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ORIGINAL ARTICLE

Effect of Direct Oral Anticoagulants, Warfarin, and Antiplatelet Agents on Risk of Device Pocket Hematoma

Combined Analysis of BRUISE CONTROL 1 and 2

See Editorial by DeSimone et al

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BACKGROUND: Oral anticoagulant use is common among patients undergoing pacemaker or defibrillator surgery. BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial; NCT00800137) demonstrated that perioperative warfarin continuation reduced clinically significant hematomas (CSH) by 80% compared with heparin bridging (3.5% versus 16%). BRUISE-CONTROL-2 (NCT01675076) observed a similarly low risk of CSH when comparing continued versus interrupted direct oral anticoagulant (2.1% in both groups). Using patient level data from both trials, the current study aims to: (1) evaluate the effect of concomitant antiplatelet therapy on CSH, and (2) understand the relative risk of CSH in patients treated with direct oral anticoagulant versus continued warfarin.

METHODS: We analyzed 1343 patients included in BRUISE-CONTROL-1 and BRUISE-CONTROL-2. The primary outcome for both trials was CSH. There were 408 patients identified as having continued either a single or dual antiplatelet agent at the time of device surgery.

RESULTS: Antiplatelet use (versus nonuse) was associated with CSH in 9.8% versus 4.3% of patients ($P<0.001$), and remained a strong independent predictor after multivariable adjustment (odds ratio, 1.965; 95% CI, 1.202–3.213; $P=0.0071$). In multivariable analysis, adjusting for antiplatelet use, there was no significant difference in CSH observed between direct oral anticoagulant use compared with continued warfarin (odds ratio, 0.858; 95% CI, 0.375–1.963; $P=0.717$).

CONCLUSIONS: Concomitant antiplatelet therapy doubled the risk of CSH during device surgery. No difference in CSH was found between direct oral anticoagulant versus continued warfarin. In anticoagulated patients undergoing elective or semi-urgent device surgery, the patient specific benefit/risk of holding an antiplatelet should be carefully considered.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifiers: NCT00800137, NCT01675076.

VISUAL OVERVIEW: A visual overview is available for this article.

The full author list is available on page 7.

Key Words: anticoagulant ■ defibrillators ■ hematoma ■ heparin ■ pacemaker

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WHAT IS KNOWN?

- Oral anticoagulant use is common among patients undergoing pacemaker or defibrillator surgery.
- Hematomas associated with pacemaker or defibrillator surgery are associated with an increased risk of reoperation, hospitalization duration, and serious device infection.

WHAT THE STUDY ADDS?

- Concomitant antiplatelet use in anticoagulated patients undergoing device surgery is associated with a 2-fold increase in the risk of clinically significant hematoma.
- In patients undergoing elective or semi-urgent device surgery, efforts should be made to hold the antiplatelet if no absolute indication.
- Either strategy of direct oral anticoagulant (interrupted or continued) versus continued warfarin during device surgery is acceptable in terms of avoiding clinically significant hematomas.

Highly varying incidences of device pocket hematomas have been observed in recent studies ranging from 1.2% when no anticoagulant is present, 2.3% to 6.5% on continued warfarin therapy, and 7% to 16% during heparin bridging.[1–4] Hematomas associated with pacemaker or defibrillator surgery are not benign; they are associated with an increase in the risk of reoperation, increased hospitalization duration,[5] and can extend the duration off anticoagulation.[6,7] However, most important is their association with serious device infection.[8–14] A clinically significant hematoma (CSH), defined as a hematoma that required reoperation or resulted in prolongation of hospitalization or required interruption of oral anticoagulation, was associated with an >7-fold increase in the subsequent risk of serious device infection in BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial; BC-1).[8] If reintervention is required, the chance of infection is increased more than 15-fold.[9,10] Device hematomas are also associated with an increase in mortality as observed in population-based studies.[5] In an effort to prevent CSHs, carefully considered periprocedural use of oral anticoagulant and antiplatelet management is of significant importance.[15]

The BC-1 trial demonstrated 80% fewer device pocket hematomas when surgery was performed without interruption of warfarin, compared with warfarin-treated patients who had their anticoagulation interrupted and received heparin bridging (3.5% versus 16%, respectively).[1] BRUISE CONTROL-2 (BC-2)[16] subsequently evaluated the use of direct oral anticoagulants (DOACs) in patients with atrial fibrillation undergoing device surgery. The trial was terminated early due to futility, with no significant difference in CSH observed between the continued DOAC arm (2.1%; 95% CI, 0.9%–4.3%) and the patients in the interrupted DOAC arm (2.1%; 95% CI, 0.9%–4.3%; *P*=0.97).

In this current substudy, using patient-level data from the BC-1 and BC-2 trials, we evaluated the effect of concommitant antiplatelet use on CSH, and also sought to understand the relative risk of wound hematoma in patients treated with DOAC versus continued warfarin.

METHODS

Study Design

Details of BC-1 (URL: https://www.clinicaltrials.gov. Unique identifier: NCT00800137) and BC-2 (URL: https://www.clinicaltrials.gov. Unique identifier: NCT01675076) studies have been previously described.[1,16] This substudy included all patients who were randomized in BC-1 and BC-2. Both were multicenter single-blind randomized controlled trials. Institutional Review Board approval was obtained, and subjects in BC-1 and BC-2 gave informed consent. The data that support the findings of this study are available from the corresponding author on reasonable request.

Patients

The study included 1343 patients: 681 patients from BC-1 and 662 patients from BC-2 (Figure 1). BC-1 enrolled patients with an annual predicted risk of thromboembolism of 5% or more, who were taking warfarin and were planned for elective cardiac implantable device surgery. BC-2 enrolled patients with nonrheumatic atrial fibrillation and CHA_2DS_2-VASc score ≥2, treated with a DOAC and who were planned for elective cardiac implantable device surgery.

Study Procedures

BC-1 randomly assigned patients to continued warfarin treatment versus interrupted warfarin with bridging heparin or low molecular weight heparin. For patients in the continued warfarin arm, the international normalized ratio on the day of surgery was targeted to be 3.0 or lower, except for patients with one or more mechanical valves, for whom an international normalized ratio of 3.5 or less was permitted. Patients in the heparin bridging group discontinued warfarin 5 days before the procedure and started receiving full therapeutic doses of low molecular weight heparin or intravenous heparin 3 days before the procedure. The last dose of low molecular weight heparin was given the morning of the day before the procedure, and intravenous heparin was stopped at least 4 hours before surgery. Both were restarted 24 hours post procedure. Clopidogrel was stopped for 5 days before surgery in patients who had undergone implantation of a bare-metal stent more than 1 year previously. Clopidogrel was continued in patients with more recently implanted bare-metal stents and in patients with drug-eluting stents. The timing of reinitiation of clopidogrel therapy after device surgery was at the physician's discretion. Patients who were on aspirin continued without interruption.

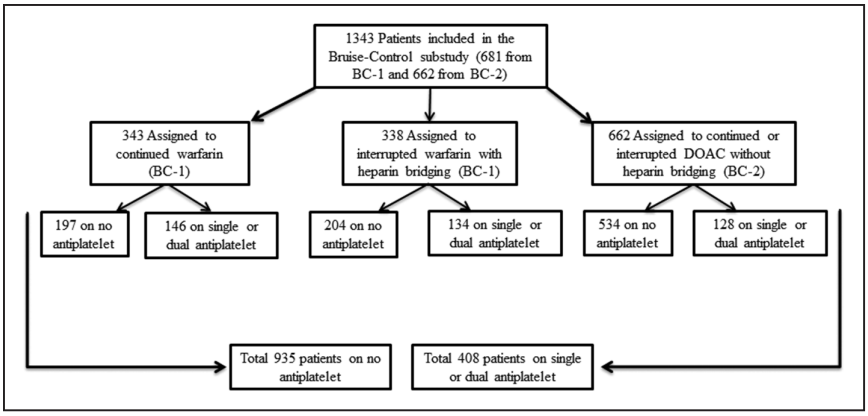

Figure 1. Flowchart of study patients included in the BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial; BC) combined analysis based on presence or absence of single or dual antiplatelet medication. DOAC indicates direct oral anticoagulant.

BC-2 randomized patients to continued versus interrupted oral DOAC. In the continued arm, all patients continued their DOAC throughout the surgical period, and took their morning dose before 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 the 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. Aspirin was continued in all patients with an indication for concomitant aspirin and DOAC therapy; other antiplatelet drugs were managed at the physician's discretion.

Outcome Measures

The primary outcome in BC-1 and BC-2 was CSH defined as a hematoma that required reoperation or resulted in prolongation of hospitalization or required interruption of oral anticoagulation. In both studies, 2 patient-care teams were identified at each center. One team had knowledge of the treatment assignment and was responsible for device implantation but was not involved in the follow-up evaluation or management of a CSH. The second team, which had no knowledge of the treatment assignment, was responsible for monitoring the wound during the initial hospitalization, at 1 to 2 weeks of follow-up, during any subsequent visits, and for diagnosing and making all decisions about the management of device pocket hematomas. Patients with CSH were followed until resolution.

Statistical Analysis

Patients were stratified according to presence of an antiplatelet. Patients who had clopidogrel withheld for >5 days and were not on aspirin were not included in the antiplatelet group. Baseline demographics and procedural characteristics were summarized as means and SD and frequencies with percentage. The continuous variables were compared by *t* test or Wilcoxon rank-sum test, and the categorical variables were compared by χ^2or fisher exact test. Primary and secondary outcomes were compared between treatment arms using the χ^2 test or fisher exact test. All outcomes were analyzed by intention to treat and included all randomized patients. A multivariable analysis for prespecified predictors of CSH was performed, and included BC-1/BC-2 study group, age, sex, de novo versus non-denovo surgery, body mass index, presence of diabetes mellitus, hypertension, duration of surgery, and presence of any antiplatelet agent. Variables with a *P* value of <0.05 were considered significant and retained in the final model. Analyses were conducted using SAS software, version 9·4 (SAS Institute). A data and safety monitoring board oversaw both BC-1 and BC-2 studies.

RESULTS

Of the 1343 patients included in the study (681 from BC-1 and 662 from BC-2), 408 patients (30.4%) were identified as being on at least one antiplatelet medication at the time of device surgery, and 935 patients were not (69.6%; Table 1). Of the patients on antiplatelet medication, 383/408 (93.9%) were on aspirin, 50/408 (12.3%) were on clopidogrel, and 25/408 (6.1%) were on both. There was no other type of antiplatelet drug used. Compared with patients without antiplatelet therapy, patients who were on an antiplatelet were younger (70.9±10 years versus 73.5±9.4 years), more likely to be male, have a diagnosis of cardiomyopathy, prior myocardial infarction, and be on a statin or a β-blocker (Table 1).

Operative details are presented in Table 2. Patients on antiplatelet medication were less likely to have device generator change only or de novo pacemaker implantation, but more likely to have de novo implantable cardioverter-defibrillator implantation. The duration of the procedure was longer in patients on antiplatelet medication, median 50 minutes (interquartile range, 30–80.5 minutes) compared with a median 41 minutes (interquartile range, 26–66 minutes) if no antiplatelet was present (*P*<0.001). Sandbag application postoperatively was more likely to occur if the patient was on an antiplatelet (9.3% versus 4.9%, *P*=0.003).

Outcomes

The primary outcome of CSH occurred in 40/408 (9.8%) patients on an antiplatelet as compared to 40/935 (4.3%) who were not on an antiplatelet (*P*<0.001; Table 3). This was driven by significantly more hematomas requiring reoperation (2% versus 0.6%) and hematomas requiring interruption of oral anticoagulation (OAC; 9.1% versus 3.9%). In patients who were on dual antiplatelet therapy (DAPT), development of a CSH occurred in 2/25

Table 1. Baseline Characteristics

	No Antiplatelet (N=935)	Single/Dual Antiplatelet (N=408)	*P* Value
Age, y	73.5±9.4	70.9±10.0	<0.001
Female sex	292 (31.2%)	77 (18.9%)	<0.001
Body mass index, kg/m²*	28.4±5.7	28.9±5.7	0.061
Medical history			
Stroke	132 (14.1%)	61 (15.0%)	0.689
Transient ischemic attack	113 (12.1%)	63 (15.4%)	0.094
Peripheral embolus	25 (2.7%)	12 (2.9%)	0.783
Hypertension	685 (73.3%)	293 (71.8%)	0.583
Diabetes mellitus	320 (34.2%)	168 (41.2%)	0.015
Cardiomyopathy	474 (50.7%)	292 (71.6%)	<0.001
Prior myocardial infarction	257 (27.5%)	231 (56.6%)	<0.001
CHA_2DS_2-VASc score	3.9±1.5	4.2±1.7	0.001
Anticoagulant			
Dabigatran 110 mg twice daily	94 (10.1%)	30 (7.4%)	<0.001
Dabigatran 150 mg twice daily	70 (7.5%)	10 (2.5%)	
Rivaroxaban 15 mg once daily	44 (4.7%)	11 (2.7%)	<0.001
Rivaroxaban 20 mg once daily	130 (13.9%)	27 (6.6%)	
Apixaban 2·5 mg twice daily	50 (5.4%)	11 (2.7%)	<0.001
Apixaban 5 mg twice daily	146 (15.6%)	39 (9.6%)	
Warfarin	401 (42.9%)	280 (68.6%)	<0.001
Perioperative management†			
Bridging heparin (during warfarin interruption)	204 (21.8%)	134 (32.8%)	<0.001
Continued warfarin	197 (21.1%)	146 (35.8%)	<0.001
Direct oral anticoagulant (continued or interrupted without heparin bridging)	534 (57.1%)	128 (31.4%)	<0.001
Other medications			
Aspirin	Not applicable	383 (93.9%)	…
Clopidogrel continued	Not applicable	50 (12.3%)	…
Clopidogrel stopped ≥5 days before surgery	7 (0.8%)	3 (0.8%)	1.000
Statin	620 (66.3%)	335 (82.1%)	<0.001
β-Blocker	646 (69.1%)	331 (81.1%)	<0.001

Date are n (%), mean (SD) or n/N (%). BC indicates BRUISE CONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial).

*Variable only available for the BC-2 patients.

†Differing perioperative anticoagulation strategies according to BC-1 or BC-2.

(8%) as compared with 38/383 (9.9%) who were on a single antiplatelet agent (*P*=1.000). For secondary outcomes, there were more non-CSHs (7% versus 2.3%, *P*=0.010) and unscheduled outpatient visits for wound assessment (15.4% versus 7.5%, *P*<0.001) if the patient was on an antiplatelet at the time of device surgery.

In multivariable analysis adjusting for antiplatelet use, there was no difference in CSH between interrupted or continued DOAC versus continued warfarin (odds ratio [OR], 0.858; 95% CI, 0.375–1.963; *P*=0.7174; Figure 2). Antiplatelet agent use in addition to continued or interrupted OAC was a significant predictor of CSH (OR, 1.965; 95% CI, 1.202–3.213; *P*=0.0071). Other significant predictors of CSH development included a heparin bridging strategy versus continued warfarin (OR, 6.32; 95% CI, 3.212–12.434; *P*<0.0001), and a longer procedure duration (OR, 1.005; 95% CI, 1–1.01; *P*=0.0418). The presence of diabetes mellitus was protective against CSH (OR, 0.554; 95% CI, 0.327–0.941; *P*=0.0288).

DISCUSSION

In this combined analysis of 2 large randomized trials, BC-1 and BC-2, the presence of antiplatelet

Table 2. Cardiac Implantable Device Therapy Operative Details

	No Antiplatelet (N=912)	Single/Dual Antiplatelet (N=396)	*P* Value
New implant of a pacemaker	273 (29.9%)	68 (17.2%)	<0.001
Single	127 (13.9%)	29 (7.3%)	<0.001
Dual	125 (13.7%)	38 (9.6%)	0.039
Cardiac resynchronization	21 (2.3%)	1 (0.3%)	0.008
New implant of an implantable cardioverter-defibrillator	180 (19.7%)	135 (34.1%)	<0.001
Single	77 (8.4%)	65 (16.4%)	<0.001
Dual	37 (4.1%)	24 (6.1%)	0.114
Cardiac resynchronization	66 (7.2%)	46 (11.6%)	0.009
Device replacement or revision	459 (50.3%)	193 (48.7%)	0.597
Device generator change only	177 (19.4%)	52 (13.1%)	0.006
Device generator change with additional lead*	121 (13.3%)	56 (14.1%)	0.671
Other	161 (17.7%)	85 (21.5%)	0.105
Details of surgery			
Duration of procedure (minutes) median (IQR)	41 (26–66)	50 (30–80.5)	<0.001
Venous-access guidance			
Peripheral venogram	215 (23.6%)	109 (27.5%)	0.278
Ultrasonography	22 (2.4%)	4 (1.0%)	0.082
Intrapocket administration of prohemostatic agent	32 (3.5%)	15 (3.8%)	0.806
Pressure dressing applied postoperatively	559 (61.3%)	232 (58.6%)	0.357
Sandbag applied postoperatively	45 (4.9%)	37 (9.3%)	0.003

Data are n (%), median (IQR), mean (SD) or n/N (%). IQR indicates interquartile range.
*Variable was only available for BC-2 patients.

Table 3. Primary and Secondary Outcomes

	No Antiplatelet (N=935)	Single/Dual Antiplatelet (N=408)	*P* Value
Primary outcome			
Clinically significant hematoma	40 (4.3%)	40 (9.8%)	<0.001
Components of the primary outcome			
Hematoma prolonged hospitalization	13 (1.4%)	10 (2.5%)	0.168
Hematoma requiring interruption of anticoagulation	36 (3.9%)	37 (9.1%)	<0.001
Hematoma requiring reoperation	6 (0.6%)	8 (2.0%)	0.039
Secondary outcomes			
Non clinically significant hematoma*	12 (2.3%)	9 (7.0%)	0.010
Any hematoma*	22 (4.1%)	12 (9.4%)	0.016
All-cause mortality	5 (0.5%)	2 (0.5%)	1.000
Pneumothorax	3 (0.3%)	1 (0.3%)	1.000
Hemothorax	0	0	…
Cardiac tamponade	1 (0.1%)	1 (0.3%)	0.516
Significant pericardial effusion	1 (0.1%)	0	1.000
Stroke	2 (0.2%)	2 (0.5%)	0.589
Transient ischemic attack	1 (0.1%)	0	1.000
Non-CNS systemic embolism	0	0	…
Myocardial infarction	0	1 (0.3%)	0.304
Deep vein thrombosis or pulmonary embolism	0	0	…
Superficial wound infection	4 (0.4%)	1 (0.3%)	1.000
Device system infection	4 (0.4%)	5 (1.2%)	0.141
Unscheduled out–patient visit	70 (7.5%)	63 (15.4%)	<0.001

Data are n/N (%). CNS indicates central nervous system.
*Variables only available for BC-2 patients.

medication (combined with anticoagulation) was a highly significant predictor, associated with a 2-fold increase in the risk of CSH. The presence of an antiplatelet agent also significantly increased the number of unscheduled outpatient visits for wound assements. Longer procedure duration was predictive of CSH as was a heparin bridging strategy as compared with continued warfarin even when accounting for the presence of an antiplatelet. Importantly, we found no difference in the frequency of CSH between a strategy of warfarin continuation versus a strategy of interrupted or continued DOAC at the time of device surgery. This is the first large study to compare use of a DOAC versus warfarin continuation at the time of device surgery.

Antiplatelet use has not received the same focus as OAC use at the time of device surgery. This may be in part due to older studies that did not find a significantly increased risk of hematoma in the setting of aspirin alone. Previous trials examined the risk of hematoma with antiplatelet use in nonanticoagulated patients.[2,17,18] Wiegand et al[17] reported in a retrospective review of 3164 patients (40.3% on aspirin) undergoing device surgery, that there was no increased risk of hematoma when the patient was on aspirin alone. In a prospective study, Kutinsky et al[18] found that clopidogrel use (most frequently in combination with aspirin), and not aspirin alone, was associated with a 2.3-fold increased risk of hematoma.[18] This risk was reduced in patients whose clopidogrel was held greater than 4 days before the procedure. Increased bleeding with DAPT was also reported by Tompkins et al[2] who retrospectively analyzed 1388 patients undergoing device implantation. The bleeding risk was not significantly higher in patients taking aspirin alone as compared with no antiplatelet medication (3.9% versus 1.6%; *P*=0.078), but significantly increased with a combination of aspirin and clop-

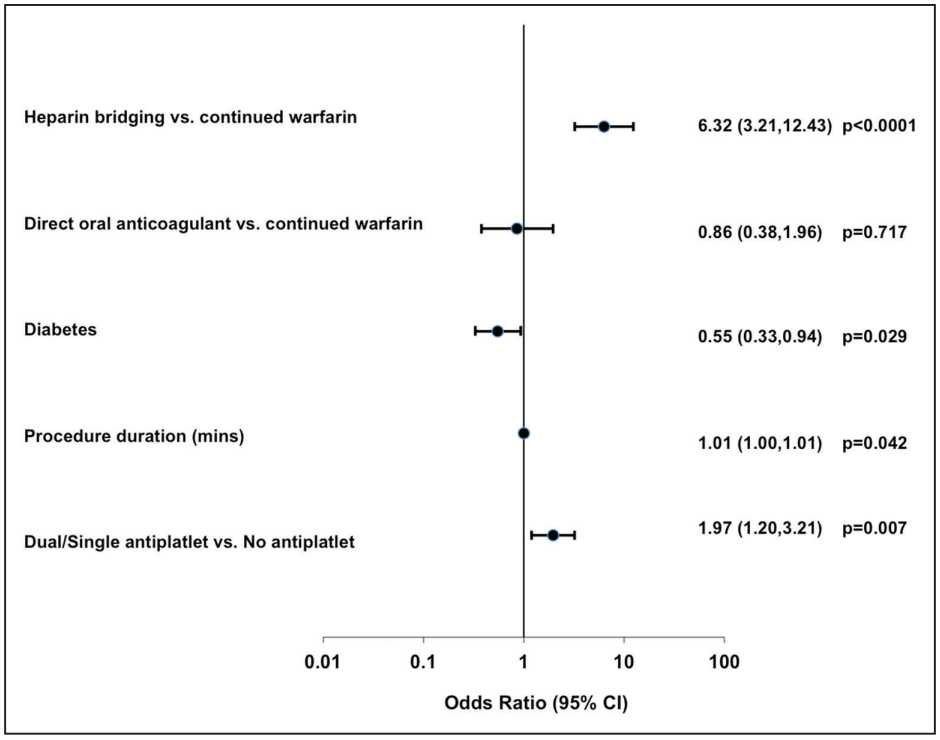

Figure 2. Multivariable analysis: predictors of clinically significant hematoma. Variables entered into multivariable analysis model were: BC-1/BC-2 (BRUISE CONTROL [Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial]) study group (heparin bridging, continued warfarin, direct oral anticoagulant), age, sex, denovo vs non-denovo surgery, body mass index (kg/m^2), diabetes mellitus, hypertension, duration of surgery, dual/single antiplatelet agent vs no antiplatelet agent. Only variables that remained with $P<0.05$ were retained in the final model.

idogrel (7.2% versus 1.6%; $P=0.004$).[2] A meta-analysis that included studies of varying antiplatelet and OAC bridging strategies reinforced the findings of increased bleeding with DAPT (OR, 5.0; 95% CI, 3.0–8.3) but not with aspirin alone (OR, 1.5; 95% CI, 0.9–2.3).[19]

There are likely 2 main reasons for the contrast between our finding that concomitant single antiplatelet use led to a doubling of CSH and prior data suggesting no association. First, and most importantly all prior work examined antiplatelets alone; that is, without additional OAC use. There is no data on the risk associated with combined antiplatelet and OAC use during device surgery. Second, prior studies evaluating risk factors for pocket hematoma did not use the same objective definition of CSH and were not in the context of randomized trials.[2,5,17,18,20] We did not find additional bleeding risk with DAPT in context of OAC (triple therapy), as demonstrated in other clinical situations,[21,22] however, this may be due to the very small number of patients on triple therapy in our study.

Similar to our findings, prior studies have found that longer procedure duration has been associated with an increased risk for hematoma.[2] Whether longer procedure duration creates the increased risk or increased pocket oozing leads to prolonged efforts to achieve hemostasis is uncertain. Other reported risk factors for pocket hematoma include increased age,[5,20,23] congestive heart failure and renal dysfunction,[5,20] subpectoral ICD placement,[17,20] implant technique (increased risk with subclavian or axillary as compared to cephalic approach),[18] biventricular device implantation,[20] permanent versus paroxysmal atrial fibrillation, and higher stroke risk profile.[20] Conversely, the presence of diabetes mellitus was unexpectedly associated with a reduced risk of CSH in our study. Active measures to prevent CSH have included judicious use of electrocautery, intrapocket administration of prohemostatic agents,[24] and application of pressure dressings or sandbags; however none of these have been shown to reduce CSH. Although measures to reduce CSH were employed by operators in BC-1 and BC-2, including intrapocket administration of prohemostatic agents, and pressure dressings or sandbags applied postoperatively these were not associated with reduced CSH frequency.

The potential risk-benefit of interrupting antiplatelet therapy should consistently be estimated at the time of device surgery. It is noteworthy that in a significant proportion of patients, there may actually be no guideline indication for aspirin use in the setting of an OAC.[25] The ideal duration of DAPT after stent implantation remains inconclusive, mostly because the activation of platelets with resultant thrombosis occurs not only in response to implantation of a stent, but also as part of the process of atherosclerosis.[26] As a result, in the setting of concomitant OAC use in stable, event-free patients post stenting, discontinuation of all antiplatelet agents at 1 year is encouraged based on studies demonstrating that OACs alone are superior to aspirin post acute coronary syndrome.[27,28] Wherever possible, consideration

should be made for delaying elective device surgery until safe to stop antiplatelet medications, or temporarily interrupting antiplatelet agents that are not clearly indicated in the setting of chronic OAC use.

Limitations

The lack of operator blinding may have led to an imbalance of perioperative factors such as intrapocket prohemostatic agent, pressure dressing, and sandbag use; however, previously published BC-1 and BC-2 analyses did not find an association between these factors and the risk of CSH. This study was not powered to compare the effect of dual versus single antiplatelet therapy. Although BC-1 and BC-2 were randomized clinical trials, this study was of an observational design where causality may not be inferred.

Conclusions

In this study of combined BC-1 and BC-2 patients, concomitant antiplatelet therapy doubled the risk of CSH. No difference in CSH was found between DOAC versus continued warfarin. In anticoagulated patients undergoing elective or semi-urgent device surgery, the patient specific benefit/risk of holding an antiplatelet should be carefully considered. As such, carefully considered antiplatelet interruption should be part of the perioperative management strategy, with consideration for delaying elective device surgery until safe to stop the antiplatelet.

ARTICLE INFORMATION

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*A list of all BRUISE CONTROL Investigators is given in the Data Supplement.

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Disclosures

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