

Warfarin continuation vs interruption during procedures of cardiac rhythm devices: A Meta-analysis of randomized controlled trials

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Abstract

To compare the safety and efficacy of warfarin treatment continuation and heparin-bridging therapy during cardiac rhythm device (CRD) implantation in patients chronically treated with anticoagulants. We performed a search and analysis of peer-reviewed studies. Four randomized controlled trials (RCTs) were included in our analysis with 941 patients. The bleeding risk in patients continuing warfarin perioperatively was lower than those interrupting warfarin and using a heparin-bridge (RD -0.08, 95% CI -0.17 to 0.02, $p < 0.05$). There was no significant difference in ischaemic risk between two methods (RD 0, 95% CI -0.01 to 0.02, $p = 1.00$). Hence, in patients undergoing long-term warfarin therapy, continuation of warfarin treatment is a safe and efficacious perioperative strategy for during CRD implantations, while interruption of warfarin with a heparin bridge may increase the bleeding risk in these patients.

Keywords: Warfarin, Pacemaker, Artificial, Perioperative period.

Introduction

Warfarin is a widely used anti-coagulant used in the prevention of thrombosis and thromboembolism typically associated with a number of cardiovascular diseases including atrial fibrillation (AF), prosthetic valves, deep vein thrombosis (DVT), pulmonary embolisation (PE) and intra-cavity thrombosis.¹⁻³ Increasingly, more and more patients undergoing long-term warfarin therapy require implantation of cardiac rhythm devices (CRDs), with peri-procedural management of anti-coagulation therapy representing a common clinical challenge for all cardiologists during implantation.⁴ Peri-operative management strategies of patients with long-term anti-coagulation therapy involve continuation and interruption approaches.⁵ However, the choice of strategy remains controversial. Current guidelines recommend

discontinuation of warfarin therapy with heparin bridging in patients indicated for surgery,⁶ which could decrease the risk of bleeding and thromboembolic events, increasing procedural safety.⁷ However, some studies have implied that interruption of warfarin treatment may be inappropriate during some procedures, including CRD implantations.⁸⁻¹⁰

It has been reported that continuing warfarin therapy during pacemaker implantation could be safer than interrupting treatment.^{9,11-14} Furthermore, recent studies have suggested that heparin bridging in patients with long-term anti-coagulation therapy may increase bleeding risk.^{13,15-18} Despite these findings, large randomised controlled trials (RCTs) comparing continuation or interruption of warfarin treatment during CRD implantation are still few.

The current meta-analysis of all recent RCTs was conducted to determine whether continuation of warfarin treatment or interruption with heparin bridging is more efficacious during CRD implantation.

Material and Methods

The meta-analysis study comprised search of all peer-reviewed studies published prior to March 2014. We searched PubMed and EMBASE databases. Keywords and phrases used in the search included "pacemaker" and "warfarin" or "implantable cardioverter defibrillator" and "warfarin" or "cardiac resynchronisation therapy" and "warfarin". Reference lists from published papers were searched for any additional studies missed in the online search.

The inclusion criteria for the meta-analysis were RCTs involving patients on long-term warfarin; indication for CRD implantation; examination of continuous versus interrupted (heparin-bridge) therapy; and studies comparing bleeding (e.g. pocket hematoma) and ischaemic events.

Two independent reviewers reviewed all publications to determine if they met the inclusion criteria. A third reviewer was called upon to resolve disagreements. Studies were then finalised as having met the inclusion

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criteria (Figure-1). From each study included, the total number of participants indicated for continuation or interruption with bridging therapy was recorded in addition to follow-up time.

Clinically significant pocket haematoma was defined based on meeting at least one of the following criteria: a diameter over 2cm, requiring interruption of anti-coagulation, causing prolonged hospitalisation, or requiring extra treatments. Ischaemic events included stroke, transient ischaemic attack (TIA), or evidence of peripheral arterial ischaemia. Pacemaker, implantable cardioverter defibrillator (ICD), or cardiac resynchronisation therapy (CRT) implantation, as well as exchange or upgrade of these devices were included in as studied procedures. Details of the implantation procedure were not outlined in all the studies, including outlining the methods of stopping local bleeding in procedure, experience of the operators or post-operative care.

A random-effect model was used to summarise the results when the heterogeneity was high or medial, otherwise a fixed-effect model was used. Risk difference (RD) was used to measure effects of intervention (continuous warfarin or heparin bridge) on the incidence of pocket haematomas and ischaemic events. The combined results were drawn by fixed- or random-effect model as described by Dirsimonian and Laird.¹⁹ The Q test and I^2 index were used to check for statistical heterogeneity. $I^2 \leq 25\%$ was taken as low heterogeneity, while I^2 between 25% and 50% and $>50\%$ were taken as

medial and high heterogeneity respectively. Data analysis was performed by Review Manager 5.2 (Cochrane Centre, Copenhagen, Denmark) and $p < 0.05$ was deemed statistically significant.

Results

The search identified 725 articles and 61(8.4%) were retrieved in full text as they seemed to meet the inclusion criteria. After further review, 4(6.5%) of them were taken up for the purpose of the current study^{18,20-22} (Table-1). Together they comprised 941 patients in all the studies, warfarin discontinuance patients were given a heparin bridging therapy except for one, in which only 7 patients were given bridging. Heparin or low molecular heparin was used for the bridging treatment in 423(45%) of the total cases. The indications for chronic warfarin included atrial fibrillation, prosthetic valve, pre-existing clot (e.g. DVT, pulmonary embolism, stroke and intra-cavity thrombi), thrombophilia and heart failure, (Table-2). The most common indication of anti-coagulation was atrial fibrillation in 819(87%) patients, with some patients having multiple indications. Different CRD procedures, including pacemaker, ICD and CRT, were reviewed in our analysis, including 644(68.4%) new implantation cases and 431(46%) cases of exchanging and updating for pacemakers.

All the 4 studies reported on bleeding events following continuation or interruption of warfarin treatment with heparin bridging. Haematoma was the most common and important bleeding event. In all cases, clinically significant

Table-1: Study Characters.

	Design	Subjects	Continuing	Bridging	Follow up(weeks)
Alen Cheng 2011(20)*	RCT	100	50	7	6
David H Birnie 2013(21)	RCT	659	334	325	2
Jose M Tolosana 2009(18)	RCT	101	50	51	6
Dragan J Milic 2005(22)	RCT	81	41	40	8

*Only 7 patients were treated with bridging approach, while 43 patients were treated with discontinuing warfarin without heparin.

RCT: Randomised controlled trial.

Table-2 Indication of Warfarin and Procedure Information.

	Indication for warfarin			Preoperative INR		Procedure	
	AF#(%)	Prosthetic Valve(%)	Preexisting Clot*(%)	Continuing	Bridging	new implant	replacement/upgrade
Alen Cheng 2011	65 (65%)	18 (18%)	1 (1%)	1.4-3.0	1.0-1.6	44	56
David H Birnie 2013	603(91%)	203 (31%)	37 (6%)	2.0-2.6	1.1-1.3	308	353
Jose M Tolosana 2009	79 (78%)	54 (53%)	4 (4%)	1.7-2.3	0.9-1.3	79	22
Dragan J Milic 2005	72 (89%)	5 (6%)	45 (55%)	Null	Null	81	0

#AF-atrial fibrillation, *preexisting clot included patients with deep venous thrombosis(DVT), pulmonary embolus, or left ventricular clot; Null = data not reported.

INR: International normalised ratio.

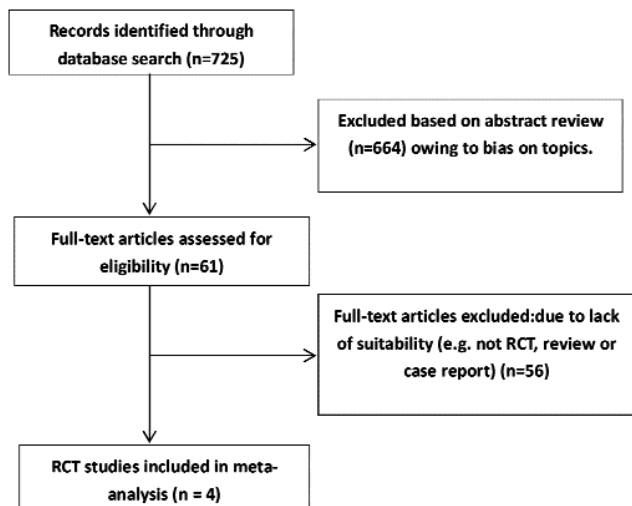


Figure-1: Flow diagram depicting search strategy and exclusion process.

pocket haematoma events happened in 155(16.5%) cases (Figure-2). Considering the relatively high statistic heterogeneity for haematoma events data ($I^2=60\%$), a random-effect model was selected to combine results from different studies. Warfarin continuation

management showed lower risk for haematoma compared with bridging treatment (RD -0.08; 95% confidence interval [CI] -0.17 to 0.02; $p<0.05$).

Among other complications reported were 2(0.2%) pericardial effusion events; 1(0.1%) in each group. Infections related to devices were observed in 9(0.9%) patients; 2(0.2%) were on continuation therapy, and 7(0.7%) with the bridging therapy. One study reported operative bleeding in 19(2%) patients, with 9(0.9%) being in the continuing group.

Of all the patients, only 4(0.4%) cases developed ischaemic events; 2(0.2%) with stroke and 2(0.2%) with TIA.²⁰⁻²² Three of the ischemic events occurred in continuing treatment cohort, but the number is so small that no statistic difference can be given. There were no significant differences between the two kinds of management in ischaemic events (RD 0; 95% CI -0.01 to 0.02; $p=1.00$) using the fixed effect model without an obvious statistic heterogeneity ($I^2=0\%$) (Figure-3).

One of the 4(25%) studies reported in-hospital data, with the continuation group showing a shorter hospital stay.¹⁸ Additionally, a higher patient

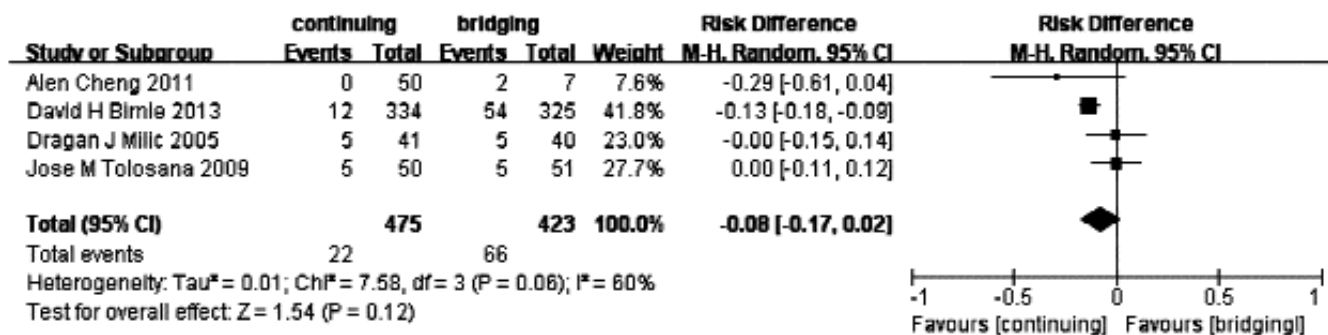


Figure-2: Forrest plot comparing the incidence of clinical hematomas in continuous versus bridging therapy. Mean differences are calculated by random-effects meta-analysis and weighted by estimated precision of the effect.

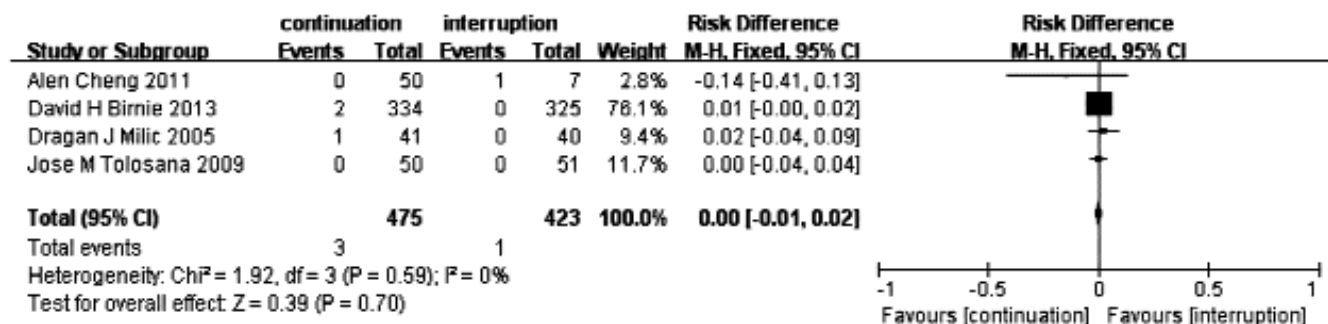


Figure-3: Forrest plot comparing the incidence of ischemic events in continuous versus bridging therapy.

satisfaction score in warfarin continuation group was reported in 1(25%) study.²¹

Discussion

Our meta-analysis of RCTs reporting on continuation or interruption of warfarin treatment with a heparin bridge during CRD implantation procedures indicates that the incidence of bleeding with warfarin continuation is reduced, suggesting that this strategy offers a safer approach compared to a heparin bridge in patients undergoing chronic warfarin therapy.

Peri-operative management of patients with chronic anti-coagulation therapy indicated for CRD implantation is a common clinical problem. While current guidelines recommend interruption of anti-coagulant therapy with heparin bridging to reduce thromboembolic and bleeding risk during surgery,⁶ there is conflicting evidence which suggests that heparin bridging therapy may not only increase bleeding risk,^{13,15-18} but that warfarin continuation during CRD implantation may be safe.^{9,11-14} To understand the conflicting nature of these findings, we focussed on published RCTs comparing the safety and efficacy of continuation or interruption of warfarin therapy with a heparin bridge during CRD implantation in patients with long-term warfarin treatment. Analysis of RCTs provides a more reliable approach compared to previous studies,^{14,23} reducing both selection bias and reducing the risk of spurious causality in the comparison of different treatment strategies.

The major finding of our meta-analysis was that continuation of warfarin treatment resulted in a lower incidence of clinically significant bleeding events. Pocket haematoma is the most common acute bleeding event after implantation, accounting for 14% to 17% of early re-operations^{24,25} with an incidence ranging between 0%²⁶ and 4.5%,²⁷ independently of treatment. The formation of pocket haematoma can lead to obvious symptoms and secondary complications, including pocket infection.

Our analysis implied that continuation of warfarin during CRD implantation would reduce the pocket haematoma risk compared to heparin bridging strategy, while the risk of stroke or embolisation (e.g. ischaemic events) and in-hospital stay showed no significant differences between the two approaches. This is in agreement with one study¹⁷ in which patients receiving bridge therapy had a 5-fold and 10-fold greater risk of pocket haematoma formation than those undergoing warfarin treatment alone following implantation. Other studies have suggested that clinically significant bleeding and thromboembolic

events are rare using either warfarin strategy,²⁸ providing further support that continuation of warfarin during perioperative CRD implantation may be preferable moving forward.

Although not included in our meta-analysis, many non-RCT studies have drawn similar conclusions to our analysis in that interruption of warfarin and heparin bridging may increase the risk of bleeding after implantation,^{9,13,29-31} while continuation of warfarin might be both safe and efficacious during implantation surgeries.^{9,11-14} While results are limited, continuation of warfarin treatment may be extended to other procedures. Specifically, it has been reported that patients with different international normalised ratio (INR) showed no significant differences in the incidence of hematoma after open inguinal herniorrhaphy.³² Furthermore, technological advances have enhanced haemostasis during invasive procedures, which could balance the increased bleeding risk caused by elevated INR to some extent. Therefore, it could be argued that similar benefits could also exist during other procedures which are less invasive. However, detailed guidelines outlining procedural safety and success with such an approach need to be discussed further.

In terms of limitations of the current study, there was statistical heterogeneity on a medial level, which was the reason why we used a random-effect model to combine the results of bleeding events. Using this method may increase the weighted differences between trials when combining the data. Therefore, larger trials comparing continuous therapy versus interruption of warfarin during implantation procedures will provide further evidence to help formulate informed surgical guidelines. Furthermore, we only analysed studies that focused on patients undergoing long-term warfarin treatment. New oral anti-coagulants, including dabigatran, rivaroxaban and apixaban, have been developed and approved to prevent DVT and stroke caused by AF. The shorter peak times and elimination half-lives³³ of these drugs may be superior to warfarin in peri-operative management, but clinical trials looking into the safety and efficacy of these drugs in patients on long-term anti-coagulant therapy during implantation procedures are currently lacking.

Conclusion

The meta-analysis suggests that warfarin continuation was a safer approach compared to heparin-bridging for CRD implantation in patients who were chronically taking warfarin. The reduced incidence of pocket haematoma events suggests that current guidelines

may need to be updated to include continuation of warfarin treatment as a strategy to reduce the risk of bleeding and thromboembolic events during implantation surgeries and to improve peri-operative management.

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References

- Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ, American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012; 141:7S-47S.
- January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC 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*. 2014; 64:e1-76.
- Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. ESC Guidelines on Management of Acute Myocardial Infarction in Patients Presenting With Persistent ST-Segment Elevation The Task Force on the Management of ST-segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J*. 2008;29:2909-45.
- Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Europace*. 2013; 15:1070-118.
- Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol*. 2010;27:92-137.
- Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008; 133:299S-339S.
- White RH, McKittrick T, Hutchinson R, Twitchell J. Temporary discontinuation of warfarin therapy: changes in the international normalized ratio. *Ann Intern Med*. 1995; 122:40-2.
- Mezzetti M, Saporito D, Calkins H. Perioperative management of oral anticoagulant therapy in cardiac arrhythmias device implantation. *Heart Rhythm*. 2012; 9:S107.
- Tischenko A, Gula LJ, Yee R, Klein GJ, Skanes AC, Krahn AD. Implantation of cardiac rhythm devices without interruption of oral anticoagulation compared with perioperative bridging with low-molecular weight heparin. *Am Heart J*. 2009; 158:252-6.
- Jamula E, Anderson J, Douketis JD. Safety of continuing warfarin therapy during cataract surgery: a systematic review and meta-analysis. *Thromb Res*. 2009; 124:292-9.
- Goldstein DJ, Losquadro W, Spotnitz HM. Outpatient pacemaker procedures in orally anticoagulated patients. *Pacing Clin Electrophysiol*. 1998; 21:1730-4.
- al-Khadra AS. Implantation of pacemakers and implantable cardioverter defibrillators in orally anticoagulated patients. *Pacing Clin Electrophysiol*. 2003; 26:511-4.
- Ahmed I, Gertner E, Nelson WB, House CM, Dahiya R, Anderson CP, et al. Continuing warfarin therapy is superior to interrupting warfarin with or without bridging anticoagulation therapy in patients undergoing pacemaker and defibrillator implantation. *Heart Rhythm*. 2010; 7:745-9.
- Ghanbari H, Phard WS, Al-Ameri H, Latchamsetty R, Jongnarngsin K, Crawford T, et al. Meta-analysis of safety and efficacy of uninterrupted warfarin compared to heparin-based bridging therapy during implantation of cardiac rhythm devices. *Am J Cardiol*. 2012; 110:1482-8.
- Marque C, De Geeter G, Klug D, Kouakam C, Brigadeau F, Jabourek O, et al. Post-operative use of heparin increases morbidity of pacemaker implantation. *Europace*. 2006; 8:283-7.
- Tompkins C, Cheng A, Dalal D, Brinker JA, Leng CT, Marine JE, 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; 55:2376-82.
- Michaud GF, Pelosi F Jr, Noble MD, Knight BP, Morady F, Strickberger SA. A randomized trial comparing heparin initiation 6 h or 24 h after pacemaker or defibrillator implantation. *J Am Coll Cardiol*. 2000; 35:1915-8.
- Tolosana JM, Berne P, Mont L, Heras M, Berrueto A, Monteagudo J, et al. Preparation for pacemaker or implantable cardiac defibrillator implants in patients with high risk of thromboembolic events: oral anticoagulation or bridging with intravenous heparin? A prospective randomized trial. *Eur Heart J*. 2009; 30: 1880-4.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7:177-88.
- Cheng A, Nazarian S, Brinker JA, Tompkins C, Spragg DD, Leng CT, et al. Continuation of warfarin during pacemaker or implantable cardioverter-defibrillator implantation: a randomized clinical trial. *Heart Rhythm*. 2011; 8:536-40.
- Birnie DH, Healey JS, Wells GA, Verma A, Tang AS, Krahn AD, et al. Pacemaker or defibrillator surgery without interruption of anticoagulation. *N Engl J Med*. 2013; 368:2084-93.
- Milic DJ, Perisic ZD, Zivic SS, Stanojkovic ZA, Stojkovic AM, Karanovic ND, et al. Prevention of pocket related complications with fibrin sealant in patients undergoing pacemaker implantation who are receiving anticoagulant treatment. *Europace*. 2005; 7:374-9.
- Bernard ML, Shotwell M, Nietert PJ, Gold MR. Meta-analysis of bleeding complications associated with cardiac rhythm device implantation. *Circ Arrhythm Electrophysiol*. 2012; 5:468-74.
- Chauhan A, Grace AA, Newell SA, Stone DL, Shapiro LM, Schofield PM, et al. Early complications after dual chamber versus single chamber pacemaker implantation. *Pacing Clin Electrophysiol*. 1994; 17:2012-5.

25. Aggarwal RK, Connelly DT, Ray SG, Ball J, Charles RG. Early complications of permanent pacemaker implantation: no difference between dual and single chamber systems. *Br Heart J*. 1995; 73:571-5.
 26. Ku YH, Kuo PH, Tsai YF, Huang WT, Lin MH, Tsao CJ. Port-A-Cath implantation using percutaneous puncture without guidance. *Ann Surg Oncol*. 2009; 16:729-34.
 27. Vardy J, Engelhardt K, Cox K, Jacquet J, McDade A, Boyer M, et al. Long-term outcome of radiological-guided insertion of implanted central venous access port devices (CVAPD) for the delivery of chemotherapy in cancer patients: institutional experience and review of the literature. *Br J Cancer*. 2004; 91:1045-9.
 28. Airaksinen KE, Korkeila P, Lund J, Ylitalo A, Karjalainen P, Virtanen V, et al. Safety of pacemaker and implantable cardioverter-defibrillator implantation during uninterrupted warfarin treatment--the FinPAC study. *Int J Cardiol*. 2013; 168:3679-82.
 29. Chow V, Ranasinghe I, Lau J, Stowe H, Hendel N, Bannon P, et al. Bridging anticoagulation strategy is associated with a high incidence of peri-operative haematoma in patients undergoing pacemaker insertion. *Heart Lung Circul*. 2010; 19:S211.
 30. Ramirez A, Wall TS, Schmidt M, Selzman K, Daccarett M. Implantation of cardiac rhythm devices during concomitant anticoagulation or antiplatelet therapy. *Expert Rev Cardiovasc Ther*. 2011; 9:609-14.
 31. Cano O, Munoz B, Tejada D, Osca J, Sancho-Tello MJ, Olague J, et al. Evaluation of a new standardized protocol for the perioperative management of chronically anticoagulated patients receiving implantable cardiac arrhythmia devices. *Heart Rhythm*. 2012; 9:361-7.
 32. Stucky CC, Garvey EM, Johnson DJ, Chapital AB, Gossage CM, Wasif N, et al. Challenging a surgical dictum: results from a 10-year experience on the safety of open inguinal herniorrhaphy in patients on chronic warfarin therapy. *Hernia: Hernia*. 2015; 19:83-7.
 33. Wang Y, Bajorek B. New oral anticoagulants in practice: pharmacological and practical considerations. *Am J Cardiovasc Drugs*. 2014; 14:175-89.
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