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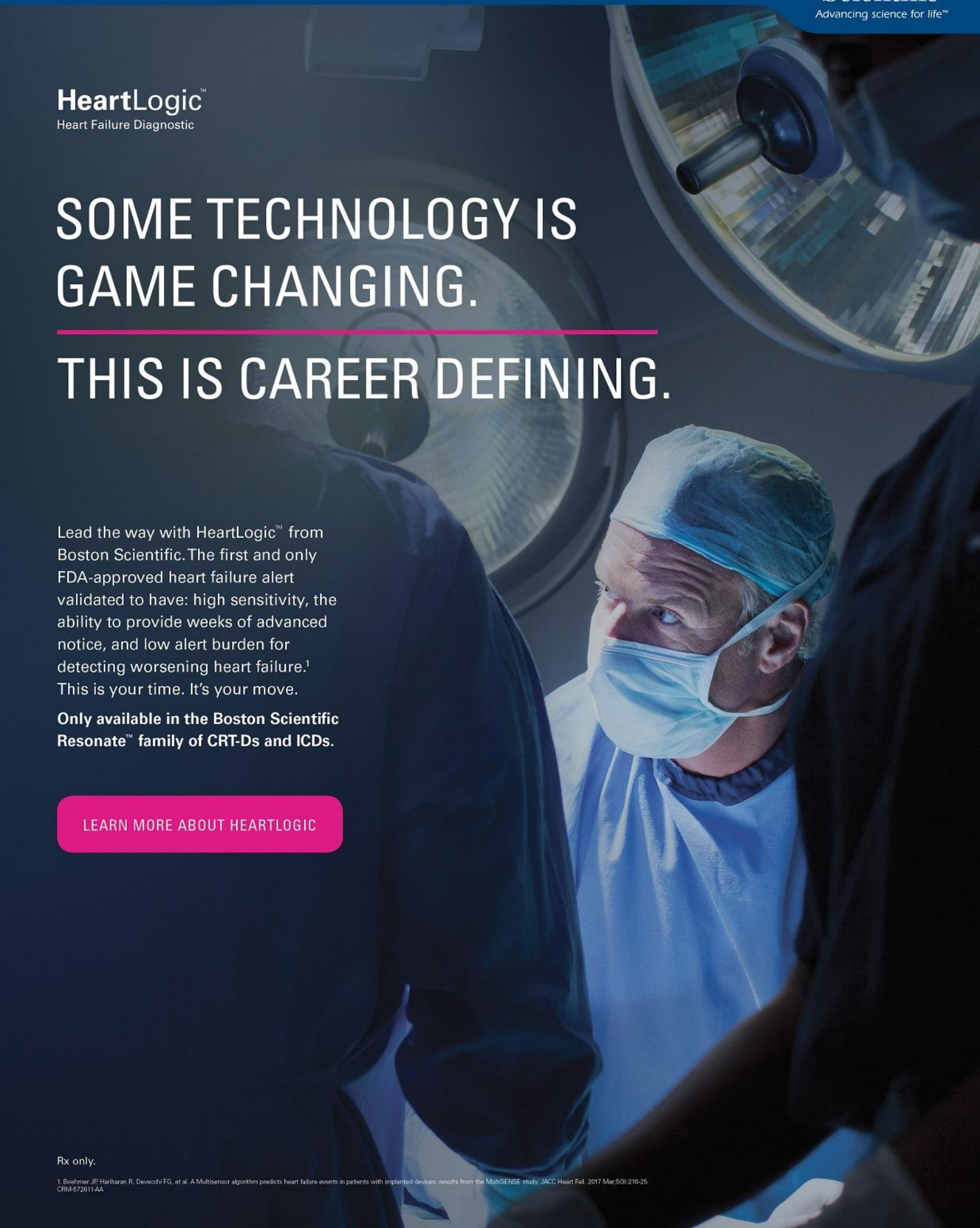

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DEVICES

Meta-Analysis of Continuous Oral Anticoagulants Versus Heparin Bridging in Patients Undergoing CIED Surgery: Reappraisal after the BRUISE Study

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Background: *Management of patients treated with oral anticoagulation (OAC) requiring a cardiovascular implantable electronic device (CIED) surgery is a challenge that requires balancing the risk of bleeding complications with the risk of thromboembolic events. Recently the approach of performing these procedures while the patient remains with a therapeutic international normalized ratio has gained interest due to several publications showing its relative safety.*

Objectives: *To evaluate the safety and effectiveness of continuous use of OAC compared with heparin bridging in the perioperative setting of CIED surgery using a meta-analysis.*

Methods: *A systematic review of PubMed/MEDLINE, Ovid, and Elsevier databases was performed. Eligible randomized controlled trials and cohort studies were included. The outcomes studied were risk of clinically significant bleeding and of thromboembolic events. Our analysis was restricted to OAC with vitamin K antagonists.*

Results: *Of 560 manuscripts initially considered relevant, seven were included in the meta-analysis, totaling 2,191 patients. Data are reported as odds ratios (ORs) with confidence interval (CI) of 95%. Maintenance of OAC was associated with a significantly lower risk of postoperative bleeding compared with heparin bridge (OR = 0.25, 95% CI 0.17–0.36, P < 0.00001). There was no difference noted in the risk of thromboembolic events between the two strategies (OR = 1.86, 95% CI 0.29–12.17, P = 0.57).*

Conclusions: *Uninterrupted use of OAC in the perioperative of CIED surgery was associated with a reduced risk of bleeding. This strategy should be considered the preferred one in patients at moderate-to-high risk of thromboembolic events. (PACE 2015; 38:417–423)*

defibrillation – ICD, pacing, CRT

Introduction

The number of patients requiring cardiovascular implantable electronic devices (CIED, e.g., pacemaker and defibrillator) surgery is increasing rapidly and at least a quarter of them are using chronic oral anticoagulation (OAC).[1] Current perioperative guidelines recommend withholding anticoagulation in this scenario and bridging the patient according to his or her thromboembolic risk.[2]

Bridging with heparin is associated with incremental healthcare costs, prolonged hospital admission, and also with an augmented relative risk of pocket hematoma.[3] Recently, some centers decided to perform this type of procedure without interrupting the OAC in patients deemed to be at a high risk for thromboembolic events.

Two previous meta-analyses were published comparing the approach of keeping the patient anticoagulated (therapeutic international normalized ratio [INR]) during the perioperative period versus bridging with unfractionated or low-molecular-weight heparin.[4,5] However, these publications included studies in which the primary endpoint was not bleeding. Also, the definition

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of the pocket hematoma was not a strict one and varied among studies. The recently published BRUISE study, the largest clinical trial on the subject, reported benefit of maintaining patients on therapeutic OAC during the perioperative period.[6] We decided to perform a meta-analysis adding this new information.

Methods

We performed a search in PubMed/MEDLINE, Ovid, and Elsevier databases for articles in English, French, Spanish, or Portuguese that compared the strategy of continued OAC versus heparin bridging in patients scheduled for a CIED surgery. Articles published before November 2013, the date on which the review was conducted, were selected. We considered as a CIED: pacemakers, biventricular pacemakers, and/or defibrillators. Procedures included were first implant, generator replacement, and device upgrade. Abstracts presented at conferences, reviews of other articles, and letters to the editor were not included in the analysis. We also searched for important articles in the references of relevant publications regarding this subject.

Two independent reviewers (RS and TL) conducted research and data extraction. When there was disagreement between reviewers, they tried to reach a consensus. We used the following keywords to search: "pacemaker OR defibrillator" AND "anticoagulation OR heparin OR Warfarin." Inclusion criteria were: (1) studies in which the primary objective was to compare continuation of OAC in the perioperative period versus its discontinuation associated with unfractionated heparin or low-molecular-weight heparin bridge; (2) studies that evaluated the occurrence of bleeding and pocket hematoma with a clear definition for these endpoints; (3) studies restricted to implantation of CIED without any associated procedure; both randomized trials and retrospective or prospective cohort studies were accepted; (4) studies with at least 20 patients included in each group; and (5) studies using vitamin K antagonists as OAC.

Endpoints Utilized and Data Extraction

We use the following outcomes for the study: (1) occurrence of significant bleeding, the criteria of which should be specified in the article and include at least one of the following: the need for interruption of anticoagulation and/or drainage of hematoma, bleeding causing prolongation of hospitalization; and (2) occurrence of thromboembolic events.

We extracted the following data of each study: number of events, hospitalization length, nature of the procedure, and risk of thromboembolism. Each item was extracted independently by two investigators (RS and TL).

Statistical Analysis

Statistical analysis was performed using the RevMan 5.4 (The Cochrane Collaboration, Oxford, UK) software. Data are reported as odds ratio (OR) and confidence interval (CI) of 95%, with a $P < 0.05$ considered statistically significant. Heterogeneity was quantified using the formula $I^2 = [(Q - df)/Q] \times 100\%$, where Q is χ^2 statistic and df its degrees of freedom. When heterogeneity was low ($I^2 < 25\%$) using a fixed-effects of the Mantel-Henzel method, this model was kept for performing the analysis. In cases of higher heterogeneity ($I^2 \geq 25\%$), the analysis model was performed using random-effects in accordance with the method of DerSimonian and Laird.[7] The presence of publication bias was assessed through a "funnel plot."[8]

Results

Seven studies were included from our literature search (Table I), as represented in the flowchart of Figure 1. Six other studies that initially were considered relevant were finally excluded for not meeting the inclusion criteria precisely. Specific reasons for this exclusion were: use of a novel OAC,[9,10] comparison of interruption of warfarin without bridging,[11] studies with a different primary objective,[12,13] and one study that had only a small number of patients (<10) in the heparin bridging group.[14]

Included studies involved a total of 2,191 patients. Heterogeneity test to compare the strategies of maintaining OAC with therapeutic INR versus bridging with heparin demonstrated a χ^2 of 9.57 and I^2 of 37%, considered as high heterogeneity, and therefore we performed the analysis using a random-effect model.

Use of OAC therapy without interruption was associated with a reduction in the relative risk of bleeding in comparison with the use of heparin bridge (OR = 0.27, 95% CI 0.17–0.47, $P < 0.00001$; Fig. 2). When the analysis was performed using the fixed-effect model, it remained statistically significant (OR = 0.25, 95% CI 0.17–0.36, $P < 0.00001$ in the fixed-effect model; Fig. 3). Benefit was evident both in the analysis of randomized trials as in cohort studies. There was no difference in the risk of thromboembolic events with the use of the two strategies (OR = 1.86, 95% CI, 0.29–12.17, $P = 0.57$; Fig. 4). This analysis was characterized by a small number of events in both groups and low heterogeneity with χ^2 of 1.01 and I^2 of 1%.

Table I.

Studies Included in the Meta-Analysis

Study	Tischenko 2009	Tolosana 2009	Ahmed 2010	Ghanbari 2012	Li 2011	Cano 2012	Birnie 2013
Reference	27	28	23	5	21	29	6
Design	Prosp cohort	RCT	Retro cohort	Retro cohort	Retro cohort	Retro cohort	RCT
Total population	155	101	345	49	423	337	681
Duration of follow-up	1 month	45 days	8 weeks	30 days	4 weeks	10 days	2 weeks
Age (mean ± SD)	O 71 ± 11	68 ± 10	71.5	66.7 ± 10.7	74.5 ± 12.8	72 ± 11	71.8± 9.9
Type of heparin	H 65 ± 11 LMWH	66 ± 11 UFH	70.9 UFH/LMWH	64.7 ± 14.9 UFH/LMWH	67.3 ± 15.1 UFH/LMWH	68 ± 15 LMWH	71.4± 10.6 LMWH
Newly implants (%)	O 54.7 H 63.2	O 76 H80	O 83.3 H 86.2	65 76	O 72.5 H 88	O 64 H 69	O 68.4 H 67.8
INR (mean ± SD)	O 2.2 ± 0.4 H 1.2 ± 0.2	O 2.0 ± 0.3 H 1.1 ± 0.2	O 2.5 ± 0.4 H 1.3 ± 0.2	2.4 ± 0.3 1.4 ± 0.3	O 2.4 ± 0.3 H 1.5 ± 0.4	O 2.5 ± 0.6 H 1.3 ± 0.2	O 2.3 (2.0–2.6)* H 1.2 (1.1–1.3)

*Interquartile range. INR = international normalized ratio; LMWH = low-molecular-weight heparin; RCT = randomized control trial; SD = standard deviation; UFH = unfractionated heparin.

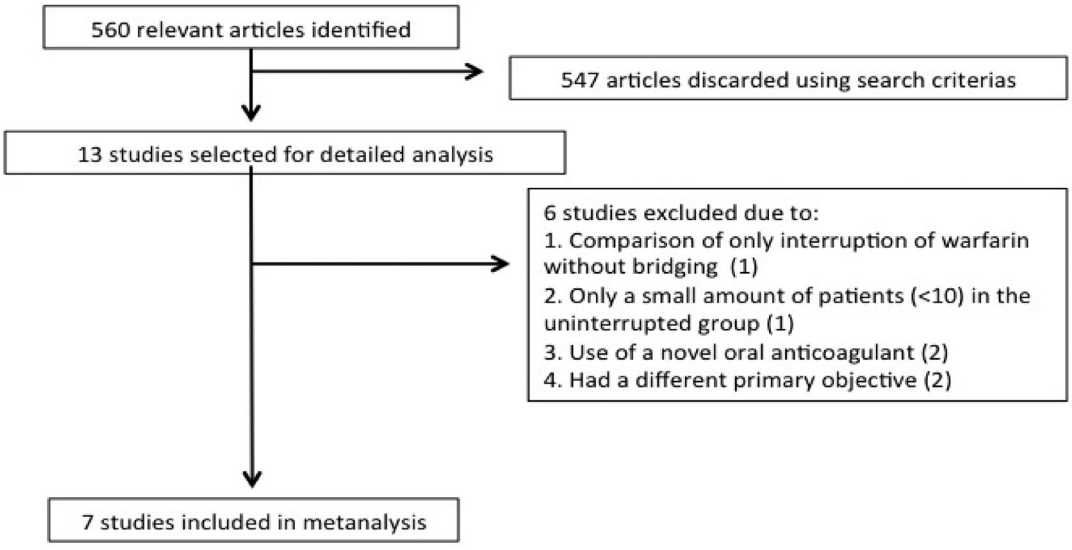

Figure 1. *Flow chart during study.*

There was no evidence of publication bias as assessed by "funnel plot" (Fig. 5).

Discussion

The results of our study demonstrate that continuous use of OAC in the perioperative setting of CIED surgery was associated with a significant reduction in the risk of developing clinically relevant hematoma. The risk of embolic events was low and similar with the use of two strategies.

The postoperative use of heparin is associated with an increased risk of bleeding events (by 14 times) when compared with patients in the control group in one study[15] and by 5–10 times in another.[16] Feng et al. hypothesize that these differences could be in part explained by the difference on the accuracy of monitoring of warfarin compared to heparin.[4] Levels considered

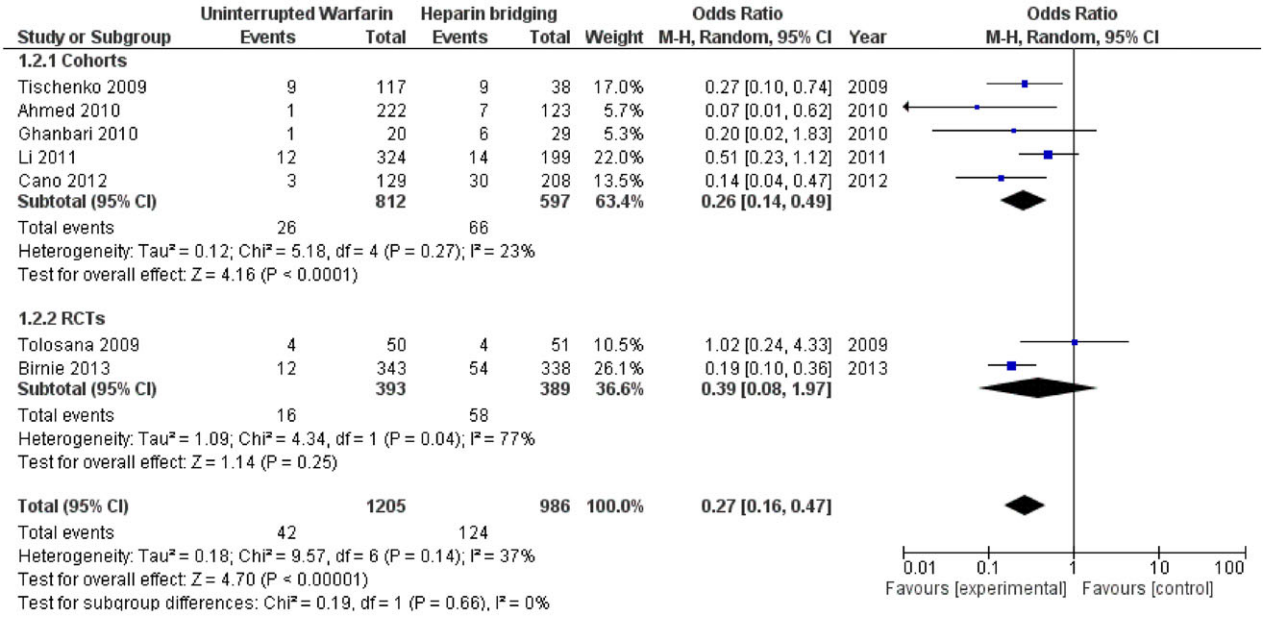

Figure 2. *Risk of pocket hematoma in patients with oral anticoagulation continuation versus heparin bridging therapy, according to study design. Random effect model.*

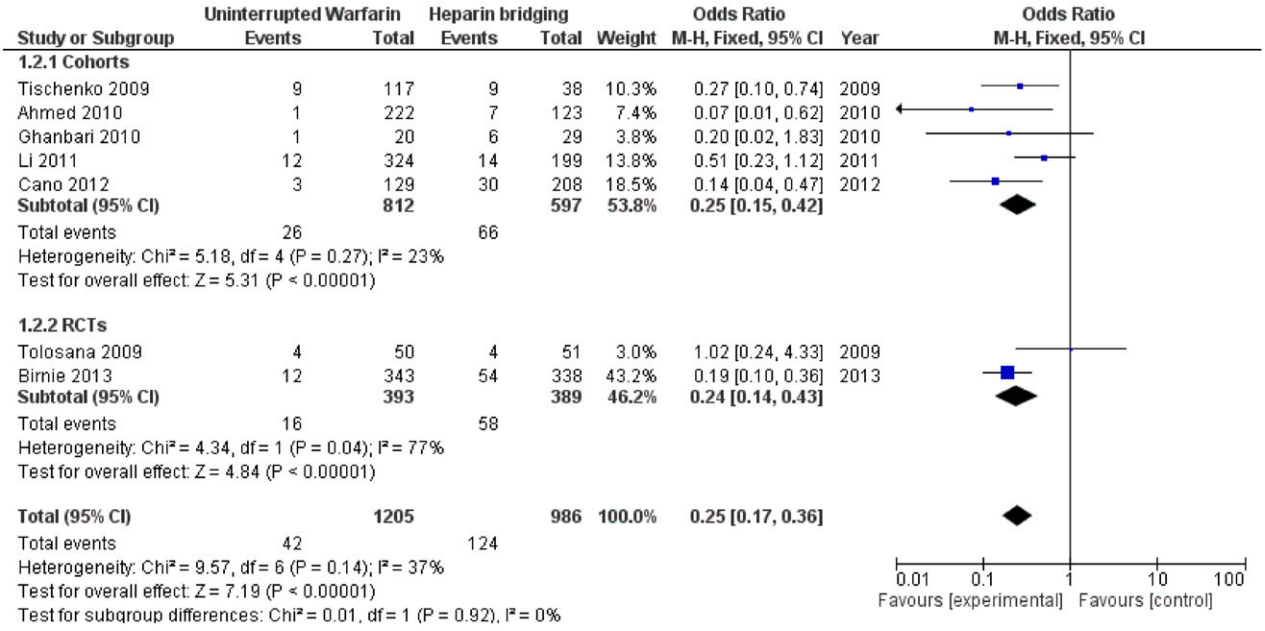

Figure 3. *Risk of pocket hematoma in patients with oral anticoagulation continuation vs. heparin bridging therapy, according to study design. Fixed effect model.*

therapeutic activated partial thromboplastin time (APTT)—1.5–2.5 times control—do not correlate well with the intensity of anticoagulation and have not been validated by randomized studies.[17] Also, heparin has antiplatelet effects that may last longer than the measurable effect on APTT and contribute to the increased risk of bleeding.[18] Meanwhile, the evidence to maintain a therapeutic INR during the procedure is based on more consistent data.[19,20]

Some authors hypothesized that when patients are undergoing surgery receiving full-dose anticoagulation, any abnormal bleeding will be

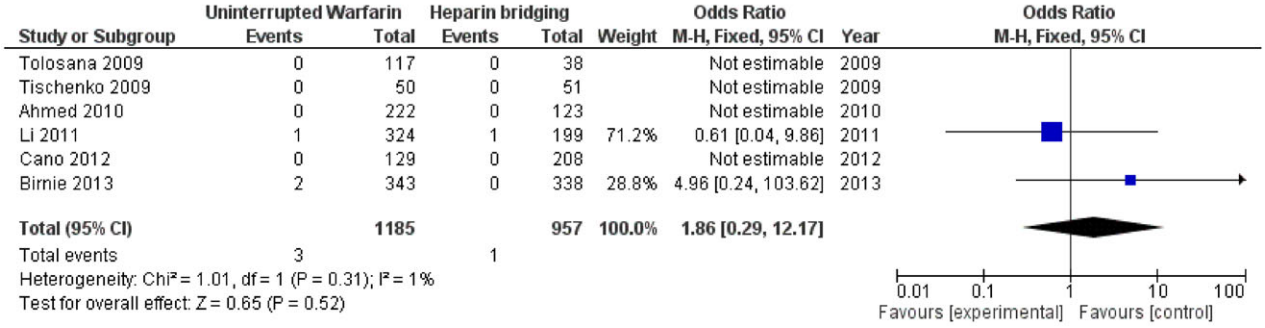

Figure 4. *Risk of embolic events in patients with oral anticoagulation continuation versus heparin bridging therapy.*

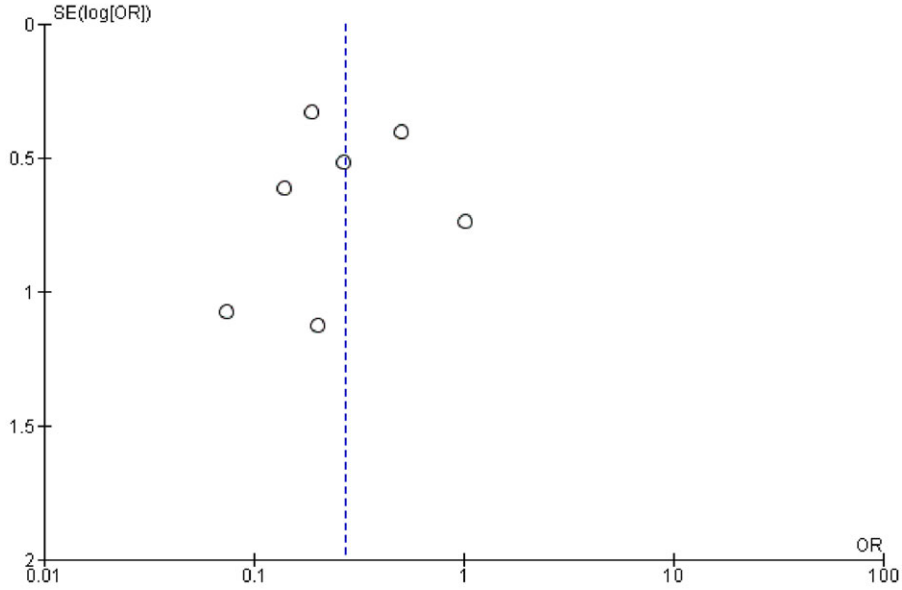

Figure 5. *The standard error (SE) of the intervention odds ratio (OR) was plotted against the OR for risk of pocket hematoma.*

detected and handled during the procedure.[6] On the other hand, bleeding caused by heparin is only apparent in the postoperative period, when full anticoagulation effect takes place and the surgical wound has already been closed. This phenomenon has been referred to as an "anticoagulation stress test."[6]

Embolic events were rare in the evaluated studies. They occurred only four times in more than 2,000 patients included in our meta-analysis, which precludes definitive conclusions about the definite risk between each strategy. In the BRUISE study, both thromboembolic events occurred in patients who were under OAC, but their INRs were below the therapeutic target at the time of the event. This suggests that the risk is probably related to the adequacy of the anticoagulation control rather than the strategy for perioperative management of OAC.

We believe that the approach of conducting CIED implant without interrupting OAC is effective in reducing the risk of periprocedural bleeding. An alternative approach would be the interruption of warfarin without heparin bridge, especially in patients deemed to be at a lower risk of thromboembolism. Interruption with no bridging was evaluated in three studies[21–23] and in one of them it was associated with increased risk of transient ischemic attack.[23] There was no significant difference in the risk of hemorrhagic complications. In accordance with the results from recent studies, the most recent AHA/ACC/HRS guideline on atrial fibrillation suggests that CIED implantation while maintaining therapeutic INR

"may be considered in those patients requiring device implantation who also have a moderate-to-high thromboembolic risk."[24] It should be emphasized that the surgery creates a prothrombotic state and that the estimation of risk in this specific period is not well defined, and it may be underestimated by the usual risk factors commonly used.

In our meta-analysis we opted not to evaluate the use of novel anticoagulants in the perioperative CIED implantation. Despite the increasing use of these drugs, few studies have addressed this question and none of them are adequately powered or designed in a randomized fashion,[9,10] preventing a more accurate analysis. In clinical practice, it seems that most centers perform the procedure after interruption of the novel OAC and without the use of heparin bridging.[25]

The main limitations present in this meta-analysis are: (1) the studies showed heterogeneous design (two randomized control trials and five cohort studies) and used different types and doses of heparin, which could influence the risk of bleeding.[26] Interestingly, we observed a similar treatment effect between RCTs and observational studies; and (2) the low number of reported thromboembolic events, which may prevent detection of small differences between groups. Of note, the total number of patients available for inclusion in this meta-analysis is insufficient to conduct a noninferiority analysis regarding risk of thromboelmolic events.

Based on our analysis of the aforementioned studies, we found that in patients with moderate-to-high risk of thromboembolic events, the strategy of performing surgery with continued warfarin is associated with a lower rate of clinically significant hematoma and bleeding complications than heparin bridging. There was no statistical difference in the occurrence of thromboembolic events in our analysis, but this may be due to the small number of events. The optimal perioperative management of short-acting novel OACs where heparin bridging is not required requires further investigation.

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