Oral anticoagulation continuation compared with heparin bridging therapy among high risk patients undergoing implantation of cardiac rhythm devices

A meta-analysis

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Summary

It was the objective of this study to systematically compare the effects of oral anticoagulation (OAC) with heparin bridging therapy among patients at high risk for thromboembolism undergoing implantation of cardiac rhythm devices. A systematic search of PubMed/MEDLINE, Ovid and Elsevier, and the Cochrane Library databases was conducted. Six trials that met our inclusion criteria were identified and included in the present study. The endpoints of this meta-analysis included pocket haematoma, severe haematoma requiring drainage/revision, thromboembolic events, and length of hospital stay. Data were expressed as odds ratios (ORs) and 95% confidence interval (CIs). There was a statistically significant reduction of pocket haematoma (OR 0.29, 95% CI: 0.17 to 0.49, p<0.00001) and haematoma drainage/revision (OR 0.15, 95%CI: 0.04 to 0.54, p=0.004), respectively, in the OAC continuation group versus the heparin bridging group. We did not detect any statistically significant differences of thromboembolic events (OR 0.48, 95%CI: 0.07 to 3.54, p=0.48) in the two groups. There was a trend that patients in bridging group had longer hospital stays. In conclusion, OAC continuation had a better risk-beneficial ratio and 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.

Keywords

Oral anticoagulation continuation, heparin bridging, cardiac rhythm devices implantation, meta-analysis

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Introduction

Increasing number of patients requiring implantation of cardiac pacemakers, implantable cardioverter defibrillators (ICDs), or cardiac resynchronisation therapy are on chronic oral anticoagulation (OAC) for the prevention thromboembolic events. The perioperative anticoagulation strategy is confronted with a dilemma because of balancing bleeding and thromboembolism, particularly for patients at high risk for thromboembolism, who are also vulnerable to major bleeding complications. Most commonly, in this setting the current guideline suggests discontinuation of OAC and initiation of bridging anticoagulation with therapeutic-dose intravenous unfractionated heparin (UFH) or subcutaneous low-molecular-weight heparin (LMWH) as heparin bridging therapy (1). This approach is confirmed by several prospective cohort studies which are associated with low incidence of thromboembolic and major bleeding complications (2–6). However, problems associated with bridging therapy still exist, including higher costs and complexity of perioperative management. Moreover, sub therapeutic international normalised ratio (INR) can be dangerous (7–9).

Several studies in the literature have demonstrated that implantation of cardiac rhythm devices (CRDs) without OAC interruption may be feasible for high risk population, but most of them were retrospective, small-scaled, and single-center studies. In order to thoroughly evaluate the safety and efficacy of OAC continuation in this situation, we performed a meta-analysis of pertinent studies comparing OAC continuation with heparin bridging therapy.

Methods

Search strategy and selection criteria

We systematically performed a search through PubMed/MEDLINE, Ovid and Elsevier, and the Cochrane Library databases for all English-only articles comparing OAC continuation with heparin bridging therapy before January 2012. The following keywords were used: pacemaker or implantable cardioverter defibrillator (or

ICD) or cardiac resynchronisation therapy (or CRT), oral anticoagulation, unfractionated heparin bridging (or UFH bridging), and low-molecular-weight heparin bridging (or LWMH bridging). We also searched references in relevant studies to confirm that no studies were missed. Duplicate publication, ongoing/unpublished studies, published as an abstract or conference proceedings, letters to the editor, and commentaries were excluded.

Inclusion criteria for the analysis were trials that: a) had clearly defined risk stratifications of patients; b) restricted the invasive procedure to cardiac rhythm devices implantation; c) compared OAC continuation with heparin bridging; d) involved more than 20 subjects in each group; and e) had explicit definitions of endpoints. Patients met any of the following conditions to be categorised as high risk for thromboembolism: i) any mechanical prosthetic valve; ii) atrial fibrillation (AF) with previous systemic embolic event, prosthetic heart valve, or mitral stenosis; iii) AF with at least three following criteria of intermediate risk of embolic events: hypertension, diabetes, left ventricular ejection fraction<35%, and age >75 years; iv) intracardiac thrombus; v) recent deep venous thrombosis (<3 months). Studies were independently screened by two reviewers at title and/or abstract level, if necessary for more detailed.

Outcome measures

The endpoints of this meta-analysis included: 1) pocket haematoma and haematoma requiring drainage/revision as safety endpoints; 2) thromboembolic events as an efficacy endpoint; 3) the length of hospital stay. Pocket haematoma was defined as palpable mass that protruded >2 cm anterior to pulse generator. Thromboembolic events were defined as pulmonary embolism, stroke, transient ischaemic attack, and deep vein thrombosis which took place during the follow up.

Data extraction and analysis

Data, including age, sex category, INR pre-procedure, intervention strategy, length of hospital stay, follow up, and numbers of events, were independently extracted from each included trials by two investigators. Disagreements were resolved by consensus or, if necessary, by a third party.

Analyses were performed using RevMan 5.0 freeware package (The Cochrane Collaboration, Oxford, UK). Data were expressed

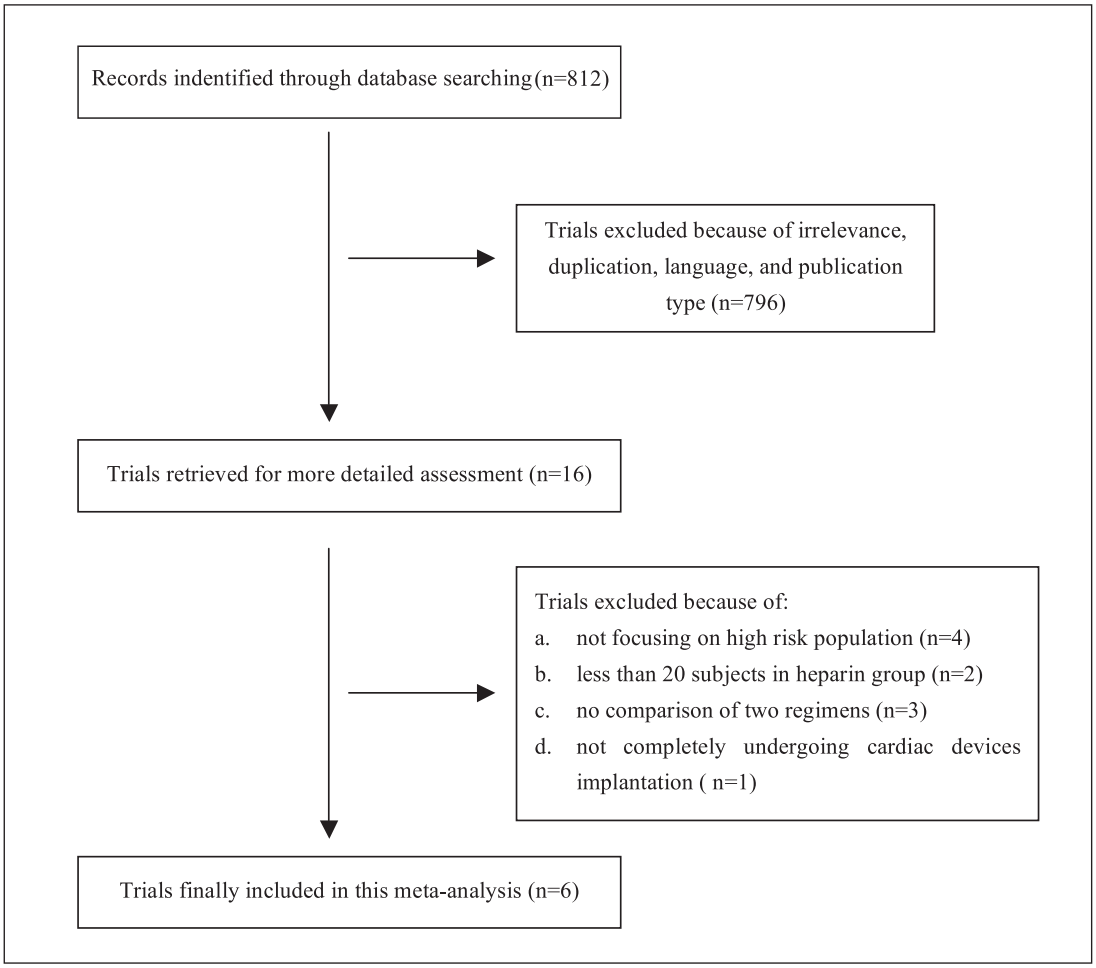

Figure 1: Flow diagram showing the process of study selection.

as odds ratios (ORs) and 95% confidence intervals (CIs). A p-value<0.05 indicated statistically significant. Statistical heterogeneity, defined as variation among the results of individual trials for a given treatment beyond that expected from chance, was quantified by means of $I^2 = [(Q - df) / Q] \times 100\%$, where Q is the Chi-squared statistic, and df is its degrees of freedom (10). In primary assessment, I^2 was calculated to heterogeneity using a fixed-effects model according to the method of Mantel-Haenzel (11). $I^2 < 50\%$ means no significant heterogeneity between trials and a fixed-effects model was adopted, whereas $I^2 > 50\%$ suggests significant heterogeneity between trials and a random-effects model according to the method of DerSimonian and Laird was adopted (12). Otherwise, descriptive analysis was performed. The presence of publication bias was evaluated by using a "funnel plot".

Results

Description of included trials

From initial citations, six trials that met our inclusion criteria were identified and included in the present study (13–18). Flow diagram of study selection is illustrated in ▶Figure 1. Six included studies totally enrolled 629 high-risk subjects with OAC continuation compared with 403 high-risk subjects receiving OAC discontinuation with heparin bridging regimen during implantation of cardiac rhythm devices. Baseline characteristics of included trials are reported in ▶Table 1. Perioperative intervention strategy of heparin bridging group in included trials are demonstrated in ▶Table 2. Four trials (13, 15–17) used warfarin as OAC, whereas another two trials used acenocumarol instead. Two trials (13, 18) used LWMH as bridging therapy, while another four trials used either UFH or LWMH with a target of activated partial thromboplastin

Table 1: Baseline characteristics of included trials. O = OAC continuation group; H = heparin bridging group; INR = international normalised ratio; RCT = Randomised Controlled Trial; SD = standard deviation; PM = pacemaker; ICD = implantable cardioverter defibrillator; CRT = cardiac resynchronisation therapy; NA = not applicable. * Mean (95% confidence intervals).

Study		Tischenko 2009	Tolosana 2009	Ahmed 2010	Ghanbari 2010	Li 2011	Cano 2011
Reference		13	14	15	16	17	18
Country		Canada	Spain	US	US	US	Spain
Design		Prospective non-randomised	RCT	Retrospective	Retrospective	Retrospective	Retrospective
Subjects and anticoagulation regimen		117 O vs. 38 H	50 O vs. 51 H	222 O vs. 123 H	20 O vs. 29 H	91 O vs. 100 H	129 O vs. 62 H
Follow up		24 hours after the implant, and at 1 week and 1 month	At discharge, and at 15 and 45 days	Within 24 hours of the procedure, and at 1 and 8 weeks	At discharge and at 15 and 30 days after the procedure	Weekly for 4 weeks	24 hours after the implant and then at 7 to 10 days
Age (years, mean ± SD)	O	71 ± 11	68 ± 10	71.5 (70.0, 73.1) *	67.7 ± 10.7	74.5 ± 12.8	72 ± 11
	H	65 ± 11	66 ± 11	70.9 (68.8, 73.0) *	64.7 ± 14.9	67.3 ± 15.1	68 ± 15
Male (%)	O	66.7	60.0	65.3	85	NA	60
	H	65.8	64.7	63.1	69	NA	52
INR preprocedure (mean ± SD)	O	2.2 ± 0.4	2.0 ± 0.3	2.57 ± 0.49	2.4 ± 0.3	2.1 ± 0.5	2.55 ± 0.62
	H	1.2 ± 0.2	1.1 ± 0.2	1.33 ± 0.20	1.4 ± 0.3	1.5 ± 0.4	1.32 ± 0.24
Aspirin (%)	O	NA	NA	57.7	NA	39.6	NA
	H	NA	NA	77.1	NA	51.0	NA
Clopidogrel (%)	O	NA	NA	1.3	NA	3.3	NA
	H	NA	NA	2.5	NA	4	NA
Newly implants (%)	O	54.7	76	83.3	65	72.5	64
	H	63.2	80	86.2	76	88	69
Type of devices new implant (%)	O	PM: 59.4 ICD: 25 CRT: 15.6	PM+CRT:68 ICD: 32	NA	ICD:100	PM: 65.2; ICD: 19.7; CRT: 9.1; Lead revision: 6.1	PM:71; ICD+CRT: 29
	H	PM:20.8 ICD: 45.8 CRT: 33.3	PM+CRT: 70.6 ICD: 29.4	NA	ICD:100	PM: 65.9; ICD: 12.5; CRT: 14.8; Lead revision: 6.8	PM:71; ICD+CRT: 29

time (aPTT) within a range from 55 to 90 seconds. In heparin bridging group, OAC was interrupted 2–5 days before the planned procedure with administration of either LWMH or UFH. OAC and heparin were all reinitiated within 24 hours (h) after the procedure, and bridging therapy was all continued until INR reached the therapeutic range except one trial (17). Four (13, 15–17) out of six trials divided patients into three groups: OAC continuation group, heparin bridging group, and control group composed of patients with no perioperative anticoagulation. We included in our meta-analysis only patients in OAC continuation group and heparin bridging group.

Safety endpoints

When data were pooled across trials, the risk of pocket haematoma was associated with significantly a 71% reduction in patients with OAC continuation compared with heparin bridging (OR 0.29, 95% CI: 0.17 to 0.49, p<0.00001, and I^2=39%) (▶Fig. 2). The I^2 was 39%, indicating no significant heterogeneity. Hence, the overall analysis from the fixed-effect model was robust. In terms of pocket haematoma requiring drainage/revision, the rate in OAC continuation group was also significantly lower as compared to bridging group (OR 0.15, 95%CI: 0.04 to 0.54, p=0.004, and I^2=0%) (▶Fig. 3), and there also existed no heterogeneity across the trials.

Efficacy endpoint

A total of 3 patients experienced thromboembolism. The incidence of thromboembolic events was not statistically significant in two groups (OR 0.48, 95%CI: 0.07 to 3.54, p=0.48, and I^2=0%) (▶Fig. 4).

Length of stay

The length of hospital stay had significant heterogeneity across the trials, even if a random-effects model was adopted (I^2=100%). Therefore, the pooled OR with 95%CI could not be calculated. However, in one study (15) patients in bridging therapy group had a longer length of stay compared to those treated with OAC continuation (3.7 ± 3.2 days vs. 2.9 ± 2.7 days, p<0.001), and in a second study (14) the duration of the hospital stay had a median of five days (4 to 7 days) and two days (1 to 4 days) in the heparin and OAC groups, respectively (p<0.001). Likewise, in a third study (18)

Table 2: Perioperative intervention strategy of heparin bridging group in included trials. UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; aPTT = activated partial thromboplastin time; INR = international normalised ratio; i.v. = intravenous; s.c. = subcutaneous; NA = not applicable.

Study	Tischenko 2009	Tolosana 2009	Ahmed 2010	Ghanbari 2010	Li 2011	Cano 2011
Reference	13	14	15	16	17	18
Type of heparin	Dalteparin	UFH	Either UFH or enoxaparin	Either UFH or enoxaparin	Either UFH or enoxaparin	Enoxaparin
Time of OAC discontinuation before the procedure (days)	5	4	3 to 5	4	3 to 4	2 to 3
Time of first heparin initiation before procedure	3 days before the procedure	At INR ≤ 2	At INR < 2	At INR ≤ 2	At INR < 2	At INR < 2
Dosage of heparin	200 U/kg/24h s.c.	i.v. bolus of 60 U/kg (maximum dosage of 4,000 U) followed by continuous infusion	UFH: NA Enoxaparin: 1 mg/kg/12h sc	UFH: NA Enoxaparin: 1 mg/kg/12h sc	UFH: NA LMWH: 1 mg/kg/12h s.c.	1 mg/kg/12h s.c.
Target aPTT (seconds)	NA	55–70	NA	60–70	60–90	NA
Time of last dose administration before the procedure (hours)	24	6	UFH: 4 to 6 Enoxaparin: 12 to 18	UFH: 4 LMWH: 12	UFH: 6 LMWH: 12	6 to 12
Time of restarting OAC after the procedure	24 hours	At night of the day of procedure	in the evening of the day of procedure	At night of the day of procedure	The same night of the procedure	The day after surgery
Time of restarting heparin after the procedure (hours)	24	24	UFH: 12 Enoxaparin: 24	UFH: 6 LMWH: NA	UFH: 24 LMWH: 24	Within 24
Time of heparin discontinuation	At INR > 2	At INR ≥ 2	At INR > 2	At INR ≥ 2	At INR ≥ 2	At INR > 2

the length of hospital stay was significantly longer in bridging group when compared with OAC continuation group (a median of 5.3 days, range 1 to 25 days vs. 1.3 days, range 0 to 7 days, respectively, p<0.0001). Hence, there was a trend that patients in OAC continuation group had shorter hospital stay than those in heparin bridging group.

Publication bias

The tests for potential publication bias in this meta-analysis showed that there was no obvious publication bias (►Fig. 5).

Discussion

To our knowledge, this was the first meta-analysis assessing OAC continuation during implantation of cardiac rhythm devices in patients who were at high risk for thromboembolism and on chronic OAC regimen. The results of the present meta-analysis suggested that OAC continuation was related to significantly 71% and 85% risk reduction of developing pocket haematoma and haematoma drainage/revision, respectively, compared with heparin bridging. Furthermore, our analysis found that both groups had similar low incidence of thromboembolic events. Finally, our results also suggested that there was a trend that patients in OAC continuation group had shorter length of hospital stay than those in heparin group. Therefore, implantation of cardiac rhythm de-

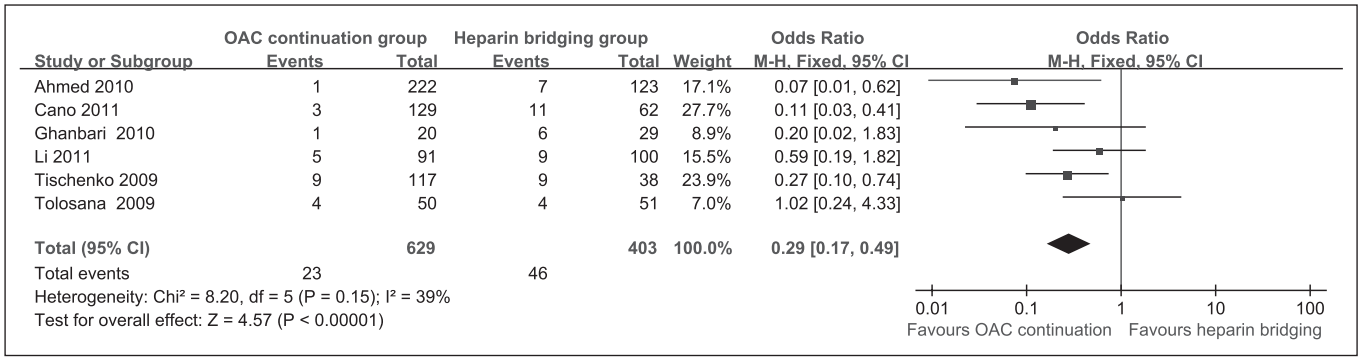

Figure 2: Risk of pocket haematoma in patients with OAC continuation vs. heparin bridging therapy. OAC = oral anticoagulation; OR = odds ratio; CI = confidence intervals.

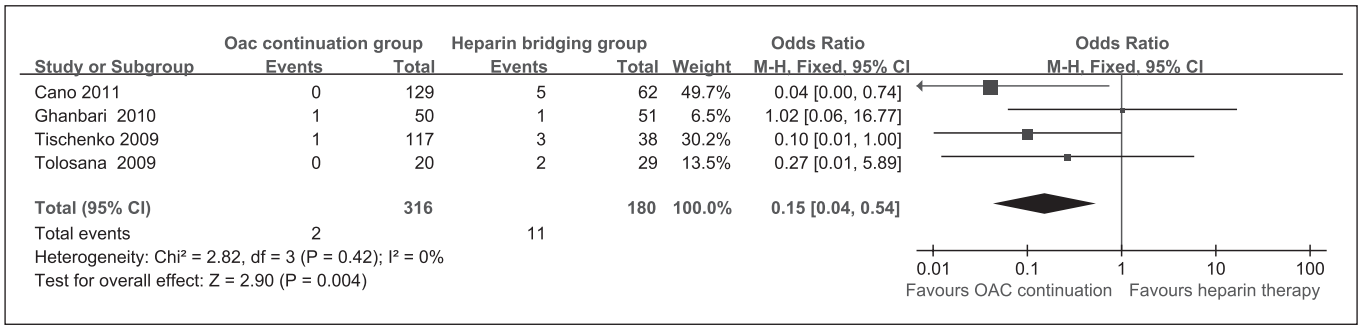

Figure 3: Risk of pocket haematoma requiring drainage/revision in patients with OAC continuation vs. heparin bridging therapy. OAC = oral anticoagulation; OR = odds ratio; CI = confidence intervals.

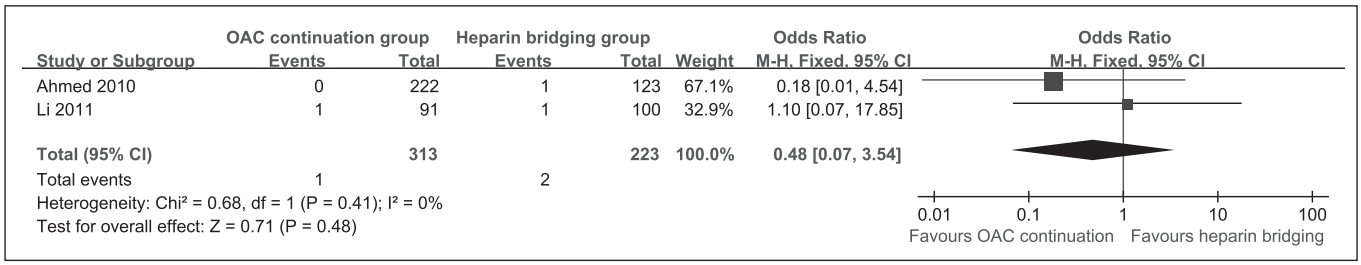

Figure 4: Risk of thromboembolic events in patients with OAC continuation vs. heparin bridging therapy. OAC = oral anticoagulation; OR = odds ratio; CI = confidence intervals.

vices without interruption of anticoagulation therapy in high-risk patients may offer the best combination of acceptable risk of bleeding complications with the lowest risk of thromboembolism compared with a heparin bridging strategy.

Unlike cataract surgery and minor dermatologic procedures (19–23), reports are scarce concerning perioperative anticoagulant management in high-risk patients undergoing cardiac rhythm device implantation. Therefore, there is no consensus on the appropriate perioperative management of anticoagulation for high risk patients who have been receiving long-term OAC therapy. Douketis (24) suggested bridging anticoagulation might not be necessary during perioperative warfarin interruption because of high risk for bleeding, low risk of thromboembolism, and type of surgery. In contrast, Spyropoulos (25) recommended that one should considering bridging anticoagulation using a standardised protocol for any high-TE risk patient on chronic vitamin K antagonists (VKA) therapy. However, they both did not draw definitive conclusions in their articles. Latest guidelines from the American College of Chest Physicians (ACCP) have only given a grade 2c recommendation for the use of bridging anticoagulation with therapeutic dose of subcutaneous LWMH or intravenous unfractionated heparin (UFH) during interruption of OAC therapy in patients with a mechanical heart valve, atrial fibrillation, or venous thromboembolism (VTE) at high risk for thromboembolism (1). A survey of physician preferences for perioperative anticoagulation showed that heparin bridging therapy was the most frequently selected anticoagulation option of physicians confronting this clinical scenario (26).

One reason for dramatically increased incidence of pocket haematoma in heparin bridging group in our study was probably the post-operative use of heparin. Marquie et al. (27) found that patients with mechanical valve or AF who received heparin post-operatively had a 14-fold increased risk of haemorrhagic severe adverse events in comparison with control patients. The study by Michaud et al. (28) also showed that high-risk patients who received heparin after pacemaker or defibrillator implantation had a five- to 10-fold greater risk of pocket haematoma than did patients treated with no anticoagulation or warfarin alone. Another explanation might be that a widely accepted therapeutic aPTT range of 1.5 to 2.5 times control did not correlate well with heparin anticoagulation strength. Because adjusting the dose of heparin to maintain a therapeutic range is established on the result of a post-hoc subgroup analysis of a descriptive study (29) and it has not been confirmed by randomised trials. Further, the measured response to the aPTT varies between reagents and instruments used to measure the aPTT (30–33). In contrast, the evidence for maintaining INR within a therapeutic range in patients treated with OAC continuation is strong because it is based on consistent results of randomised trials and case control studies (34–37).

The current study did not detect any difference of thromboembolic events in two groups. On the one hand, the number of totally enrolled patients might be underpowered to detect such differences. On the other hand, the risk of thromboembolism was, indeed, very low in two groups because of active anticoagulation therapy perioperatively. Our study also demonstrated that bridging therapy was associated with a trend of longer hospital stay after the procedure. This finding is likely due to in-hospital administration of UFH bridging therapy until a therapeutic INR is achieved. In addition, the higher incidence of haematoma in bridging therapy, in turn, contributed to the longer hospital stay of involved

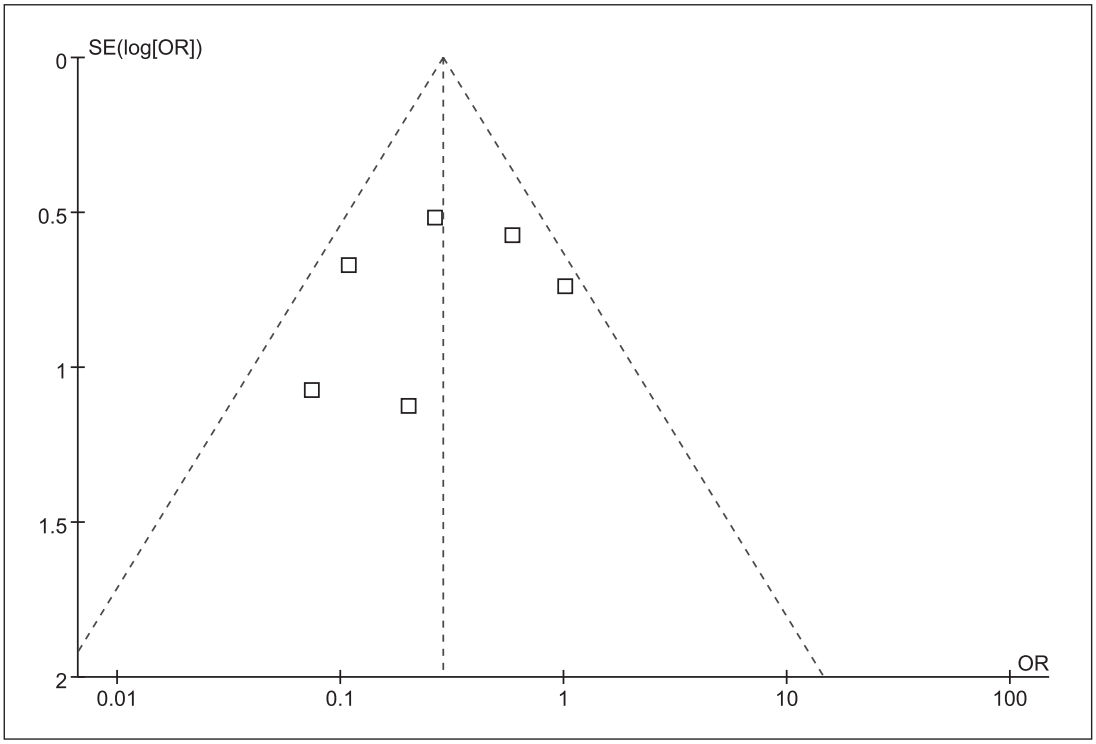

Figure 5: Publication bias. The standard error (SE) of the ln OR was plotted against the OR for risk of pocket haematoma.

patients who required more observation, more tests for blood coagulation, and/or haematoma drainage (14, 15, 18).

A number of limitations preclude definitive conclusions to be draw from our work. First, the major one is that five out of six trials were not randomized clinical trials (RCTs), and the total number of patients involved in this meta-analysis was relatively small. Second, the heparin bridging group used different types of heparin, either UFH or LWMH (full dose vs. half dose). Spyropoulos et al. (5) found that overall adverse events, including thromboembolism and bleeding, were similar for patients treated with LMWH or UFH. In our study, one included trial (14) also demonstrated no difference in risk of pocket haematoma formation between the use of LMWH and UFH in the bridging group (OR 1.54, 95%CI: 0.23 to 10.15, p=0.65). On the other hand, Kovacs et al. (2) showed that a full dose (200 IU/kg daily) of dalteparin might contribute to more bleeding events than a low dose (5,000 IU daily) for high-risk patients requiring temporary interruption of warfarin for elective surgery. Meanwhile, the timing of postoperative initiation of heparin was different, although, for a patient treated with the bridging regimen, a pocket haematoma might be independent of restarting heparin 6 h or 24 h after the implantation (28). Third, proportions of type of cardiac rhythm devices implanted in included trials were different. From a procedural risk perspective, there exists heterogeneity between a pacemaker implantation vs. an ICD or CRT implantation. Lee et al. (38) found that CRT-D implantation and the number of new leads implanted were significant predictors of major complications. Fourth, patients may receive OAC and antiplatelet agents, such as aspirin and clopidogrel, at the same time for a specific situation. For example, for patients with AF at high risk of stroke after placement of an intracoronary stent with recent ACS, antiplatelet therapy needs to be added to the chronic OAC regimen, which can increase the risk of bleeding. Therefore, more well-designed RCTs with lager sample size are required to confirm the findings of our study.

Conclusion

In conclusion, for high-risk patients undergoing implantation of CRDs, continuation of OAC offers the best combination of a lower risk of bleeding complications, thromboembolism, and hospital stay when compared to heparin bridging therapy. The findings of our study seem to suggest that OAC continuation might be a safe alternative to heparin bridging in such procedures, but more studies are required before definitive recommendations can be made.

Conflicts of interest

None declared.

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