The safety and efficacy of antithrombotic therapy in patients undergoing cardiac rhythm device implantation: a meta-analysis

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Aims

The meta-analysis was to assess the safety and efficacy of periprocedural antithrombotic therapy and to evaluate the risk factors potentially associated with bleeding among patients undergoing cardiac implantable electronic devices implantations.

Methods and results

A systematic literature search of PubMed, EMBASE, and Cochrane Controlled Trials Register was performed. Anticoagulation and antiplatelet therapies were assessed separately. Uninterrupted anticoagulation was associated with significantly lower bleeding risk compared with heparin bridging strategy (odds ratio (OR) = 0.31, 95% confidence interval (CI) 0.18–0.53, and \( P < 0.0001 \)), but there was no significant difference in thromboembolic risk between these two strategies (OR = 0.82, 95% CI 0.32–2.09, and \( P = 0.65 \)). The haematoma rate was significantly increased in dual antiplatelet therapy group (OR = 6.84, 95% CI 4.16–11.25, and \( P < 0.0001 \)), but not in single antiplatelet therapy (OR = 1.52, 95% CI 0.93–2.46, and \( P = 0.09 \)). Clopidogrel increased the risk of haematoma vs. aspirin (OR = 2.91, 95% CI 1.27–6.69, and \( P = 0.01 \)). Otherwise, a lower risk of haematoma was observed in pacemaker group vs. cardiac resynchronization therapy and/or implantable cardioverter defibrillator group (OR = 0.64, 95% CI 0.50–0.82, and \( P = 0.0004 \)).

Conclusion

This meta-analysis suggested that uninterrupted oral anticoagulation seems to be the better strategy, associated with a lower risk of bleeding complications rather than heparin bridging, and dual antiplatelet therapy carried a significant risk of bleeding whereas single antiplatelet therapy was relatively safe among patients undergoing cardiac implantable electronic devices implantations. Meanwhile, cardiac resynchronization therapy and/or implantable cardioverter defibrillator implantations increase the bleeding.

Keywords

Uninterrupted anticoagulation therapy • Heparin-bridging therapy • Antiplatelet therapy • Bleeding complications • Thromboembolic risk • Cardiac rhythm devices implantation • Meta-analysis

Introduction

Since the first permanent pacemaker (PPM) was implanted, the development of the cardiac implantable electronic devices (CIEDs) in a wide range of heart rhythm disorders is remarkable.1 Apart from the conventional use of PPMs, more sophisticated devices including cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillator (ICD) are increasingly used.2 Many patients with CIEDs implantation are receiving oral anticoagulation (OAC) drug because of atrial fibrillation (AF) or heart valve diseases,3 or antiplatelet for primary or secondary prevention of cardiovascular events such as myocardial infarction (MI) or stroke.4

The most common complication after CIEDs implantation is pocket haematoma.5 In addition to causing significant patient discomfort, it can have serious consequences for patients, such as prolongation of hospitalization, need for further surgery, and an increased risk of infection.6 The incidence of pocket haematoma formation varies greatly, depending on the periprocedural anticoagulation...
and antiplatelet medications used.7 Besides, it is challenging for such patients that interruption therapy may increase the risk of embolic stroke, which can be fatal or associated with major disability in 70% of patients.8

Current guidelines recommend a heparin-bridging strategy (HBS) for anticoagulated patients with moderate/high risk for thrombosis.9 But some studies reported lower risk of bleeding and undifferentiated thromboembolic events with uninterrupted OAC rather than HBS.10–19 On the other hand, recently, questions are raised as to whether and when pre-existing antiplatelet therapy should be interrupted in patients with upcoming operative or invasive procedures, but no consensus was reached.20 Three previous meta-analyses, performed in 2012,21–23 found that uninterrupted OAC throughout CIEDs implantation was associated with decreased risk of bleeding without increasing risk of thromboembolic events, compared with HBS, but the total number of patients involved was relatively small and only one mentioned antplatelet therapy. Moreover, the predictors of pocket haematoma have not been studied. Clearly, more clinical trials, especially randomized control trials (RCTs) are needed to draw a definitive conclusion, and the safety of antiplatelet therapy requires further study. Therefore, this meta-analysis enrolling 17 trials was performed to investigate the safety and efficacy of both anticoagulation and antplatelet therapy in patients undergoing the CIEDs implantations and also to evaluate the predictors of haematoma formation.

Methods

Trials selection

All published randomized and non-randomized controlled clinical trials that examined the safety and efficacy of antithrombotic therapy in patients who are undergoing the CIEDs implantations were collected. Studies with original data related to the rate of bleeding complications and thrombotic events during the CIEDs implantations were enrolled.

Search strategy

A systematic literature search of PubMed, EMBASE, and Cochrane Controlled Trials Register up to 2014 was performed to identify trials in English and Chinese language. The inclusion criteria for the analysis were: (i) the restricted procedure to CIEDs implantation; (ii) logical groups included antplatelet and/or anticoagulation therapy (discontinuation of OAC and HBS); (iii) involved more than 50 subjects in each group; and (iv) had explicit definitions of endpoints.

Outcome measures

The endpoints of this meta-analysis included: (i) haemorrhagic complications: pocket haematoma and/or the need for pocket exploration and/or blood transfusion and/or unplanned or prolonged hospitalization and/or interruption of warfarin therapy or incremental outpatient follow-up. Pocket haematoma was defined as palpable mass that protruded >2 cm anterior to pulse generator; (ii) thromboembolic (TE) events were defined as myocardial infarction (MI), transient ischaemic attack (TIA), stroke, deep vein thrombosis, and pulmonary embolism.

The TE risk was considered high if any of the following were present: (i) atrial fibrillation with CHADS2 score ≥2; (ii) mechanical heart valve; (iii) venous thromboembolism in the previous 6 months, or with antiphospholipid antibody syndrome or malignancy, or during previous interruption of warfarin therapy; (iv) history of stroke or TIA.24

Data extraction and analysis

Two investigators (Yang and Wang) independently selected studies using the following steps: (i) examining titles and abstracts to remove obviously irrelevant reports; (ii) retrieving the full text of potentially relevant reports; (iii) examining full-text reports for compliance of studies with eligibility criteria; and (iv) making final decisions on study inclusion and proceeding to data collection. Any discrepancies were resolved by consensus. If a consensus could not be reached, the senior author (Hou) made the final decision.

The methodological quality was assessed using the Methodological Index for Non-Randomized Studies (MINORS).25 Data were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity was assessed by using the Q statistic (Qdf), the I² statistic (where I² > 50% indicates a high degree of statistical heterogeneity), and P < 0.10 represents statistical heterogeneity. All statistical analyses were performed by using Review Manager, version 5.0. A random-effect model according to the method of DerSimonian and Laird was adopted. Statistical significance was defined when P ≤ 0.05. Funnel plots were created to determine the influence of publication bias.

Results

Description of included trials

In total, 1430 articles (with duplicates deleted) were identified by the literature search and 17 studies5,7,10–19,26–30 enrolling 10 715 patients finally entered into this meta-analysis (see Supplementary material online, Figure S1). The baseline characteristics of included trials are shown in Table 1. The 17 eligible trials were divided into two parts: the first part included 10 trials comparing uninterrupted OAC and HBS, while the second including 7 trials was designed to evaluate the influence of antiplatelet drug on bleeding events. In heparin-bridging group, OAC was interrupted 2–5 days before the planned procedure with administration of either low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH). Oral anticoagulation and heparin were all reinitiated within 24 h after the procedure, and bridging therapy was continued until International normalized ratio (INR) reached the therapeutic range except one trial.15 Implants were postponed if the patient INR was ≥3 pre-procedure except three trials.11,12,16 Oral antiplatelet therapy was managed differently in the included seven studies, which were continued in two trials, on treatment in the other two, and at the discretion of physician in the left three.

Effect of anticoagulation on endpoint

After data were pooled together, continued OAC was found to have a lower incidence of pocket haematoma than HBS group (OR 0.31, 95% CI 0.18–0.53, P < 0.0001, and I² = 42%) (Figure 1). Moreover, there was no significant difference in TE events between the two strategies (OR = 0.82, 95% CI 0.32–2.09, P = 0.65, and I² = 0%) (Figure 1). Subgroup analysis was performed to assess the effect of heparin type, administration time as well as TE rate stratification on the haemorrhagic complications. The results showed a lower haematoma complications rate in the continued OAC compared with HBS using either LMWH (OR = 0.23, 95% CI 0.12–0.43, and P < 0.001) or UFH (OR = 0.54, 95% CI 0.31–0.95, and P = 0.03) and whenever heparin was administered ≥24 h (OR = 0.34, 95% CI 0.21–0.55, and P < 0.0001) or ≤12 h after...
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Subjects</th>
<th>No. of patients</th>
<th>Intervention group 1</th>
<th>Intervention group 2</th>
<th>Control group</th>
<th>Intervention drug 1</th>
<th>Intervention drug 2</th>
<th>Control drug</th>
<th>Follow-up (weeks)</th>
<th>No. of devices implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milic2005</td>
<td>Prospective RCT</td>
<td>81</td>
<td>51% (41)</td>
<td>49% (40)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH)</td>
<td>8</td>
<td>100% (81)</td>
</tr>
<tr>
<td>Tischenko2009</td>
<td>Prospective cohort</td>
<td>272</td>
<td>14% (38)</td>
<td>43% (117)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (LMWH)</td>
<td>1</td>
<td>31% (84) 26% (70)</td>
</tr>
<tr>
<td>Tolosana2009</td>
<td>Prospective RCT</td>
<td>101</td>
<td>49% (50)</td>
<td>51% (51)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH)</td>
<td>6</td>
<td>78% (79) 32% (31)</td>
</tr>
<tr>
<td>Ahmed2010</td>
<td>Retrospective cohort</td>
<td>459</td>
<td>27% (124)</td>
<td>48% (220)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH or LMWH)</td>
<td>8</td>
<td>–</td>
</tr>
<tr>
<td>Ghanbari2010</td>
<td>Retrospective cohort</td>
<td>123</td>
<td>23% (28)</td>
<td>16% (20)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH)</td>
<td>4</td>
<td>– 100% (123)</td>
</tr>
<tr>
<td>Cheng2011</td>
<td>Prospective RCT</td>
<td>100</td>
<td>50% (50)</td>
<td>7% (7)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH or LMWH)</td>
<td>6</td>
<td>24% (24) 22% (22)</td>
</tr>
<tr>
<td>Li2011</td>
<td>Retrospective cohort</td>
<td>766</td>
<td>42% (322)</td>
<td>26% (200)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH or LMWH)</td>
<td>4</td>
<td>60% (462) 17% (128)</td>
</tr>
<tr>
<td>Cano2011</td>
<td>Retrospective cohort</td>
<td>419</td>
<td>31% (130)</td>
<td>50% (210)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (LMWH)</td>
<td>1</td>
<td>67% (279) 33% (140)</td>
</tr>
<tr>
<td>Perrin2012</td>
<td>Retrospective cohort</td>
<td>129</td>
<td>7% (9)</td>
<td>18% (23)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH or LMWH)</td>
<td>–</td>
<td>52% (67) 23% (30)</td>
</tr>
<tr>
<td>Birnie2013</td>
<td>Prospective RCT</td>
<td>681</td>
<td>51% (343)</td>
<td>49% (338)</td>
<td></td>
<td></td>
<td>Uninterrupted OAC</td>
<td>–</td>
<td>Heparin bridging (UFH or LMWH)</td>
<td>1-2</td>
<td>17% (115) 28% (192)</td>
</tr>
<tr>
<td>Wregand2004</td>
<td>Prospective cohort</td>
<td>3164</td>
<td>41% (1305)</td>
<td>7% (23)</td>
<td>24% (765)</td>
<td></td>
<td>SAPT</td>
<td>DAPT</td>
<td>NAT</td>
<td>4</td>
<td>73% (2312) 10% (302)</td>
</tr>
<tr>
<td>Kutinsky2010</td>
<td>Prospective cohort</td>
<td>935</td>
<td>33% (310)</td>
<td>7% (66)</td>
<td>17% (164)</td>
<td></td>
<td>SAPT</td>
<td>DAPT</td>
<td>NAT</td>
<td>–</td>
<td>51% (479) 49% (456)</td>
</tr>
<tr>
<td>Thal.2010</td>
<td>Retrospective cohort</td>
<td>179</td>
<td>47% (84)</td>
<td>8% (15)</td>
<td>24% (43)</td>
<td></td>
<td>SAPT</td>
<td>DAPT</td>
<td>NAT</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>Tompkins 2010</td>
<td>Retrospective cohort</td>
<td>1388</td>
<td>4% (54)</td>
<td>10% (139)</td>
<td>18% (255)</td>
<td></td>
<td>SAPT</td>
<td>DAPT</td>
<td>NAT</td>
<td>–</td>
<td>40% (557) 60% (833)</td>
</tr>
<tr>
<td>Cano2011</td>
<td>Prospective cohort</td>
<td>849</td>
<td>25% (213)</td>
<td>7% (60)</td>
<td>44% (375)</td>
<td></td>
<td>SAPT</td>
<td>DAPT</td>
<td>NAT</td>
<td>1</td>
<td>69% (586) 31% (262)</td>
</tr>
<tr>
<td>Oscan2013</td>
<td>Retrospective and Prospective cohort</td>
<td>574</td>
<td>41% (233)</td>
<td>4% (24)</td>
<td>36% (209)</td>
<td></td>
<td>SAPT</td>
<td>DAPT</td>
<td>NAT</td>
<td>6</td>
<td>100% (574) –</td>
</tr>
<tr>
<td>Samir2013</td>
<td>Retrospective control</td>
<td>495</td>
<td>40% (198)</td>
<td>20% (99)</td>
<td>40% (198)</td>
<td></td>
<td>SAPT</td>
<td>DAPT</td>
<td>NAT</td>
<td>–</td>
<td>100% (495) –</td>
</tr>
</tbody>
</table>

RCT, randomized controlled trial; OAC, oral anticoagulation; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; NAT, no anticoagulation/antiplatelet therapy; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.
device implantation (OR = 0.25, 95% CI 0.13–0.51, and \( P < 0.01 \). In addition, when the patients were classified into low or moderate/high TE risk by the standardized protocol, the uninterrupted OAC was associated with lower risk of bleeding in the moderate/high TE risk group (OR = 0.30, 95% CI 0.18–0.51, \( P < 0.0001 \), and \( I^2 = 34% \)), but no significant difference was found in the low TE risk group (OR = 0.63, 95% CI 0.20–1.93, \( P = 0.41 \), and \( I^2 = 0% \) (Figure 2). Funnel plots were visually symmetrical, suggesting no significant publication bias (see Supplementary material online, Figure S2).

**Predictors of pocket haematoma**

We also assessed some predictors of haematoma during the CIEDs implantations, with the included 17 studies separately, and analysed the data by Review Manager 5.0. As a result, the factors such as age, sex, hypertension, diabetes, renal insufficiency, platelet number and whether new implantation or replacement were not found to be related to haematoma. But INR procedure, mechanical prosthesis, and structural heart disease were proved to be closely associated with haematoma (Table 2). Besides, there was a significant difference in risk of bleeding between the pacemaker (PM) group and ICD ± CRT group (OR = 0.64, 95% CI 0.50–0.82, \( P = 0.0004 \), and \( I^2 = 0% \) (Figure 5). No heterogeneity was detected across the trials.

**Discussion**

Our meta-analysis showed that HBS and DAPT carry a significant risk of bleeding, but continuation of OAC and SAPT is relatively safe among patients undergoing the CIEDs implantations. The
continuation of OAC was as efficient as HBS in reducing TE events. Furthermore, ICD + CRT implantations increase the risk of haematoma. It is crucial to re-establish the appropriate periprocedural management for anticoagulation and antiplatelet medications and assess the risks of TE events vs. bleeding complications.

The safety and efficacy of anticoagulation therapy

Currently, for patients in the moderate/high risk of TE events who were undergoing the CIEDs implantations, bridging with heparin remains a commonly employed strategy. Of note, recent data challenge the practice of heparin bridging in high risk patients who are on chronic anticoagulation. Most of the studies have demonstrated that HBS is associated with an increased risk of bleeding complications compared with warfarin continuation. Experts commented that patients with moderate or high risk of perioperative thrombosis should be considered for CIEDs implantations without the interruption of therapeutic warfarin anticoagulation within the INR range of 2–3. Our meta-analysis also suggested that HBS carries a significant risk of bleeding compared with the interrupted OAC.

When the included patients were classified into low or moderate/high TE risk group by the standardized protocol, the uninterrupted OAC was associated with lower risk of bleeding in the moderate/high TE risk group (OR = 0.30, 95% CI 0.18–0.51, and P < 0.0001). However, no significant difference was discovered between OAC and HBS in the low TE risk group (OR = 0.63, 95% CI 0.20–1.93, and P = 0.41). It was recommended that OAC continuation had a better risk–beneficial ratio, shorter length of hospital stay, and was more convenient to implement compared with heparin-bridging therapy among patients at high risk for thromboembolism undergoing implantation of cardiac rhythm devices. Consistently, the ACCP guidelines recommended that in patients with a mechanical heart valve or AF at low risk for thromboembolism, low-dose LMWH or no bridging is recommended during interruption of OAC. However, only two studies were enrolled into the low TE risk group, which was underpowered to detect such differences. More RCTs or clinical trials about the anticoagulation management of low TE risk patients are needed.

Heparin-bridging therapy is to prevent the thrombotic events in patients with high risk of TE and who suffered from the mechanical valves, AF, and other thromboembolic diseases. Embolic events had been evaluated in the previous meta-analysis, but the number of patients was considered to be underpowered to detect differences between the HBS and continuation of OAC. BRUISE CONTROL, a recently published multicenter, single-blind, randomized, controlled trial with TE events as the secondary outcome was included in our study. The result suggested that there is no significant difference in TE events between the uninterrupted OAC and HBS. In fact, the risk of TE events was very low in two groups on account of the effective anticoagulation therapy during the implantation.
The currently approved novel oral anticoagulation (NOAC) agents include rivaroxaban, apixaban, and dabigatran, which have been widely used within the past few years. They have short half-lives, and were prescribed at fixed doses without the need for laboratory-guided dose adjustment. However, the safety and efficacy of NOACs in patients undergoing CIEDs implantations have not been clearly defined. Our meta-analysis cannot state whether it is better for patients without discontinuation of the NOACs or with temporary cessation on account of the absence of data. Several studies have evaluated that. An analysis by Jennings et al. suggested that the incidence of bleeding complications is similar during CIED implantation with uninterrupted dabigatran or warfarin. Kosiuk et al. performed a trial with 176 patients and found that bleeding and TE complications in patients treated with dabigatran or rivaroxaban are rare. The famous randomized evaluation of long-term anticoagulation therapy study concluded that dabigatran and warfarin

### Meta-analysis of safety and efficacy of antithrombotic therapy

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DAPT</th>
<th>NA</th>
<th>Odds ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tompkins 2010</td>
<td>10</td>
<td>139</td>
<td>4.86 [1.50, 15.81]</td>
</tr>
<tr>
<td>Kutinsky 2010</td>
<td>16</td>
<td>166</td>
<td>5.51 [2.29, 13.24]</td>
</tr>
<tr>
<td>Samir 2013</td>
<td>11</td>
<td>164</td>
<td>6.06 [1.88, 19.57]</td>
</tr>
<tr>
<td>Cano 2011</td>
<td>12</td>
<td>60</td>
<td>10.17 [4.07, 25.39]</td>
</tr>
<tr>
<td>Thal 2010</td>
<td>3</td>
<td>15</td>
<td>24.36 [1.18, 503.79]</td>
</tr>
<tr>
<td>Ozcan 2013</td>
<td>1</td>
<td>24</td>
<td>26.74 [1.06, 675.34]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>403</td>
<td>1244</td>
<td>6.84 [4.16, 11.25]</td>
</tr>
</tbody>
</table>

**Figure 3**  Bleeding risk in patients receiving DAPT (3.1) and SAPT (3.2) vs. NA. DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy; NA, control group; OR, odds ratio; CI, confidence interval.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>SAPT</th>
<th>NA</th>
<th>Odds ratio M-H, fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kutinsky 2010</td>
<td>15</td>
<td>310</td>
<td>0.88 [0.37, 2.05]</td>
</tr>
<tr>
<td>Cano 2011</td>
<td>7</td>
<td>220</td>
<td>1.34 [0.49, 3.64]</td>
</tr>
<tr>
<td>Samir 2013</td>
<td>6</td>
<td>198</td>
<td>1.52 [0.42, 5.46]</td>
</tr>
<tr>
<td>Thal 2010</td>
<td>1</td>
<td>84</td>
<td>1.56 [0.06, 39.18]</td>
</tr>
<tr>
<td>Tompkins 2010</td>
<td>21</td>
<td>536</td>
<td>2.56 [0.87, 7.53]</td>
</tr>
<tr>
<td>Ozcan 2013</td>
<td>3</td>
<td>196</td>
<td>7.58 [0.39, 147.67]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1544</td>
<td>1244</td>
<td>1.52 [0.93, 2.46]</td>
</tr>
</tbody>
</table>

**Figure 4**  Bleeding risk in patients receiving clopidogrel vs. ASP; ASP, aspirin; OR, odds ratio; CI, confidence interval.
were associated with similar rates of periprocedural bleeding. Further and larger studies are required to define the optimal anticoagulation management in CIEDs during the perioperative period.

The safety of antiplatelet therapy

Coincidently, choosing the optimal management strategy for antiplatelet medications at the time of cardiac device implantation can be challenging. Samir et al. reported that DAPT in patients undergoing PM implantations resulted in a significantly increased frequency and severity of haemorrhagic complications, compared with the use of aspirin alone. But some reports declared no increased rate of bleeding complications in patients receiving clopidogrel or DAPT. Perioperative guidelines published by the ACC/AHA support continuing low-dose aspirin monotherapy for non-cardiac surgical procedures, noting only a small increase in procedure-related bleeding (relative risk 1.5). But the suggestion pertaining to the management on antiplatelet therapy of patients in the period of the CIEDs implantations is less definitive.

It was suggested in our meta-analysis that DAPT increased the risk of bleeding largely during the CIEDs implantations compared with control group (OR 6.84, 95% CI 4.16–11.25, P < 0.00001), which was in accordance with most previous studies. Antiplatelet medications disrupt haemostasis by targeting specific sites along the coagulation cascade. Aspirin affects platelet activation and aggregation by irreversibly inhibiting cyclooxygenase (COX) enzyme and thromboxane A2 (TXA2) production, while aspirin inhibits TXA2 production only. Clopidogrel is a P2Y12 platelet receptor inhibitor, and also inhibits ADP binding to the platelet ADP receptor (P2Y12). So, when the DAPT with aspirin and clopidogrel is taken, to some extent, the haemostasis is destroyed and haemorrhage would increase. Nevertheless, Lee et al. suggested that haematoma formation after PPM implantation was rare, even among those who were on the DAPT. But there were only 260 patients in the trial, and the number of totally enrolled patients might be too small to detect such differences. Dreger et al. also demonstrated no increased bleeding complications in DAPT therapy patients, but in this study a vacuum drainage system was applied to all patients. Regarding DAPT therapy, the reported bleeding risk varies between 0.7 and 24%. This great variability is due to differences in the definition of bleeding complications, and patients and procedural disparities. As mentioned before, a recent coronary stent implantation (<30 days) represents a particular problem since DAPT therapy should not be safely interrupted, even for a short time period. However, we have to acknowledge that specific data on patients with the recent percutaneous coronary intervention undergoing CIEDs implantations are lacking. So, the optimal management of antiplatelet therapy aiming at the CIEDs implantations is still required.

Our result that SAPT did not increase the risk of bleeding during CIEDs implantations (OR = 1.52, 95% CI 0.93–2.46, and P = 0.09) is consistent with the ACC/AHA rules. We expect to assess the influence of aspirin and clopidogrel on bleeding, respectively, but there are only two studies covering the appropriate data in the clopidogrel group and no convincing conclusion could be reached. So, we compared the aspirin group with clopidogrel group directly. There is a significant higher risk of haemorrhage in the SAPT therapy with clopidogrel than aspirin (OR = 2.91, 95% CI 1.27–6.69, and P = 0.01). Clopidogrel is a P2Y12 platelet receptor inhibitor, and also inhibits TXA2 production, while aspirin inhibits TXA2 production only.

### Table 2 Analysis of predictors of pocket haematoma with the enrolling patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>P-value</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.94</td>
<td>0.69</td>
<td>0.70–1.27</td>
</tr>
<tr>
<td>Age</td>
<td>0.00</td>
<td>1.00</td>
<td>3.47 to 3.46</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.21</td>
<td>0.35</td>
<td>0.81–1.80</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.00</td>
<td>0.98</td>
<td>0.71–1.43</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>0.56</td>
<td>0.05</td>
<td>0.32–0.99</td>
</tr>
<tr>
<td>Platelet number</td>
<td>16.32</td>
<td>0.07</td>
<td>1.29 to 33.92</td>
</tr>
<tr>
<td>INR</td>
<td>0.16</td>
<td>0.02</td>
<td>0.02–0.30</td>
</tr>
<tr>
<td>Mechanical prosthesis</td>
<td>0.31</td>
<td>&lt;0.00001</td>
<td>0.19–0.48</td>
</tr>
<tr>
<td>Structural heart diseases</td>
<td>0.54</td>
<td>&lt;0.0001</td>
<td>0.40–0.74</td>
</tr>
<tr>
<td>Device type (PM vs. ICD ± CRT)</td>
<td>0.64</td>
<td>0.0004</td>
<td>0.50–0.82</td>
</tr>
</tbody>
</table>

PM, pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy.

### Figure 5 Bleeding risk in patients receiving PM vs. ICD ± CRT implantations; PM, pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; OR, odds ratio; CI, confidence interval.
Based on the difference in mechanism, we considered that clopidogrel could inhibit platelet aggregation and activation more efficiently. Mosleh et al. also demonstrated that clopidogrel alone markedly inhibited ADP-mediated platelet aggregation compared with monotherapy with aspirin. Moreover, the other likely reason is aspirin resistance, which was known to reduce platelet production of thromboxane A2 and thereby affects platelet activation and aggregation.

The predictors for haemorrhage risk

It must be noted that there are very particular factors associated with risk of bleeding complications except anticoagulation and antiplatelet treatments in the CIEDs implantations. Several studies have examined the potential risk factors for bleeding complications, including the characteristics of the patients, venous access for lead manipulation and placement, the experience of operators, the type of the procedure or devices, and so on. In our included studies, we could only access some predictors with the applicable data. As a result, the age, sex, hypertension, diabetes, renal insufficiency, platelet number and new CIEDs implantations or replacements were not found to be related to pocket haematoma. But INRs, mechanical prosthesis, structural heart disease were closely associated with bleeding complications. This was predictable because they were concerned with anticoagulation and antiplatelet therapies. Besides, the ICD ± CRT implantations increase the risk of bleeding. The excellent Danish national pacing cohort analysis by Kirkefeldt et al. suggested that higher complication risks were observed in dual-chamber ICD and CRT-D procedures, compared with dual-chamber PM procedures, primarily lead-related re-interventions (dual-chamber ICD: 3.6 vs. 2.3%, P = 0.001; CRT-D: 4.7 vs. 2.3%, P = 0.001). Lee et al. also found that CRT implantation and the number of new leads implanted were significant predictors of major complications. This can be attributed to the more complex structure, larger calibre, and increased rigidity of high-voltage leads, which in addition require more stringent implant and follow-up lead parameters.

Limitations

First, most studies included in our meta-analysis were retrospectively observational studies, only four are RCTs. This bears the inherent limitations of such studies. Second, most studies included in our meta-analysis did not report the exact duration of follow-up. In addition, we only access the safety and efficacy of antithrombotic therapy during the CIEDs implantations in according to the data from the limited studies. Above all, further studies, especially the RCTs, are needed to evaluate the safety and efficacy of OAC and antiplatelet therapies in these patients, preferably including the novel drugs.

Conclusions

In conclusion, the perioperative use of HBS and DAPT significantly increases the risk of bleeding complications in patients following the CIEDs implantations. Uninterrupted OAC seems to be the better strategy, associated with a lower risk of bleeding complications and thromboembolism. Moreover, SAPT is relatively safe, especially aspirin, compared with clopidogrel. Meanwhile, the ICD ± CRT implantations increase the risk of bleeding compared with the PM group.

Supplementary material

Supplementary material is available at Europace online.

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