Chapter 4

Management of Anticoagulation Around Cardiac Implantable Electronic Device Surgery

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Abstract

The number of patients requiring cardiovascular implantable electronic device (CIED, e.g., pacemaker and defibrillator) surgery is increasing rapidly and at least a quarter of them are using chronic oral anticoagulation (OAC). Recently, the traditional approach of withholding anticoagulation and using heparin bridging has been challenged by studies showing safety of performing CIED surgery under anticoagulation with vitamin K antagonists. Bridging with heparin is associated with incremental healthcare costs, prolonged hospital admission, and also with an augmented relative risk of pocket hematoma. The risk of embolic events seems to be low and similar with the use of two strategies (heparin bridging and continuous warfarin). Experience with novel oral anticoagulants is limited. Few studies suggest that withholding 48–72 hours before surgery and performing the procedure under anticoagulation are safe alternatives. However, larger randomized clinical trials are needed before definitive conclusions. In this chapter, we review the management of anticoagulation around cardiac implantable electronic device surgery under new conditions.

Keywords: cardiac resynchronization therapy, implantable cardiac defibrillator, uninterrupted warfarin

1. Introduction

Each year, around 1.25 million pacemakers and 410,000 implantable cardioverter defibrillators (ICDs) are implanted worldwide. It is estimated that 25–35% of patients undergoing cardiac implantable electronic device (CIED) surgery receive long-term oral anticoagulation (OAC).

Many patients are also receiving oral antiplatelet therapy for primary or secondary cardiovascular events [1] and are exposed to an increased risk of bleeding during the perioperative period.

Pocket hematoma formation is the most common complication of CIED implantation [2]. Although benign in most cases, it can have serious consequences, such as prolongation of hospitalization, need for further surgery, and an increased risk of infection.

The periprocedural management of OAC poses a challenge, particularly in patients with moderate or higher risk (>5%/y) of arterial thromboembolic events (ATEs). Subtherapeutic anticoagulation exposes patients with atrial fibrillation (AF) to potential thromboembolic complications, with a calculated daily risk ranging from 0.01 to 0.05% [3]. Heparin is expected to reduce venous and arterial thromboembolism by 66–80% [4], but is associated with an increased risk of pocket hematoma.

Conversely, subtherapeutic anticoagulation exposes patients with AF to potential thromboembolic complications, with a calculated daily risk ranging from 0.01 to 0.05% [3]. This dilemma led some centers to perform this type of procedure without interrupting the OAC in patients deemed to be at a high risk for thromboembolic events.

2. Strategies for management of anticoagulation around CIED surgery

There are three perioperative anticoagulation strategies that can be employed:

1. Uninterrupted warfarin.
2. Withholding warfarin without bridging.
3. Withholding warfarin with perioperative bridging using heparin.

Theoretically, each strategy has its own advantages and limitations. The traditional strategy is to withhold warfarin with perioperative bridging using heparin in high-risk patients. This approach was linked to potential complications: a high risk of hematoma (between 17 and 31%), increased duration and costs of hospital stays, and increased risk of reoperation [5].

In a meta-analysis, we compared uninterrupted warfarin versus bridging using heparin. Maintenance of OAC, when compared to heparin bridge with unfractionated heparin or enoxaparin, had a lower risk of perioperative bleeding (OR = 0.25, 95% CI 0.17–0.36, $P < 0.00001$) (**Figure 1**). The risk of ATE was very low in our study, with only three events occurring in the group that received uninterrupted warfarin and one event in the group that received heparin bridging (OR = 1.86; 95% CI, 0.29–12.17; $P = 0.57$) [6].

Particularly, in the BRUISE study, thromboembolic events occurred in patients who were under OAC, but with INRs below the therapeutic range at the time of the event. Therefore, risk is probably more related to the adequacy of the anticoagulation control rather than the strategy applied.

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Importantly, device pocket hematomas can necessitate prolonged cessation of anticoagulation with the attendant risk of ATE [6, 7]; they can significantly increase the duration and cost of hospitalization; and sometimes reoperation is required. Uslan et al. [8] have also highlighted the strong link between pocket hematoma and reintervention, the latter is an independent predictor of ICD infections.

Proietti et al. [9] found similar results in a meta-analysis with similar design that included 15 studies. Heparin bridging was associated with an increased risk of bleeding (OR = 4.47; 95% CI, 3.216.23; $P < 0.00001$), and prolonged hospital stay (9.13 ± 1.9 days vs. 5.11 ± 1.39 days; $P < 0.00001$). Adding heparin decreased the risk of ATE when compared with no anticoagulation (0.50% vs. 1.07%, $P = 0.02$), but there was no difference when heparin was compared with continuous OAC ($P = 0.83$). Results from this study discourage adoption of a strategy of OAC suspension with no heparin bridging.

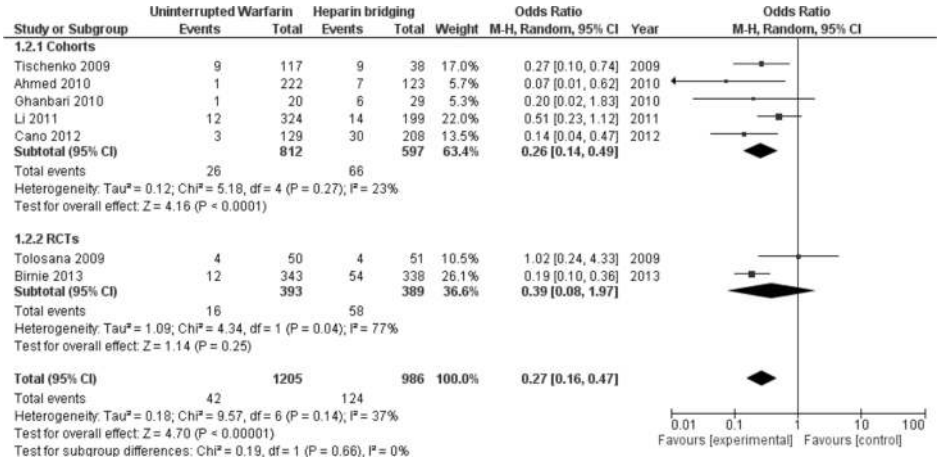

Figure 1. Risk of pocket hematoma in patients with oral anticoagulation continuation versus heparin bridging therapy, according to study design. Random effect model.

The BRIDGE study was a large randomized trial that compared bridging with low-molecular-weight heparin or placebo in patients anticoagulated with warfarin undergoing different types of surgeries [10]. Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure. During these periods, patients received low-molecular-weight heparin or placebo. Both groups had a similar low risk of ATE (0.4% in the no-bridging group and 0.3% in the bridging group). The incidence of major bleeding, however, was lower in the no-bridging group (relative risk, 0.41; 95% CI, 0.20–0.78; $P = 0.005$ for superiority).

This study included patients with low- to moderate-risk ATE—with a mean CHADS2 score of 2.3 and no mechanical heart valves. Studies during the perioperative period of CIED surgery included patients with moderate- to high-risk ATE. Also, CIED surgery represents a different

scenario in which bleeding rarely is life threatening and is simple to diagnose. Therefore, we do not believe that results from BRIDGE should be applied to CIED surgery with the possible exception of patients with low risk of ATE.

The increased risk of bleeding related to heparin bridging has multiple causes. Feng et al. [11] hypothesize that the variations on the accuracy of monitoring of warfarin compared with heparin can partially explain differences in the observed risk of bleeding. Activated partial thromboplastin time (APTT) levels of 1.5–2.5 time control do not correlate well with the intensity of anticoagulation and have not been validated by randomized studies [12]. Moreover, heparin has antiplatelet effects that may last longer than the measurable effect of heparin and APTT [13]. Meanwhile, the evidence to maintain a therapeutic INR during the procedure is based on more consistent data of cohorts and randomized trials [14, 15]. Performing surgery under anticoagulation can facilitate the detection of small bleedings during the procedure [16]. This allows surgeons to make the necessary interventions at the time of the procedure and potentially reduce the risk of hematoma in the postoperative period. This phenomenon has been referred to as an "anticoagulation stress test."

Figure 2 shows a simplified guide for management of patients using OAC with vitamin K antagonists and requiring CIED surgery.

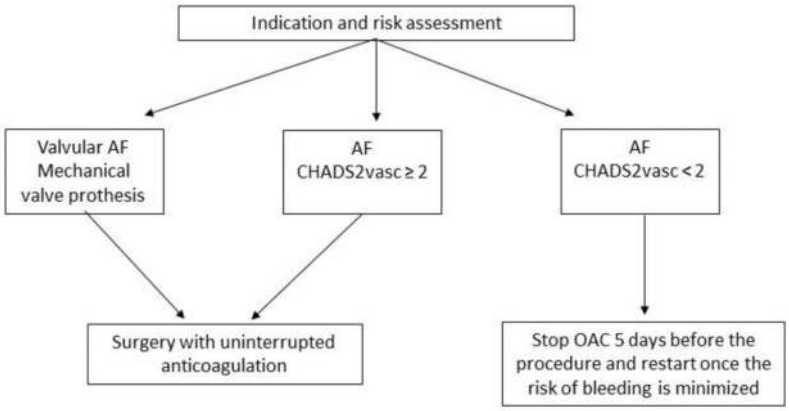

Figure 2. Guide for management of patients using OAC with vitamin K antagonists and requiring CIED surgery.

2.1. Role of novel anticoagulants

The use of novel anticoagulants (NOACs) has increased dramatically since its introduction with about 1/3 of patients with AF using them for stroke prophylaxis [17]. They represent a safe and efficacious alternative to warfarin. However, unlike warfarin, NOACs have a predictable dose-response curve. When prescribing these drugs, there is no need to monitor the INR levels to achieve therapeutic doses.

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All NOACs are at least noninferior to warfarin in terms of efficacy for prevention of stroke in patients with nonvalvular AF [18–20]. In the same population, they are also at least as safe as warfarin in terms of major bleeding. NOACs are also at least as effective and as safe as warfarin for the treatment of venous thromboembolism [21, 22]. In patients with mechanical heart valves, dabigatran was inferior to warfarin in terms of stroke prevention and bleeding risk [23]; therefore, the use of NOAC was contraindicated in this population.

However, recommendations for periprocedural use of NOAC are not well established as they pose particular challenges:

1. Number of agents available on the market—dabigatran, rivaroxaban, apixaban, and edoxaban—each one with a unique pharmacokinetic profile.
2. Unavailability of an efficacious and widespread antidote in the case of urgent need to reverse anticoagulation.
3. Unavailability of a reliable laboratory test to measure the anticoagulation effect.

Some authors recommend that in patients with an annual risk of ATE (>5%), NOAC could be resumed 24 hours after surgery. In patients with a lower risk of ATE (<5%), it would seem reasonable to wait for >48 hours after surgery [24, 25].

Randomized trials like the planned BRUISE CONTROL-2 trial, which will compare continued vs. interrupted novel oral anticoagulant (dabigatran, rivaroxaban, or apixaban) at the time of device surgery [23], will bring more definitive answers.

In cases of clinical significant bleeding and need of urgent reversal of anticoagulation, several strategies have been studied and proposed in this setting. Mar et al. [26] suggest that if criteria for activated charcoal or hemodialysis use are not met, the use of four-factor prothrombin complex concentrate (25 U/kg, maximum dose of 2500 U) may be attempted to reverse dabigatran, as well as rivaroxaban and apixaban. Recently, a novel recombinant human factor Xa, andexanet alfa (AnXa), that binds with high affinity to apixaban and rivaroxaban has showed promising results in phase 3 studies [27].

Until more conclusive results are published, we recommend withholding NOAC four half-lives before elective procedures and restart the drug as soon as the risk of bleeding is minimized.

2.2. Cost-effectiveness

Bridging therapy is associated with increased costs due to increased need for hospitalization and the high price of LMWH [27]. In the BRUISE CONTROL STUDY, the overall cost of continued warfarin therapy was dramatically lower than heparin bridging therapy, primarily due to lower costs for medication and hospitalizations [28]. From the perspective of the Canadian healthcare system, continued warfarin therapy, when compared with heparin bridging, showed a cost saving of $1800 per patient.

2.3. Antithrombotic therapy in patients undergoing cardiac rhythm device implantation

Optimal management of antiplatelet therapy (AT) around CIED implantation is also challenging. Medications used as AT (e.g., aspirin and clopidogrel) have long half-lives and no efficient antidote; therefore, planning is essential to minimize the risk of bleeding while keeping a low risk of thrombotic complication.

Tompkins et al. reported that dual antiplatelet therapy in patients undergoing pacemaker implantation significantly increased frequency and severity of hemorrhagic complications, compared with the use of aspirin alone [29]. Other authors found no increased risk of bleeding complication in patients receiving clopidogrel or DAPT [30, 31].

ACC/AHA guidelines support continuing low-dose aspirin monotherapy for noncardiac surgical procedures, noting only a small increase in procedure-related bleeding (relative risk 1.5). Management of dual AT or clopidogrel use is still a matter of debate. Yang et al. performed a meta-analysis to evaluate the effects of different antiplatelet combinations in patients undergoing CIED surgery [1]. Dual antiplatelet therapy increased the risk of bleeding largely during CIED implantations compared with control group (OR = 6.84, 95% CI 4.16–11.25, $P < 0.00001$). Single antiplatelet therapy did not increase the risk of bleeding during CIED implantations (OR = 1.52, 95% CI 0.93–2.46, $P = 0.09$). Single antiplatelet therapy with clopidogrel increases the risk of hemorrhage when compared with aspirin (OR = 2.91, 95% CI 1.27–6.69, $P = 0.01$).

Abbreviations

AF	atrial fibrillation
ATE	arterial thromboembolic events
APTT	activated partial thromboplastin time
CIED	cardiac implantable electronic device
OAC	oral anticoagulation
NOAC	novel anticoagulant

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References

[1] Yang X, Wang Z, Zhang Y, et al. The safety and efficacy of antithrombotic therapy in patients undergoing cardiac rhythm device implantation: a meta-analysis. Europace 2015; 17:1076–1084.

[2] Wiegand UKH, LeJeune D, Boguschewski F, Bonnemeier H, Eberhardt F, Bode HSF. Pocket hematoma after pacemaker or implantable cardioverter defibrillator surgery. Chest 2004; 126:1177.

[3] Vanleeuwen Y, Rosendaal FR, Cannegieter SC. Prediction of hemorrhagic and thrombotic events in patients with mechanical heart valve prostheses treated with oral anticoagulants. J Thromb Haemost 2008; 6:451–456.

[4] Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med 1997; 336:1506–1515.

[5] Robinson M, Healey JS, Eikelboom J, et al. Postoperative low-molecular weight heparin bridging is associated with an increase in wound hematoma following surgery for pacemakers and implantable defibrillators. Pacing Clin Electrophysiol 2009; 32:378–382.

[6] Sant'anna RT, Leiria TL, Nascimento T, et al. Meta-analysis of continuous oral anticoagulants versus heparin bridging in patients undergoing CIED surgery: reappraisal after the BRUISE study. PACE 2015; 38:417–423.

[7] Romeyer-Bouchard C, Da Costa A, et al. Prevalence and risk factors related to infections of cardiac resynchronization therapy devices. Eur Heart J 2010; 31:203–210.

[8] Uslan DZ, Gleva MJ, Warren DK, et al. Cardiovascular implantable electronic device replacement infections and prevention: results from the REPLACE Registry. Pacing Clin Electrophysiol 2012; 35:81–87.

[9] Proietti R, Porto I, Levi M, 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 2015; 19:1461–1479.

[10] Douketis JD, Spyropoulos AC, Kaatz S, et al. Perioperative bridging anticoagulation in patients with atrial fibrillation. N Engl J Med 2015; 373:823–833.

[11] Feng L, Li Y, Li J, et al. Oral anticoagulation continuation (compared with heparin bridging therapy among high risk patients undergoing implantation of cardiac rhythm devices: a meta-analysis. Thromb Haemost 2012; 108:1124–1131.

[12] Basu D, Gallus A, Hirsh J, et al. A prospective study of the value of monitoring heparin treatment with the activated partial thromboplastin time. N Engl J Med 1972; 287:324–327.

[13] Carr ME Jr, Carr SL. At high heparin concentrations, protamine concentrations which reverse heparin anticoagulant effects are insufficient to reverse heparin anti-platelet effects. Thromb Res 1994; 15:617–630.

[14] Johnston M, Harrison L, Moffat K, et al. Reliability of the international normalized ratio for monitoring the induction phase of warfarin: comparison with the prothrombin time ratio. J Lab Clin Med 1996; 128:214–217.

[15] van den Besselaar AM, Chantarangkul V, et al. Thromboplastin standards. Biologicals 2010; 38:430–436.

[16] Birnie DH, Healey JS, Wells GA, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. N Engl J Med 2013; 368:2084–2093.

[17] Lauffenburger JC, Farley JF, Gehi AK, et al. Factors driving anticoagulant selection in patients with atrial fibrillation in the United States. Am J Cardiol. 2015; 115:1095–1101.

[18] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139–1151.

[19] Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365:981–992.

[20] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883–891.

[21] Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2014; 369:799–808.

[22] Bauersachs R, Berkowitz SD, Brenner B, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010; 363:2499–2510.

[23] Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N Engl J Med 2013; 369:1206–1214.

[24] Birnie DH, Healey JS, Essebag V. Management of anticoagulation aroundpacemaker and defibrillator surgery. Circulation 2014; 129:2062–2065.

[25] Essebag V, Healey JS, Ayala-Paredes F, et al. Strategy of continued vs. interrupted novel oral anticoagulant at time of device surgery in patients with moderate to high risk of arterial thromboembolic events: The BRUISE CONTROL-2 trial. Am Heart Journal 2016; 173:102–107.

[26] Gold M, Crowther M, Levy G, et al. Annexatm-R: a Phase 3 randomized, double-blind, placebo-controlled trial, demonstrating reversal of rivaroxaban-induced anticoagulation in older subjects by andexanet alfa (Prt064445), a universal antidote for factor Xa (Fxa) inhibitors. J Am Coll Cardiol 2015; 65:A23.

[27] Spyropoulos AC, Jenkins P, Bornikova L. A disease management protocol for outpatient perioperative bridge therapy with enoxaparin in patients requiring temporary interruption of long-term oral anticoagulation. Pharmacotherapy 2004; 24:649–658.

[28] Coyle D, Coyle K, Essebag V, et al. Cost effectiveness of continued-warfarin versus heparin-bridging therapy during pacemaker and defibrillator surgery. J Am Coll Cardiol 2015; 65:957–959.

[29] Tompkins C, Cheng A, Dalal D, 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 2010; 55:2376–2382.

[30] Ozcan KS, Osmonov D, Yildirim E, et al. Hematoma complicating permanent pacemaker implantation: the role of periprocedural antiplatelet or anticoagulant therapy. J Cardiol 2013; 62:127–130.

[31] Przybylski A, Derejko P, Kwasniewski W, et al. Bleeding complications after pacemaker or cardioverter defibrillator implantation in patients receiving dual antiplatelet therapy: results of a prospective, two-center registry. Neth Heart J 2010; 18:230–235.