



Concomitant anti-platelet therapy in warfarin-treated patients undergoing cardiac rhythm device implantation: A secondary analysis of the BRUISE CONTROL trial

Vidal Essebag^{a,b,*}, Ahmed AlTurki^a, Riccardo Proietti^c, Jeff S. Healey^d, George A. Wells^e, Atul Verma^f, Andrew D. Krahn^g, Christopher S. Simpson^h, Felix Ayala-Paredesⁱ, Benoit Coutu^j, Richard Leather^k, Kamran Ahmad^l, Satish Toal^m, John Sappⁿ, Marcio Sturmer^b, Katherine Kavanagh^o, Eugene Crystal^p, Tiago L.L. Leiria^q, Colette Seifer^r, Claus Rinne^s, David Birnie^e, for the BRUISE CONTROL Investigators

^a McGill University Health Centre, Montreal, Quebec, Canada

^b Hôpital Sacré-Coeur de Montréal, Montreal, Quebec, Canada

^c Department of Cardiac, Thoracic and Vascular Sciences, University of Padua, Padua, Italy

^d Population Health Research Institute, Hamilton, Ontario, Canada

^e University of Ottawa Heart Institute, Ottawa, Ontario, Canada

^f Southlake Regional Health Centre, Newmarket, Ontario, Canada

^g Division of Cardiology, University of British Columbia, Vancouver, Canada

^h Queen's University and Kingston General Hospital, Kingston, Ontario, Canada

ⁱ Université de Sherbrooke, Sherbrooke, Quebec, Canada

^j Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada

^k Royal Jubilee Hospital, Victoria, British Columbia, Canada

^l St Michael's Hospital, Toronto, Ontario, Canada

^m New Brunswick Heart Center, St John, New Brunswick, Canada

ⁿ Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada

^o Libin Cardiovascular Institute of Alberta, Calgary, Alberta, Canada

^p Sunnybrook Health Science Centre, Toronto, Ontario, Canada

^q Instituto de Cardiologia Fundação Universitaria Cardiologia, Porto Alegre, Brazil

^r University of Manitoba, Winnipeg, Manitoba, Canada

^s St Mary's General Hospital, Kitchener, Ontario, Canada

ARTICLE INFO

Article history:

Received 22 January 2019

Received in revised form 3 March 2019

Accepted 23 April 2019

Available online 26 April 2019

Keywords:

Anti-platelet

Aspirin

Pocket hematoma

Cardiac implantable electronic device

ABSTRACT

Background: Anti-platelet therapy is commonly used in patients receiving oral anticoagulation and may increase bleeding risk among patients undergoing cardiac implantable electronic device (CIED) surgery. We sought to determine the proportion of anticoagulated patients who are concomitantly receiving anti-platelet therapy, the associated risk of clinically significant hematoma (CSH), and the proportion of patients in whom anti-platelet usage is guideline-indicated.

Methods: A secondary analysis of the Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL). Patients who were receiving warfarin, had an annual predicted risk of thromboembolism of $\geq 5\%$ and were scheduled to undergo non-emergent CIED surgery were randomized to continued warfarin versus heparin bridging. In the current analysis, patients were divided into those receiving anti-platelet therapy and those not receiving anti-platelet therapy. The incidence of CSH was compared in both groups. The proportion of patients on potentially inappropriate and potentially interruptible antiplatelet therapy was estimated.

Results: All 681 patients enrolled in BRUISE CONTROL were included, of whom 280 received and 401 did not receive anti-platelet therapy. Anti-platelet therapy increased the risk of CSH (relative risk, 1.72; 95% confidence interval (CI), 1.09 to 2.72; $P = 0.02$). Of the 280 patients receiving anti-platelet therapy, 97 (34.6%) had no guideline indication for concomitant anti-platelet therapy and an additional 146 (52.1%) were on anti-platelet therapy that could potentially have been interrupted around CIED surgery.

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; CIED, cardiovascular implantable electronic device; CSH, clinically significant hematoma; DAPT, dual anti-platelet therapy; INR, international normalized ratio; MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; RR, relative risk.

* Corresponding author at: McGill University Health Centre, 1650 Cedar Ave, Room E5-200, Montreal, QC H3G 1A4, Canada.

E-mail address: vidal.essebag@mcgill.ca (V. Essebag).

Conclusions: Concomitant anti-platelet therapy in patients receiving anticoagulation is associated with a significant risk of CSH. The majority of concomitant anti-platelet therapy is potentially inappropriate or interruptible.

Trial registration: clinicaltrials.gov Identifier: (NCT00800137)

© 2019 Elsevier B.V. All rights reserved.

1. Background

Cardiovascular implantable electronic devices (CIED) are frequently implanted worldwide [1]. The development of a device pocket hematoma is a feared complication of CIED surgery occurring in 1% to 16% of patients depending on antithrombotic use [2]. Most importantly, clinically significant pocket hematomas (CSH) have been associated with an almost 8-fold increase in the risk of serious device system infection [3]. Device hematomas are costly to the health care system [4,5], can prolong hospitalization [6,7] and in some patients require surgical evacuation [8]. Therefore, strategies to reduce the development of pocket hematoma should be prioritized.

A significant proportion, up to 35%, of patients undergoing CIED implantation is receiving anticoagulation [9,10]. Heparin use at the time of implantation is associated with a 16% to 20% risk of pocket hematoma [7,11–13]. In the Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL), among patients receiving chronic warfarin therapy who underwent CIED implantation, continued warfarin was associated with a significant reduction in the incidence of pocket hematoma compared to a bridging strategy with heparin [11]. The use of antiplatelet therapy has also been associated with an increase in pocket hematoma [12].

In patients receiving anticoagulation therapy, the use of concurrent antiplatelet agents may be potentially inappropriate [14] and represents a group of patients who may develop preventable bleeding episodes [15] including CSH. Current guidelines regarding oral anticoagulation (OAC) and antiplatelet therapy are summarized in Table 1.

Discerning the proportion of potentially preventable episodes of CSH is of clinical interest. Therefore, we conducted an analysis of the BRUISE CONTROL trial (that enrolled patients between October 2009 and February 2013) with the primary aim of ascertaining the proportion of patients who were on potentially inappropriate concomitant antiplatelet therapy (according to current guidelines) [16–18] or were on potentially interruptible antiplatelet therapy.

2. Methods

2.1. Study design and participants

The BRUISE CONTROL trial (NCT00800137) was a multicenter single-blind randomized controlled trial designed to determine whether a strategy of continued warfarin, compared to bridging with heparin, at the time of pacemaker or defibrillator surgery reduced the incidence of CSH in patients with moderate to high risk of thromboembolic events. The design and primary results of the BRUISE CONTROL trial have been previously described [11,19]. The Ethics Committee of each of the participating institutions approved the protocol and all patients gave written, informed consent. The BRUISE CONTROL trial randomized 681 eligible patients in a 1:1 ratio to continued warfarin treatment or bridging therapy with heparin. To be eligible for inclusion, patients had an annual predicted risk of thromboembolism of 5% or more, were receiving warfarin and were scheduled to undergo non-emergent device surgery (implantation of a new device, pulse-generator change, lead replacement, or pocket revision).

2.2. Antithrombotic use

Patients in the continued-warfarin group, had an international normalized ratio (INR) target of 3.0 or lower on the day of the procedure. For patients with a mechanical valve, an INR of 3.5 or less was permitted. In the heparin-bridging group, warfarin was discontinued 5 days before the procedure and patients were started on full therapeutic doses of low-

Table 1
Guideline recommendations on antiplatelet therapy in patients with atrial fibrillation in need of oral anticoagulation.

	European Society of Cardiology guidelines for the management of AF 2016 [16]	Canadian Cardiovascular Society guidelines for the management of AF 2016 [18]	American College Cardiology/American Heart Association guidelines for the management of AF 2014 [27]
After ACS- low bleeding risk	OAC monotherapy after 12 months of dual therapy with OAC and antiplatelet (including 6 months of OAC and DAPT)	OAC monotherapy after 12 months of dual therapy with OAC and clopidogrel (includes three months of DAPT initially if underwent PCI). No distinction between low and high bleeding risk ^g	No recommendation regarding antithrombotic use in CAD and AF
After ACS- high bleeding risk	OAC monotherapy after 12 months of dual therapy with OAC and antiplatelet (including 6 months of OAC and DAPT)	OAC monotherapy after 12 months of dual therapy with OAC and clopidogrel. No distinction between low and high bleeding risk ^g	No recommendation regarding antithrombotic use in CAD and AF
After elective PCI- low bleeding risk	OAC monotherapy after 12 months of dual therapy with OAC and antiplatelet (including 6 months of OAC and DAPT)	OAC monotherapy after 12 months of dual therapy with OAC and clopidogrel. No distinction between low and high bleeding risk ^g	No recommendation regarding antithrombotic use in CAD and AF
After elective PCI - high bleeding risk	OAC monotherapy after 6 months of dual therapy with OAC and antiplatelet (including 1 month of OAC and DAPT)		No recommendation regarding antithrombotic use in CAD and AF
Stable CAD	OAC monotherapy	OAC monotherapy	No recommendation regarding antithrombotic use in CAD and AF
Peripheral arterial disease	OAC monotherapy ^a	OAC monotherapy	No recommendation regarding antithrombotic use in patients with AF though OAC monotherapy not recommended for PAD alone ^d
Cerebrovascular disease	OAC monotherapy	OAC monotherapy ^c	OAC monotherapy (unless ACS or recent stent) ^e
Mechanical prosthetic valves	VKA+ aspirin in patients not at high bleeding risk ^b	No recommendation regarding antithrombotic use in mechanical valve and AF	VKA + aspirin in all mechanical valves. Aspirin is reasonable in bioprosthetic valves ^f

^a From the ESC 2017 PAD guidelines [24].

^b From the EHRA antithrombotic therapy in atrial fibrillation associated with valvular heart disease consensus document [17].

^c From the Canadian stroke best practice recommendations 2017 [23].

^d From the ACC/AHA PAD guidelines 2016 [32].

^e From the AHA/ASA 2014 stroke guidelines [25].

^f From the ACC/AHA VHD guideline 2017 [20].

^g The CCS 2018 antiplatelet guideline suggests that patients with ACS/post PCI who are at low risk of bleeding and who have high risk clinical and angiographic features (diabetes mellitus, prior ACS, chronic renal dysfunction (creatinine clearance <60 mL/min), multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold implantation) be continued on aspirin in addition to the OAC (weak recommendation; low quality evidence) [28].

molecular-weight heparin or intravenous heparin 3 days before the procedure. Warfarin was resumed at next scheduled dose following the procedure and heparin bridging reinitiated 24 h post procedure and continued until therapeutic INR achieved.

2.3. Anti-platelet management

Selection of baseline anti-platelet therapy was at the discretion of treating physicians and was not dictated by the Bruise Control protocol [11]. However, the protocol suggested that indicated aspirin should be continued peri-operatively. Furthermore, the protocol recommended that in patients who had undergone implantation of a bare-metal stent >1 year prior, clopidogrel should be stopped for 5 days before the procedure. In patients with more recently implanted bare-metal stents and in patients with drug-eluting stents, clopidogrel was continued [11].

2.4. Definitions

Potentially inappropriate concomitant antiplatelet therapy was defined as the absence of a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within the preceding 12 months (or with date unspecified), as well as the absence of any mechanical valves [16–18,20]. Potentially interruptible (in the perioperative period) concomitant antiplatelet therapy was defined as the absence PCI or CABG in the preceding 12 months. Patients taking clopidogrel for a coronary stent or acute coronary syndrome (ACS) were not considered potentially inappropriate or potentially interruptible. Patients were defined as being on continued clopidogrel if clopidogrel was not interrupted ≥ 5 days prior to surgery.

2.5. Blinding and study outcomes

Due to differences in the route of delivery, blinding was not possible and thus patients were aware of the assigned study treatment. All potential CSH were adjudicated by a blinded team of evaluators. Patients in whom a CSH developed were followed until CSH resolution; this encompassed monitoring for any additional complications related to the hematoma including infection.

The primary outcome was clinically significant device-pocket hematoma, defined as a hematoma requiring further surgery, resulting in prolongation of hospitalization (extended hospitalization or rehospitalization for at least 24 h), or requiring interruption of oral anticoagulation therapy.

2.6. Statistical analysis

Patients were divided into two groups depending on whether the patient was receiving antiplatelet medication at the time of surgery (aspirin and/or continued clopidogrel). Descriptive statistics were reported for baseline patient characteristics and details related to CIED surgery. Continuous variables were presented as mean $\pm$ SD for normally distributed variables and medians and interquartile ranges (IQR) for non-normally distributed variables. Categorical variables were presented as frequencies with percentages. The primary outcome was the occurrence of clinically significant device-pocket hematoma as

previously defined. Subgroup analysis was performed according to randomization allocation to either continued warfarin or bridging strategy. Relative risk (RR) and 95% confidence intervals (CI) were calculated for comparisons of outcomes between patient receiving anti-platelet therapy and those not receiving anti-platelet therapy. The proportion of patients on potentially inappropriate antiplatelet therapy and the proportion of potentially preventable CSH were calculated.

3. Results

All 681 patients enrolled in the BRUISE CONTROL trial were included in this study; 280 and 401 patients were on and not on anti-platelet therapy at the time of device surgery respectively (Supplementary Fig. 1).

3.1. Patient characteristics

Indications for anticoagulation were similar between the two groups (anti-platelet versus no anti-platelet therapy) with atrial fibrillation being the most common indication. Patients on anti-platelet therapy were more likely have history of myocardial infarction (MI), ischemic cardiomyopathy, PCI or CABG surgery compared to patients not receiving anti-platelet therapy. Baseline patient characteristics are summarized in Table 2. Operative details were similar between patients receiving anti-platelet therapy and those not receiving anti-platelet therapy and are summarized in Supplementary Table 1. Patients receiving anti-platelet therapy had longer procedure times and were more likely to have a sand-bag applied post-procedure.

3.2. Potentially inappropriate and potentially interruptible anti-platelet therapy

A total of 280 patients were receiving anti-platelet therapy concomitant with anticoagulation therapy. Most patients were receiving aspirin alone (250; 89.3%), while 18 (6.4%) were receiving dual anti-platelet therapy (DAPT) with aspirin and clopidogrel, and the remaining 12 (4.3%) were receiving clopidogrel alone. There were no patients receiving ticagrelor or prasugrel.

Regarding indications for anti-platelet therapy, 97 (34.6%) of the 280 patients had no current indication for (potentially inappropriate) concomitant anti-platelet therapy in the presence of ongoing OAC therapy

Table 2
Baseline patient characteristics.

Characteristics	Anti-platelet therapy N = 280	No anti-platelet N = 401
Continuous warfarin – no. (%)	146 (52.1%)	197 (49.1%)
Bridging – no. (%)	134 (47.9%)	204 (50.9%)
Demographics		
Age – yr	70.5 $\pm$ 10.2	72.4 $\pm$ 10.3
Male sex – no. (%)	222 (79.3%)	273 (68.1%)
Body mass index – kg/m ²	29.0 $\pm$ 6.0	27.9 $\pm$ 5.9
Past medical history		
Rheumatic heart disease – no. (%)	19 (6.8%)	39 (9.8%)
Embolic transient ischemic attack – no. (%)	54 (19.3%)	71 (17.7%)
Embolic stroke – no. (%)	48 (17.1%)	77 (19.2%)
Non – CNS embolus – no. (%)	9 (3.2%)	12 (3.0%)
Hypertension – no. (%)	200 (71.4%)	284 (70.8%)
Diabetes mellitus – no. (%)	117 (41.8%)	149 (37.2%)
Atrial fibrillation and/or atrial flutter – no. (%)	245 (87.5%)	358 (89.3%)
Myocardial infarction – no. (%)	157 (56.1%)	112 (27.9%)
Cardiomyopathy – no. (%)	211 (75.4%)	235 (58.6%)
Ischemic cardiomyopathy – no. (%)	167 (59.6%)	109 (27.2%)
Percutaneous coronary intervention – no. (%)	94 (33.6%)	42 (10.5%)
Percutaneous coronary intervention <1 year ago – no. (%)	15 (5.4%)	2 (0.5%)
Coronary artery bypass surgery – no. (%)	108 (38.6%)	75 (18.7%)
Coronary artery bypass surgery <1 year ago – no. (%)	7 (2.5%)	2 (0.5%)
Mechanical heart valve replacement – no. (%)	83 (29.6%)	120 (29.9%)
Mean CHADS ₂ score	3.0 $\pm$ 1.3	2.8 $\pm$ 1.3
Deep vein thrombosis or pulmonary embolus – no. (%)	17 (6.1%)	15 (3.7%)

No anti-platelet = not receiving aspirin or clopidogrel; no. = number; CNS = central nervous system;

(including 94 patients on aspirin alone, 1 patient receiving clopidogrel alone and 2 patients receiving DAPT). The majority of these patients had stable coronary artery disease including PCI or CABG greater than a year prior to the trial (Table 3). Another 146 (52.1%) of the 280 patients were on antiplatelet therapy that was potentially interruptible perioperatively. The remaining 37 (13.2%) of the 280 patients had an indication for antiplatelet therapy continuation perioperatively. The reasons to continue anti-platelet perioperatively were mainly due to PCI and CABG less than one year prior to CIED surgery.

3.3. Anti-platelet therapy and outcomes

The primary outcome of CSH occurred in 36 of 280 patients (12.9%) in the anti-platelet group as compared with 30 of 401 (7.5%) in the no anti-platelet group (RR, 1.72; 95% CI, 1.09 to 2.72; $P = 0.02$). This was primarily due to hematomas requiring interruption of anticoagulation (RR 1.82; 95% CI: 1.11, 2.97, $P = 0.02$). While there was a trend toward an increased risk of hematomas requiring hospitalization and hematomas requiring reoperation, this did not meet statistical significance (Table 4). There were no differences in the secondary outcomes. CSH occurred in 31 out of 243 (12.8%) patients on potentially inappropriate or potentially interruptible anti-platelet therapy compared to 35 out of 438 (8.0%) patients on appropriate therapy (not on anti-platelet or on appropriately continued anti-platelet therapy) ($P = 0.04$). Among the 30 patients receiving clopidogrel, of whom 18 were receiving aspirin as well (DAPT), the incidence of CSH was 13.3%.

3.4. CSH in patients receiving heparin bridging

In patients who were randomized to heparin bridging, the risk of CSH was higher in patients receiving anti-platelet therapy compared to those not receiving anti-platelet therapy (RR 1.76; 95% CI: 1.08, 2.88, $P = 0.02$). Patients with potentially inappropriate and potentially interruptible concomitant anti-platelet therapy had an incidence of CSH at 25.6% and 21.6% respectively. In contrast, those not on anti-platelet therapy had a lower incidence of CSH at 12.3% (Supplementary Table 2).

3.5. CSH in patients receiving continued warfarin

Overall, there were fewer CSH events in patients receiving warfarin. While there was a higher risk of CSH in patients receiving anti-platelet therapy compared to those not on anti-platelet therapy (RR 1.88; 95% CI: 0.61, 5.83, $P = 0.27$), this did not reach statistical significance. Patients with potentially inappropriate concomitant anti-platelet therapy had a CSH incidence of 3.7%, those with potentially interruptible antiplatelet therapy had a CSH incidence of 2.8% and patients not receiving anti-platelet therapy had an incidence of 2.8% (Supplementary Table 3).

4. Discussion

This study evaluates the outcomes associated with potentially inappropriate and potentially interruptible anti-platelet therapy in patients

who undergo CIED surgery through a sub-analysis of a randomized controlled trial. The main finding of this paper is that a significant proportion of the anti-platelet therapy received by patients who undergo CIED surgery is potentially not required (34.6% potentially inappropriate and another 52.1% potentially interruptible).

In those with atrial fibrillation who suffer an ACS or undergo an elective PCI, current guidelines recommend a combination of OAC and at least one antiplatelet for one year after the event, followed by antiplatelet interruption and OAC continuation [16,18]. This is due to a similar reduction in thromboembolic events but an increased risk of bleeding in anticoagulated patients who continue antiplatelet therapy [21,22]. Similarly, guidelines recommend OAC alone without antiplatelet therapy in patients with cerebrovascular and peripheral arterial disease who have an indication for OAC [23–25]. Aspirin is recommended for one year following coronary artery bypass grafting (CABG) [26] but data and guidance is lacking in patients receiving OAC. Combination of OAC and aspirin may also be recommended in patients with mechanical heart valves with low bleeding risk [16–18].

In the current analysis, the definition of concomitant anti-platelet therapy potentially inappropriate according to current guidelines was restrictive, in order to provide a conservative estimate of potentially inappropriate anti-platelet therapy. All patients with mechanical valves were excluded from the non-indicated category though there is much debate as to whether all these patients should receive concomitant anti-platelet therapy [16,27]. With regards to potentially interruptible anti-platelet therapy, all patients with CABG and PCI in the prior 12 months were excluded to provide a conservative estimate. However, current guidelines allow interruption of anti-platelet therapy 3–6 months after PCI [28]. Furthermore, the benefit of anti-platelet therapy after CABG in patients receiving OAC is unclear with most of the benefit occurring early [29]. Therefore, anti-platelet therapy is likely interruptible.

Inappropriate anti-platelet therapy is an important clinical problem due to the risk of bleeding. In the ORBIT-AF registry, which enrolled 10,126 patients with atrial fibrillation, of whom 7347 were receiving OAC, the combination of OAC and aspirin did not improve the outcomes of stroke and MI compared to OAC alone (MI 0.48% vs 0.38% and stroke 0.65% vs 0.42% respectively). However, the use of combination therapy was associated with a 50% increase in major bleeding. Around 40% of patients on combined therapy did not have an indication for concomitant aspirin therapy [30]. In a retrospective study of 948 patients with non-valvular atrial fibrillation that excluded patients with ACS, 430 patients were receiving OAC and concomitant aspirin. Of the 430 patients, at least 46% had no indication for concomitant anti-platelet therapy [31]. The highest rates of bleeding were seen in patients who received bridging with heparin and concomitant aspirin therapy; this emphasizes that in patients at the highest risk of bleeding, who are receiving anticoagulation and need concomitant anti-platelet therapy, it is much safer to continue warfarin than to bridge with heparin.

Medical encounters provide an opportunity for correction of medical errors, and invasive procedures are an opportunity to reexamine the need for anti-thrombotic therapy. As shown in Table 1, there are numerous recommendations from various guidelines recommending

Table 3
Indication for concomitant antiplatelet therapy.

Indication	Patients on aspirin N = 250	Patients on clopidogrel N = 12	Patients on aspirin and clopidogrel N = 18
Percutaneous coronary intervention <1 year ago ^a – no. (%)	43 (17.2%)	5 (41.7%)	12 (66.7%)
Percutaneous coronary intervention ≥1 year ago – no. (%)	28 (11.2%)	2 (16.7%)	4 (22.2%)
Coronary artery bypass surgery <1 year ago ^a – no. (%)	67 (26.8%)	3 (25.0%)	4 (22.2%)
Coronary artery bypass surgery ≥1 year ago – no. (%)	30 (12.0%)	1 (8.3%)	3 (16.7%)
Clopidogrel due to coronary stent no. (%)	N/A	6 (50.0%)	13 (72.2%)
Clopidogrel due to ACS no. (%)	N/A	4 (33.3%)	1 (5.6%)
Clopidogrel due to previous TIA/stroke no. (%)	N/A	4 (33.3%)	3 (16.7%)
Mechanical valve	80 (32.0%)	3 (25.0%)	0

^a Including those with date unspecified.

Table 4

Primary and secondary outcomes in patients receiving concomitant anti-platelet therapy compared to those not receiving anti-platelet therapy.

	Anti-platelet therapy N = 280	No anti-platelet N = 401	Relative risk	P-value
Primary outcome				
Clinically significant hematoma – no. (%)	36 (12.9%)	30 (7.5%)	1.72 (1.09,2.72)	0.021
Components of the primary outcome				
Hematoma prolonged hospitalization – no. (%)	10 (3.6%)	10 (2.5%)	1.43 (0.60,3.40)	0.415
Hematoma requiring interruption of anti-coagulation – no. (%)	33 (11.8%)	26 (6.5%)	1.82 (1.11,2.97)	0.017
Hematoma requiring re-operation – no. (%)	7 (2.5%)	4 (1.0%)	2.51 (0.74,8.48)	0.140
Secondary outcomes				
All-cause mortality – no. (%)	2 (0.7%)	2 (0.5%)		1.000
Transient ischemic attack – no. (%)	0	1 (0.3%)		1.000
Stroke – no. (%)	1 (0.4%)	1 (0.3%)		1.000
Superficial wound infection – no. (%)	1 (0.4%)	3 (0.8%)		0.647
Device system infection – no. (%)	5 (1.8%)	4 (1.0%)		0.499
Myocardial infarction – no. (%)	1 (0.4%)	0		0.411

discontinuation of anti-platelet therapy in patients receiving OAC. These pertain to patients with stable coronary artery disease (CAD), peripheral arterial disease and cerebrovascular disease [23,28,32]. Deprescribing is the act of stopping medications that a patient no longer needs or when the risks currently outweigh the benefits [33]. There has been a large movement toward deprescribing in the geriatric population receiving polypharmacy [34]. Several studies have documented the benefits of deprescribing [35]. We propose that concomitant anti-platelet therapy be considered for deprescribing in light of the recent evidence and guidelines that outline the unfavorable risk to benefit profile. In patients undergoing CIED surgery, concomitant anti-platelet therapy significantly increases the risk CSH, which is associated with prolonged hospitalization and infection [3]. Therefore, physicians should consider upcoming CIED surgery as an opportunity to reexamine anti-thrombotic regimens. In addition, utilizing the opportunity to deprescribe concomitant anti-platelet therapy may also prevent other long-term bleeding events. Given the numerous barriers to deprescribing such as limited knowledge, fear of withdrawal side effects and limited consulting time [33], simple solutions, such as reminders and prompts that have been shown to be useful in assisting physicians with deprescribing, should be considered [36,37].

Initiation of aspirin perioperatively has been shown to increase bleeding without reducing the thromboembolic risk [38]. The effects of potentially inappropriate aspirin therapy in patients undergoing surgical procedures was well delineated in the POISE 2 trial which randomized 10,000 patients who were undergoing non-cardiac surgery to receive aspirin or placebo. Patients were further subdivided according to whether they had not been taking aspirin before the study (initiation stratum) or if they were already on an aspirin regimen (continuation stratum). There was no difference in the composite score of death or MI between aspirin and placebo regardless of the stratum. However, major bleeding was more common in patients on aspirin [38].

The higher rate of bleeding in patients with an ongoing indication for aspirin therapy, namely PCI or CABG in the preceding year, is a cause for concern. Given current recommendations to interrupt anti-platelet therapy 6–12 weeks after PCI as well as data demonstrating that the majority of the benefit of continued anti-platelet therapy after CABG occurs very early, strong consideration should be given to interrupting anti-platelet therapy perioperatively in patients undergoing CIED surgery.

While the BRUISE CONTROL trial was designed and conducted according to best practice recommendations and the established standard of care at that time, current results highlight the prevalence of concomitant antiplatelet use in patients with stable CAD receiving OAC. In addition, potentially inappropriate concomitant anti-platelet therapy continues to be a prevalent problem [30,31,39] despite current guideline recommendations [23,25,27,28], which suggests that uptake of these guidelines remains sub-optimal. The evaluation of a patient referred for an interventional procedure such CIED surgery is a golden opportunity for all stakeholders, internists, cardiologists and electrophysiologists, to

reassess the indications for ongoing anti-platelet therapy as well the potential for interrupting anti-platelet therapy. While clinical trials like BRUISE CONTROL [11] and FinPAC [40] have shown the safety of continued warfarin during CIED surgery, concomitant anti-platelet therapy increases the risk of CSH.

4.1. Limitations

There are some noteworthy limitations of this analysis. The timing of patients' previous MI was unavailable. However, given the low proportion of PCI or CABG in the year prior to the procedure, which is the mainstay treatment for MI in enrolling institutions, most of these were likely remote infarctions. The trial was not powered to show a difference in bleeding associated antiplatelet therapy within the continued warfarin and bridging groups. However, the comparative risk of CSH in the anti-platelet group was statistically significant in the bridging group, which had a greater number of events.

5. Conclusions

The use of antiplatelet therapy in addition to OAC is common and may be avoided in many patients if current guidelines for antiplatelet therapy discontinuation in anticoagulated patients are followed. Deprescribing antiplatelet therapy may significantly reduce the risk of CSH in patients undergoing CIED surgery. Patients referred for elective CIED surgery should have careful review of antithrombotic therapy with attention to interrupting potentially inappropriate therapy in order to decrease risk of avoidable bleeding complications and risk of infection associated device pocket hematomas.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.04.066>.

Funding

Supported by an operating grant from the Canadian Institutes of Health Research (CIHR), a CIHR Clinician Scientist Award (Dr. Essebag), a Clinical Research Scholar Award (Dr. Essebag) from Fonds de recherche du Québec – Santé (FRQS), and an Innovations grant from the University of Ottawa Heart Institute Academic Medical Organization Alternate Funding Program (funded by the Ministry of Health of Ontario).

Disclosures

None.

Acknowledgements

We thank Leslie Carlin and Karen MacDonald for central study coordination and Keri O'Reilly for data entry. We thank staff at the UOHI

CVS Research Methods Center for database and statistical support/analysis: Lily Chen, My-Linh Tran, Jordan Bernick, and Liz Yetisir.

Author contributions

Drs Essebag and Birnie had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design

Essebag, AlTurki, Proietti, Birnie.

Acquisition, analysis, or interpretation of data

Essebag, AlTurki, Healey, Wells, Verma, Krahn, Simpson, Ayala-Paredes, Coutu, Leather, Ahmad, Toal, Sapp, Sturmer, Kavanagh, Crystal, Leiria, Seifer, Rinne, Birnie.

Drafting of the manuscript

Essebag, AlTurki.

Critical revision of the manuscript for important intellectual content

Healey, Wells, Verma, Krahn, Simpson, Ayala-Paredes, Coutu, Leather, Ahmad, Toal, Sapp, Sturmer, Kavanagh, Crystal, Leiria, Seifer, Rinne.

Statistical analysis

Essebag, AlTurki, Birnie.

Obtained funding

Essebag, Birnie.

Study supervision

Essebag, Birnie.

References

- [1] H.G. Mond, A. Proclemer, The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009—a World Society of Arrhythmia's project, *Pacing Clin. Electrophysiol.* 34 (8) (2011) 1013–1027.
- [2] Nichols CI, Vose JG. Incidence of bleeding-related complications during primary implantation and replacement of cardiac implantable electronic devices. *J. Am. Heart Assoc.* 2017;6(1).
- [3] V. Essebag, A. Verma, J.S. Healey, A.D. Krahn, E. Kalfon, B. Coutu, et al., Clinically significant pocket hematoma increases long-term risk of device infection: BRUISE CONTROL INFECTION study, *J. Am. Coll. Cardiol.* 67 (11) (2016) 1300–1308.
- [4] M.R. Sohail, C.A. Henrikson, M.J. Braid-Forbes, K.F. Forbes, D.J. Lerner, Mortality and cost associated with cardiovascular implantable electronic device infections, *Arch. Intern. Med.* 171 (20) (2011) 1821–1828.
- [5] A.R. Sridhar, V. Yarlagadda, M.R. Yeruva, A. Kanmanthareddy, A. Vallakati, B. Dawn, et al., Impact of haematoma after pacemaker and CRT device implantation on hospitalization costs, length of stay, and mortality: a population-based study, *Europace*. 17 (10) (2015) 1548–1554.
- [6] M.R. Reynolds, D.J. Cohen, A.D. Kugelmass, P.P. Brown, E.R. Becker, S.D. Culler, et al., The frequency and incremental cost of major complications among medicare beneficiaries receiving implantable cardioverter-defibrillators, *J. Am. Coll. Cardiol.* 47 (12) (2006) 2493–2497.
- [7] R. Proietti, I. Porto, M. Levi, A. Leo, V. Russo, E. Kalfon, et al., Risk of pocket hematoma in patients on chronic anticoagulation with warfarin undergoing electrophysiological device implantation: a comparison of different peri-operative management strategies, *Eur. Rev. Med. Pharmacol. Sci.* 19 (8) (2015) 1461–1479.
- [8] J.C. de Oliveira, M. Martinelli, S.A. Nishioka, T. Varejao, D. Uipe, A.A. Pedrosa, et al., Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial, *Circ. Arrhythm. Electrophysiol.* 2 (1) (2009) 29–34.
- [9] A. AlTurki, R. Proietti, D.H. Birnie, V. Essebag, Management of antithrombotic therapy during cardiac implantable device surgery, *J. Arrhythm.* 32 (3) (2016) 163–169.
- [10] A.D. Krahn, J.S. Healey, C.S. Simpson, V. Essebag, S. Sivakumaran, D.H. Birnie, Anticoagulation of patients on chronic warfarin undergoing arrhythmia device surgery: wide variability of perioperative bridging in Canada, *Heart Rhythm.* 6 (9) (2009) 1276–1279.
- [11] D.H. Birnie, J.S. Healey, G.A. Wells, A. Verma, A.S. Tang, A.D. Krahn, et al., Pacemaker or defibrillator surgery without interruption of anticoagulation, *N. Engl. J. Med.* 368 (22) (2013) 2084–2093.
- [12] C. Tompkins, A. Cheng, D. Dalal, J.A. Brinker, C.T. Leng, J.E. Marine, et al., Dual antiplatelet therapy and heparin "bridging" significantly increase the risk of bleeding complications after pacemaker or implantable cardioverter-defibrillator device implantation, *J. Am. Coll. Cardiol.* 55 (21) (2010) 2376–2382.
- [13] R.T. Sant'anna, T.L. Leiria, T. Nascimento, J.R. Sant'anna, R.A. Kalil, G.G. Lima, et al., Meta-analysis of continuous oral anticoagulants versus heparin bridging in patients undergoing CIED surgery: reappraisal after the BRUISE study, *Pacing Clin. Electrophysiol.* 38 (4) (2015) 417–423.
- [14] C.N. Floyd, A. Ferro, Indications for anticoagulant and antiplatelet combined therapy, *BMJ.* 359 (2017) j3782.
- [15] J.W. Eikelboom, J. Hirsh, Combined antiplatelet and anticoagulant therapy: clinical benefits and risks, *J. Thromb. Haemost.* 5 (Suppl. 1) (2007) 255–263.
- [16] P. Kirchhof, S. Benussi, D. Kotecha, A. Ahlsson, D. Atar, B. Casadei, et al., 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS, *Eur. Heart J.* 37 (38) (2016) 2893–2962.
- [17] Lip GYH, Collet JP, Caterina R, Fauchier L, Lane DA, Larsen TB, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace*. 2017;19(11): 1757–1758.
- [18] L. Macle, J. Cairns, K. Leblanc, T. Tsang, A. Skanes, J.L. Cox, et al., 2016 focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation, *Can. J. Cardiol.* 32 (10) (2016) 1170–1185.
- [19] D. Birnie, J.S. Healey, A. Krahn, V. Essebag, S. Sivakumaran, A. Tang, et al., Bridge or continue Coumadin for device surgery: a randomized controlled trial rationale and design, *Curr. Opin. Cardiol.* 24 (1) (2009) 82–87.
- [20] R.A. Nishimura, C.M. Otto, R.O. Bonow, B.A. Carabello, J.P. Erwin 3rd, L.A. Fleisher, et al., 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines, *J. Am. Coll. Cardiol.* 70 (2) (2017) 252–289.
- [21] L.D. Fiore, M.D. Ezekowitz, M.T. Brophy, D. Lu, J. Sacco, P. Peduzzi, et al., Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study, *Circulation.* 105 (5) (2002) 557–563.
- [22] M. Hurlen, M. Abdelnoor, P. Smith, J. Erikssen, H. Arnesen, Warfarin, aspirin, or both after myocardial infarction, *N. Engl. J. Med.* 347 (13) (2002) 969–974.
- [23] T. Wein, M.P. Lindsay, R. Cote, N. Foley, J. Berlingieri, S. Bhogal, et al., Canadian stroke best practice recommendations: secondary prevention of stroke, sixth edition practice guidelines, update 2017, *Int. J. Stroke* 1747493017743062 (2017).
- [24] V. Aboyans, J.B. Ricco, M.E.L. Bartelink, M. Björck, M. Brodmann, T. Cohnert, et al., ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries endorsed by: the European Stroke Organization (ESO) the task force for the diagnosis and treatment of peripheral arterial diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS), *Eur Heart J.* 39 (9) (2018) 763–816.
- [25] W.N. Kernan, B. Ovbiagele, H.R. Black, D.M. Bravata, M.I. Chimowitz, M.D. Ezekowitz, et al., Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke.* 45 (7) (2014) 2160–2236.
- [26] T.P. Gavaghan, V. GebSKI, D.W. Baron, Immediate postoperative aspirin improves vein graft patency early and late after coronary artery bypass graft surgery. A placebo-controlled, randomized study, *Circulation.* 83 (5) (1991) 1526–1533.
- [27] C.T. January, L.S. Wann, J.S. Alpert, H. Calkins, J.E. Cigarroa, J.C. Cleveland Jr., et al., 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society, *J. Am. Coll. Cardiol.* 64 (21) (2014) e1–76.
- [28] S.R. Mehta, K.R. Bainey, W.J. Cantor, M. Lordkipanidze, G. Marquis-Gravel, S.D. Robinson, et al., 2018 Canadian Cardiovascular Society/Canadian Association of interventional cardiology focused update of the guidelines for the use of antiplatelet therapy, *Can. J. Cardiol.* 34 (3) (2018) 214–233.
- [29] S. Goldman, J. Copeland, T. Moritz, W. Henderson, K. Zadina, T. Ovitt, et al., Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative study, *Circulation.* 77 (6) (1988) 1324–1332.
- [30] B.A. Steinberg, S. Kim, J.P. Piccini, G.C. Fonarow, R.D. Lopes, L. Thomas, et al., Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry, *Circulation.* 128 (7) (2013) 721–728.
- [31] C.H. So, M.H. Eckman, Combined aspirin and anticoagulant therapy in patients with atrial fibrillation, *J. Thromb. Thrombolysis* 43 (1) (2017) 7–17.

- [32] M.D. Gerhard-Herman, H.L. Gornik, C. Barrett, N.R. Barshes, M.A. Corriere, D.E. Drachman, et al., 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines, *J. Am. Coll. Cardiol.* 69 (11) (2017) 1465–1508.
- [33] C. Frank, Deprescribing: a new word to guide medication review, *CMAJ.* 186 (6) (2014) 407–408.
- [34] W. Thompson, B. Farrell, Deprescribing: what is it and what does the evidence tell us? *Can. J. Hosp. Pharm.* 66 (3) (2013) 201–202.
- [35] J. Jansen, V. Naganathan, S.M. Carter, A.J. McLachlan, B. Nickel, L. Irwig, et al., Too much medicine in older people? Deprescribing through shared decision making, *BMJ* 353 (2016) i2893.
- [36] A. Bobb, K. Gleason, M. Husch, J. Feinglass, P.R. Yarnold, G.A. Noskin, The epidemiology of prescribing errors: the potential impact of computerized prescriber order entry, *Arch. Intern. Med.* 164 (7) (2004) 785–792.
- [37] A.X. Garg, N.J. Adhikari, H. McDonald, et al., Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review, *JAMA.* 293 (10) (2005) 1223–1238.
- [38] P.J. Devereaux, M. Mrkoberda, D.I. Sessler, K. Leslie, P. Alonso-Coello, A. Kurz, et al., Aspirin in patients undergoing noncardiac surgery, *N. Engl. J. Med.* 370 (16) (2014) 1494–1503.
- [39] E. Watanabe, M. Yamamoto, I. Kodama, H. Inoue, H. Atarashi, K. Okumura, et al., Net clinical benefit of adding aspirin to warfarin in patients with atrial fibrillation: insights from the J-RHYTHM Registry, *Int. J. Cardiol.* 212 (2016) 311–317.
- [40] K.E. Airaksinen, P. Korkeila, J. Lund, A. Ylitalo, P. Karjalainen, V. Virtanen, et al., Safety of pacemaker and implantable cardioverter-defibrillator implantation during uninterrupted warfarin treatment—the FinPAC study, *Int. J. Cardiol.* 168 (4) (2013) 3679–3682.