (10.4%)	46 (13.8%)
Rivaroxaban 15 mg once daily	28 (8.5%)	27 (8.1%)
Rivaroxaban 20 mg once daily	78 (23.8%)	79 (23.7%)
Apixaban 2.5 mg twice daily	35 (10.7%)	26 (7.8%)
Apixaban 5 mg twice daily	90 (27.4%)	95 (28.4%)
Other medications		
Aspirin	55 (16.8%)	60 (18.0%)
Clopidogrel	10 (3.1%)	14 (4.2%)
Other antiplatelet agent	0	0
Statin	232 (70.7%)	233 (69.8%)
Beta-blocker	231 (70.4%)	229 (68.6%)

Date are *n* (%), mean (SD) or *n*/*N* (%). There were no significant between-group differences in any variables at *P*-value less than 0.05.
eGFR, estimated glomerular filtration rate.
[a]The body mass index is the weight in kilograms divided by the square of the height in metres.
[b]This includes the 63 patients who were recruited under the original version of the protocol (during which all dabigatran-treated patients received 110 mg b.i.d. for 5 days before and 5 days after surgery).

Table 2 Direct oral anticoagulant management

	Number of patients		Hours between last pre-operative dose and surgery start		Hours between surgery stop and first post-operative dose		Hours between last pre-operative dose and first post-operative dose	
	Continued DOAC	Interrupted DOAC	Continued DOAC	Interrupted DOAC	Continued DOAC	Interrupted DOAC	Continued DOAC	Interrupted DOAC
Dabigatran with eGFR > 50 mL/min	76	88	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	21	18	4 (2, 6)	64 (61, 67)	8 (5, 10)	30 (28, 34)	12 (11, 20)	96 (95, 96)
Rivaroxaban	104	103	16 (10, 19)	41 (39, 49)	8 (6, 19)	31 (26, 33)	24 (24, 26)	72 (72, 75)
Apixaban	118	119	5 (3, 7)	39 (37, 43)	7 (6, 9)	32 (29, 34)	13 (12, 14)	72 (72, 76)
All patients	319	328	6 (3, 14)	40 (38, 45)	8 (6, 10)	31 (27, 34)	14 (12, 24)	72 (72, 76)

Time data are presented as medians (IQR). Only 647 patients who completed surgery were included for this analysis.
DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate.
$P < 0.001$ for all comparisons between continued DOAC and interrupted DOAC.

scenario, either management strategy (continued DOAC or interrupted DOAC) might be reasonable, at least for patients similar to those enrolled in our trial. Our results are consistent with a number of small cohort studies that continued DOAC during device surgery.[17,18] They are also consistent with a sub-analysis of the RE-LY trial (dabigatran vs. warfarin for atrial fibrillation).[19]

We had specifically hypothesized that device surgery performed with continued DOAC may reduce the rate of haematoma. This was based on the results of BRUISE CONTROL where continued warfarin significantly reduced the risk of haematoma compared to warfarin interruption with heparin bridging.[3] One postulated explanation for this finding was the concept of an 'anticoagulant stress test'. That is, if patients undergo surgery while fully anticoagulated, any excessive bleeding may be detectable and managed while the wound is still

Table 3 Operative details

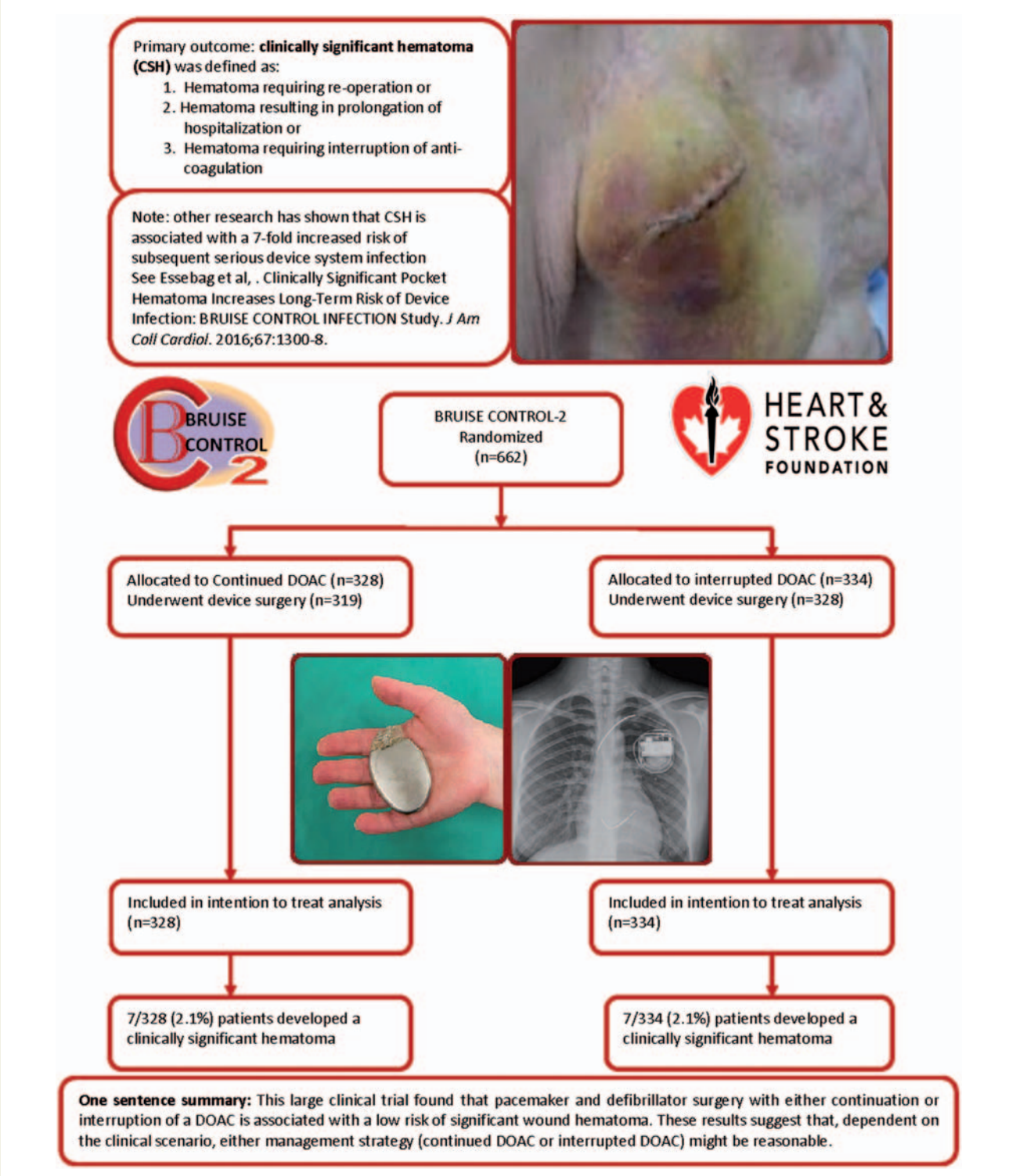
	Continued DOAC ($n = 319$)	Interrupted DOAC ($n = 328$)
New implant of a pacemaker	111/319 (34.8%)	115/328 (35.1%)
Single	43/111 (38.7%)	55/115 (47.8%)
Dual	61/111 (55.0%)	48/115 (41.7%)
Cardiac resynchronization	7/111 (6.3%)	12/115 (10.4%)
New implant of an implantable cardioverter-defibrillator	60/319 (18.8%)	62/328 (18.9%)
Single	30/60 (50.0%)	27/62 (43.5%)
Dual	17/60 (28.3%)	20/62 (32.2%)
Cardiac resynchronization	13/60 (21.7%)	15/62 (24.2%)
Device replacement or revision	148/319 (46.4%)	151/328 (46.0%)
Pulse generator change only	113/148 (76.4%)	116/151 (76.8%)
Pulse generator change with additional[a]	29/148 (19.6%)	32/151 (21.2%)
Other	6/148 (4.1%)	3/151 (2.0%)
Details of surgery		
Duration of procedure (min)	39 (25–57)	38 (22–60)
Venous access guidance		
Peripheral venogram	69/319 (21.6%)	77/328 (23.4%)
Ultrasonography	7/319 (2.1%)	10/328 (3.1%)
Intra-pocket administration of pro-haemostatic agent	21/319 (6.6%)	10/328 (3.1%)
Pressure dressing applied post-operatively	217/319 (68.0%)	197/328 (60.1%)
Sandbag applied post-operatively	17/319 (5.3%)	18/328 (5.5%)
Defibrillator threshold testing performed	12/60 (20.0%)	13/60 (21.6%)
Cardioversion performed	6/319 (1.9%)	2/328 (0.6%)
Specialty of physician performing surgery		
Electrophysiologist	296/319 (92.8%)	312/328 (95.1%)
Surgeon	17/319 (5.3%)	12/328 (3.7%)
General cardiologist	6/319 (1.9%)	4/328 (1.2%)
Fellow/resident participation in the procedure	146/319 (45.8%)	165/328 (50.3%)
Venous access for leads	$n = 203$	$n = 209$
Cephalic	60/203 (29.6%)	50/209 (23.9%)
Subclavian	83/203 (40.9%)	73/209 (34.9%)
Axillary	68/203 (33.5%)	88/209 (42.1%)

Data are *n* (%), median (IQR), mean (SD) or *n*/*N* (%). There were no significant between-group differences in any variables, except for intra-pocket administration of pro-haemostatic agent and application of dressing post-operatively (both $P = 0.035$).
[a]Additional procedures included the repositioning or addition of one or more leads, device pocket revision, and upgrade from pacemaker to implantable cardioverter-defibrillator.

open.[3] As such, if good haemostasis is achieved by the end of the procedure, there is no reason for a haematoma to spontaneously develop post-procedure. However, unlike the findings of BRUISE CONTROL[3] (where heparin bridging was restarted 24 h post-operatively and resulted in a 16% rate of haematomas), restarting DOAC (at a median of 31 h after surgery) was not associated with an increased risk of haematoma. This may be explained by the additional delay in restarting the DOAC, differences in pharmacokinetic properties, and/or differences in anticoagulant mechanisms between heparin and the DOACs.

There is some accumulating experience regarding other surgical procedures performed without DOAC interruption. A sub-study of the ARISTOTLE trial (apixaban vs. warfarin for atrial fibrillation) reported on perioperative bleeding; periprocedural management of apixaban was up to physician's discretion.[20] Major bleeding occurred in 28 of 1752 (1.6%) of patients operated on without interruption of apixaban.[20] There is an additional report showing that dental extractions can be performed without interruption of DOACs.[21] The most extensive experience with continued DOAC is during atrial fibrillation ablation. In the largest study, the incidence of major bleeding on continued dabigatran was 1.6% compared to 6.9% on continued warfarin.[22] Reflecting some of these data, recent guidelines have suggested that it is reasonable to perform surgery/procedures without interrupting DOAC in situations where the intervention carries 'no clinically important bleeding risk' and/or when adequate local haemostasis is possible.[13,23]

Given the similar and low rates of device pocket haematoma in both arms of our trial, neither continuation nor interruption of DOAC should be considered specifically as a strategy to reduce haematoma rate. However, there are some scenarios where clinical judgement might favour operating without interrupting DOAC. These may include surgeries where the situation suggests that waiting



Take home figure Main results of Bruise Control 2.

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.[9,10,24] For other scenarios, physicians and patients may prefer brief interruptions of DOAC. Recently a specific reversal agent for dabigatran, idarucizumab[25] has been approved and agents to reverse the other DOACs are at various stages of

development and approval.[26] As these agents become available, physicians may become more comfortable operating without interrupting DOACs.

The trial has some limitations. It was designed as a superiority trial, and the event rate was much lower than anticipated. In the absence of better data at the time of study design, we speculated that the rate of clinically significant haematoma with interrupted DOAC would be similar to that observed in the interrupted warfarin arm of BRUISE CONTROL, specifically 16%.[3] With the observed event rate of 2.1%, a sample size of over 7000 patients would be required to have the power to detect a 40% difference between the groups. While a statistically significant difference might be detectable with a larger trial, with such low haematoma rates any difference would be of modest clinical significance and hence it seems unlikely that such a trial will be undertaken. Furthermore, despite observing the same event rate in both arms of our study, we cannot conclusively say that the strategies are equivalent without a similarly sized non-inferiority trial. A second potential limitation is the lack of operator blinding. We discussed this at the time of study design, and the consensus was that because of the limited experience with these drugs that most operators wished to be unblinded because of the risk of sudden life-threatening events (specifically cardiac tamponade). More importantly, we wished to compare clinically relevant strategies applicable to clinical practice where operators selecting either strategy will perform the procedure with knowledge of DOAC usage. The lack of operator blinding may have led to the noted imbalance of two perioperative factors (intra-pocket pro-haemostatic agent, and pressure dressing use). However, our additional analyses showed that these two factors did not have any impact on the trial result.

In conclusion, in patients who receive DOACs, pacemaker and defibrillator surgery can be performed with or without interruption of DOAC with a similar, low risk of significant wound haematoma.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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