European Review for Medical and Pharmacological Sciences 2015; 19: 1461-1479

Risk of pocket hematoma in patients on chronic anticoagulation with warfarin undergoing electrophysiological device implantation: a comparison of different peri-operative management strategies

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Abstract. – OBJECTIVE: Periprocedural management of warfarin remains challenging in patients requiring electrophysiological device surgery. For patients at high risk of thromboembolic events, guidelines recommend bridging therapy with heparin; however, this strategy is associated with a high risk of pocket hematoma. This paper systematically reviews studies appraising the risk of pocket hematoma with different perioperative anticoagulation strategies.

METHODS: All relevant studies identified in MEDLINE/PubMed, The Cochrane Collaboration CENTRAL, clinicaltrials.org and in bibliographies of key articles. Estimates were combined using a fixed effects model. Heterogeneity was assessed by *p* values of χ^2 statistics and I^2. Publication bias was assessed by visual examination of funnel plots and by Egger test. Fifteen studies enrolling 5911 patients met all inclusion criteria and were included in this review.

RESULTS: Heparin bridging compared with no heparin was associated with increased risk of pocket hematoma (OR = 4.47, 95% CI 3.21-6.23, *p* < 0.00001), and prolonged hospital stay (9.13 ± 1.9 days vs. 5.11±1.39 days, *p* < 0.00001). Warfarin continuation was not associated with increased pocket hematoma compared to warfarin discontinuation (*p* = 0.38), but was associated with reduced risk of pocket hematoma compared with heparin bridging (OR = 0.37, 95% CI 0.2-0.69, *p* = 0.002). Thromboembolic complications were reduced with heparin bridging vs. no heparin (0.50% vs.1.07%, *p* = 0.02), and no significant differences were reported between heparin bridging vs. warfarin continuation (*p* = 0.83).

CONCLUSIONS: Heparin bridging is associated with a higher risk of pocket hematoma and a prolonged hospital stay. Perioperative continuation of warfarin reduces the occurence of pocket hematoma compared with heparin bridging without any significant differences in thromboembolic complications.

Key Words:
Heparin, Coagulation, Warfarin, Device, Pacemaker, Hematoma, Pocket, Electrophysiological.

Introduction

An increasing number of patients requiring permanent pacemaker (PM) or implantable cardioverter defibrillator (ICD) implantation, as high as 35-45%[1,2], are taking the oral anticoagulant (OAC) warfarin for different indications such as valve replacement, atrial fibrillation, or high risk of embolic stroke. To reduce hemorrhagic risk in these patients, it is common practice to postpone device implantation until the international normalized ratio (INR) has returned to < 1.5 by withholding warfarin and/or adminis-

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tering coagulation factors or vitamin K. Warfarin is generally restarted the night after the procedure[3]. Nevertheless, sub-therapeutic anticoagulation exposes patients with atrial fibrillation to potential thromboembolic complications, with a calculated daily risk ranging from 0.01% to 0.05%[4,5]. For this reason, perioperative bridging with heparin is currently recommended by the American College of Chest Physicians[6] in patients at moderate-to-high risk for arterial thromboembolic events. Heparin is expected to reduce venous and arterial thromboembolism by 66% to 80%[7]. Heparin bridging, however, is associated with an increased risk of bleeding events and in particular of pocket hematoma[8], a common complication often resulting in a longer postoperative hospital stay. A recent study[9] has also highlighted the strong link between pocket hematoma and re-intervention, the latter an independent predictor of ICD infections.

In summary, there are three perioperative anticoagulation strategies that one can employ: (1) continue warfarin; or (2) stop warfarin without peri-operative bridging therapy; or (3) stop warfarin and maintain anticoagulation with peri-operative heparin bridging.

The recently published BRUISE CONTROL study[10] was a large randomized trial evaluating the safety of performing PM or ICD surgery without interruption of warfarin therapy. The study randomized 681 patients with an annual thromboembolic risk of > 5% to continued warfarin vs. heparin bridging. The primary outcome of clinically significant device-pocket hematoma occurred in 3.5% of the warfarin group compared to 16% in the heparin group (relative risk 0.19; 95% confidence interval, 0.10 to 0.36; $p < 0.001$).

The current systematic review summarizes the evidence derived from previously published primarily observational studies regarding the risk of pocket hematoma associated with different perioperative strategies in patients treated with warfarin undergoing PM/ICD implantation, pooling them with meta-analytic methods and comparing to the randomized controlled trial results of BRUISE CONTROL.

Methods

This systematic review was performed in keeping with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[11].

Data Sources and Searches

To identify studies eligible to be included in this review, two independent reviewers (AL and IP) systematically searched relevant articles published between January 1990 and December 2010 in MEDLINE/PubMed, The Cochrane Collaboration CENTRAL, and clinicaltrials.org. Studies were included if they compared the use of different perioperative anticoagulation strategies in patients undergoing PM/ICD implantation if at least a portion of these patients were receiving oral anticoagulation therapy with warfarin. Further studies were sought by means of manual search of secondary sources including references from primary articles. Divergences were resolved by consensus.

Keywords were: 'pacemaker', 'implantable cardioverter–defibrillator', 'cardiac resynchronization', 'biventricular pacemaker', 'biventricular defibrillator' 'implantation', 'device surgery', 'cardiac rhythm devices', 'anticoagulation', 'warfarin', 'complications', 'bleeding', 'hemorrhage', 'hemorrhagic complications', 'pocket hematoma'.

The main inclusion criterion for selecting studies was direct comparison of different perioperative anticoagulation strategies. Exclusion criteria were publication as abstract and unpublished data. The quality of studies was scored using The Cochrane Collaboration tool for assessing risk of bias for randomized controlled trials[12] and the Newcastle-Ottawa quality assessment scale[13] for non-randomized studies.

The primary end point was pocket hematoma, defined according to the criteria used in each study as a palpable mass that protruded > 2 cm anterior to the pulse generator and lead, or as a palpable swelling of the PM/ICD pocket exceeding the size of the generator.

Secondary end points were total length of hospital stay (in days) and thromboembolic complications, defined as a composite of cerebrovascular events (stroke and transient ischemic attacks (TIA) and deep vein thrombosis (DVT).

Statistical Analysis

Three separate analyses were performed: comparing primary and secondary outcome measures for heparin bridging vs. no heparin bridging, warfarin continuation vs. no warfarin continuation and warfarin continuation vs. heparin bridging. Binary outcomes from individual studies were combined with a fixed effect model, leading to compute pooled odds ratios (ORs) with their corresponding 95% confidence intervals. Chi

square test (χ^2 test) and I^2 were calculated[14,15] to explore statistical heterogeneity and inconsistency, respectively. Finally, small study effect/publication bias was appraised by means of funnel plot inspection and Egger regression test[16]. A two-tailed p value < 0.05 was considered statistically significant. In order to confirm the above findings, we repeated meta-analytic computations using multivariable adjusted estimates stemming from individual observational studies, and pooling them with a generic-inverse-variance weighting.

Statistical analysis was performed using Review Manager (RevMan) 5.0.16 (The Nordic Cochrane center, The Cochrane collaboration, Copenhagen, Denmark, 2008) and SPSS 11.0 (SPSS, Inc., Chicago, IL, USA).

Results

Search Results and Study Identification

We identified 192 articles of which 15 met all inclusion and exclusion criteria (Figure 1). These 15 studies enrolled 5911 patients and were included in this review. Of these, 6 studies compared heparin bridging vs. no bridging[1,17-21], 3 studies compared warfarin continuation vs. no warfarin continuation[2,22,23], 2 studies compared warfarin continuation vs. heparin bridging[24,25], 1 study compared both warfarin continuation vs. no warfarin continuation and warfarin continuation vs. heparin bridging[26], and 3 studies compared all three perioperative strategies[27-29]. Two studies were randomized trials[24,25], while the remaining were registries. Agreement between investigators regarding data search was good (Kappa = 0.9) (Table I).

Heparin Bridging vs. no Heparin

Overall, 10 of the included studies compared heparin bridging vs. no heparin[1,17-21,26-29]. These studies involved 1637 patients (61% male) treated with heparin bridging and 2411 (59% male) treated without heparin (1770 patients not on anticoagulation and 641 patients in whom anticoagulants were stopped without bridging). Of the 2278 patients on anticoagulation, indications for oral anticoagulation were atrial fibrillation/flutter (65%), prosthetic heart valves (21%), left ventricular dysfunction (9%), or intracardiac thrombus/deep vein thrombosis/pulmonary embolism/stroke prophylaxis (5%). Of the 1757 cases for which data was available, the type of implant was PM in 54% (49% DDD, 5% VVI, 3% replacements), ICD in 36% (14% DDD, 21% single chamber ICD and 1% replacements), cardiac resynchronization therapy (CRT) in 7%.

Heparin bridging compared with no heparin revealed a cumulative OR for pocket hematoma of 4.47 (95% CI 3.21-6.23) (Figure 2 a), with no significant heterogeneity among studies (I^2 = 0%;

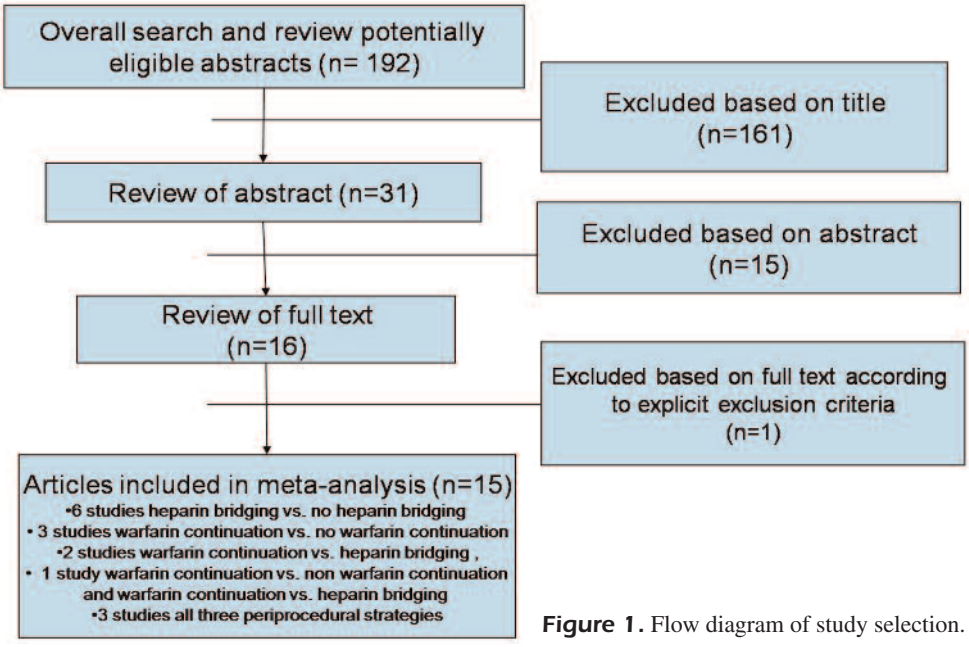

Figure 1. Flow diagram of study selection.

Table I. Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patients with indication for OAC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under OAC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Goldstein et al, 1998 Retrospective study PE definition: not defined Selection:****; Comparability:*; Outcome:***;	251/37	Group a: 37 Warfarin group Group b: 113 no warfarin group		Group a: 2,5 Group b: 1.1	Group a: 0 (0%) Group b: 0 (0%)	No thromboembolic events
Michaud et al, 2000 Retrospective study	192/49 • 37% MV • 61% AF • 2% DPV		Group a: 49 patients consecutively randomized to: a) iv heparin after 6h (26) b) iv heparin 24h postoperatively, all patient received warfarin starting the evening of surgery (30 AF, 18 mechanical valve, 1 deep venous thrombosis)	All patients had an INR < 1.5 on the day of surgery	Group a: 10 PE (20%),	Group a: no thromboembolic event
PE definition: palapable mass that protunded ≥ 2 cm anterior to the pulse generatoriand lead(S) Comparability:*; Outcome:***;			Group b: 28 patients received only postoperatory warfarin (reinstituted the night of surgical procedure) Group c: 115 no anticoagulation	Group c: 2 of 115 (2%)	Group b: 1 of 28 (4%) Group c: no • 6 PE of 26 patients (22%) iv heparin after 6h • 4 PE of 23 patients (17%) iv heparin 24h postoperatory (P0,7)	Group b: a stroke thromboembolic event Hospital stay: Post operative days was longer in the bridge group in comparison with warfarin group and control group (3.6 ± 2.9 vs 2,3 ± 1.1 vs 2.5± 2.5; $p = 0.002$)

Table continued

Table I. *Continued.* Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patients with indication for OAC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under OAC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Giudici et al, 2004	1025/473					
Retrospective study		Group a: 470 patients without reversal of oral anticoagulation		Group a: (procedural INR > 1.5 with a mean of INR 2.6 ± 1 and a range of 1.5-7.5).	Group a: 12 (2.55%)	Group a: no thromboembolic events
PE definition: not defined Selection:***; Comparability:*; Exposure:***;		Group b: 555 non anticoagulant group (included patients whose warfarin had been discontinued or reversed (3) and patients on no anticoagulant therapy)		Group b: < 1.2	Group b: 12 (2.16%)	Group b: a CVA
Marquie et al, 2004 Case control		Group a: 89 patients a) For MV (38 with mechanical valve) suspension of anticoagulant 3 days (acenocoumarol) and 4 days (warfarin, fluindione and phenindione) susbstitue it with heparin iv (aptt 60s) until 5h prior to surgery. heparin subcutaneous (30) until 12h or heparin IV (30) b) In AF group the substitution with heparin was made according to referring physician preference using subcutaneous hepain until 12h surgery	Group a: in 89 patients heparin was reinitiated post-operative (all patients with MV and 51 pt with AF). Coumadin were reinstituted and heparin suspended when INR target was reached	INR pre surgery was controlled was below 1.2 and aptt 45 s	Group a: 89 patients with heparin postprocedural: 21 patients with severe AEs with 14 pocket hematomas	No thromboembolic events
PE definition: not defined Selection:**; Comparability:*; Exposure:***;		Group b: 89 controls cases matched for gender age and surgical details	Group b: no anticoagulant		Group b: 7 patients with severe AEs with 1 pocket hematoma	Hospital stay: was prolonged from 7 days in bridge group when compared with control cases (14 ± 6.6 7.3 ± 3.9; $p < 0.0001$)

Table continued

Table I. *Continued.* Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patients with indication for OAC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under OAC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Wiegard et al, 2004 Retrospective study PE definition: any palpable swelling of the PM pocket exceeding the size of the generator Selection:****; Comparability:*; Outcome:***;	1865/1033 • 67% AF • 16% MV • 14% LV • 2% DEP	Group a: (n = 1033) oral anticoagulant therapy was discontinued 1-5 days before implantation and was replaced by heparin as soon as the INR decreased to < 2. Before implantation, therapy with IV heparin was interrupted at least for 3h, UFH for 6h and LMWH for 12h	Group a (Bridging therapy): were divided into two groups 1) High dose heparinization (n = 551): a) bolus administration of 2500-5000UI heparin followed by continuous infusion (targeted aPTT levels were 40 to 60 s) b) heparin infusion without bolus administration, with iv heparin, subcutaneous UFH or by LMWH 2) Low-dose heparin (n = 482) a) low dose heparin therapy for 1 to 5 days after implantation then oral anticoagulant was restarted with high-dose or low dose	All implantation INR < 1.5	Group a: Bridging therapy n = 79 (7.67%) High dose heparinization n = 65 (11.6%) • 28% with bole + infusion heparin • 8% with subcutaneous UFH • 11,6% with IV heparin • 16.1% with subcutaneous LMWH Low-dose heparin: n = 14 (2.9%)	Group a: 2 stroke 4 venous thrombosis
		Group b: (n = 765) control group without OAC indication	Group b: control group received low dose heparin for prophylaxis of deep venous thrombosis	Group b: n = 19 (2.5%)		Group b: 3 stroke 10 venous thrombosis
Milic et al, 2005 Prospective randomized study PE definition: a palpable mass that protruded > 2 cm Allocation sequence: yes Allocation concealed: yes Blinding: no Complete outcome data: yes Full reporting: yes	81/81 • 6%MV • 89% AF • 4% DVT	Group a: 40 patients iv heparin. Treatment with heparin was discontinued 6 h before intervention	Group a: postoperative iv heparin was infused 8h after implantation at 1000U/h without a bolus dose (target aptt 1.5-2.2 times the control value). And coumadin restarted the night of surgical procedure		Group a: 5(%); 2 minor and 3 significant (2 receiving evacuation)	Group a: no thromboembolic events
		Group b: 41 patients received warfarin for long term	Group b: warfarin continuation	Group b: 1.8-3.8	Group b: 5(%); 4 minor and 1 significant	Group b: a patient in the control group developed a stroke 2 days postoperatively Hospital stay: Patients treated with heparin remain in the hospital a mean of 4,3 ± 2.8 postoperative days Vs 2,6 ±1.3 inpatients treated with warfarin

Table continued

Table I. *Continued.* Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patients with indication for OAC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under OAC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Robinson et al, 2009 Retrospective study PE definition: A palpable swelling of the PM pocket, exceeding the size of the generator, that require reoperation or interruption of oral anticogulation. Selection:****; Comparability:*; Outcome:***;	148/148 • 73% AF/flutter • 12% LVD • 10% MV • 2% IT • 1% DEP • 1% Stroke prophylaxis	2 Preoperative strategies: 1) LMWH until evening prior and reinitiated on postoperative day 3 (106) 2) LMWH omitted on the evening before surgery (42)	Group a: postoperative LMHW at 3 days with warfarin (74; nopre 7; pre 67) Group b: no postoperative LMHW warfarin first days (74; nopre 35; pre 39)	Patients with pocket hematoma had a slighty higher INR on the day of surgery (1.24 vs 1.17)	Group a: 17 (23%) Group b: 6 (8.1%)	No thromboembolic event
Cheng et al, 2009 Retrospective study PE definition: palpable and visible soft mass in the PM pocket with or without the need of evacuation. Selection:***; Comparability:*; Outcome:***;	109/109 • 100% MV	2 Preoperative strategies: 1) 51 patients with warfarin suspended 3 days before surgery 2) 58 patients suspended < 3 days or not at all	Group a: 18 patients prescribed with low-molecular-weight heparin post-operatively Group b: 91 patients no heparin		Group a: 3 Group b: 2	Group a: no thromboembolic event Group b: one patient developed stroke

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Table I. *Continued.* Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patients with indication for OAC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under OAC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Amara et al, 2009 Retrospective study PE definition: palapable mass that protruded ≥ 2 cm anterior to the pulse generator and lead (S) Selection:****; Comparability:*; Outcome:***;	461/ 106 • 90% AF • 10% MV	Group a: 30 (6.5%) had oral anticoagulant suspended 72h before surgery and switched to heparin/LMWH. Therapy with IV heparin was interrupt at least for 6h, and LMWH for 12h suspended	Group a: bridge therapy postoperative heparin 10000UI/24h) 12h post procedure plus AOC 24 post procedure/patient with LMHW 48 h post procedure	INR < 1.5	Group a: 6/30 (20%) in the bridge group	No thromboembolic event
		Group b: 76 patients had their oral anticoagulant disrupted for 48 h before procedure	Group b: suspension anticoagulant (objective INR 1.5) and restarted the night post procedure		Group b: 2/76 (2.6) in the OAC without bridging ($p < 0.05$)	
		Group c: 355 control group	Group c: no anticoagulant		Group c: 10/355 (2.8%) in the control group ($p < 0.006$)	Hospital stay: was longer in the bridge group in comparison with OAC and control group (9 vs 7 vs 6 days $p = 0.006$)
Tischenko et al, 2009 Case control PE definition: a palpable tense swelling causing severe pain that required prolonged hospitalization and/or discontinuation of OAC or surgical evacuation or blood transfusion or incremental outpatient follow-up Selection:***; Comparability:*; Exposure:***;	272/155 • 74% AF • 18.7% Previous TIA/ICTUS • 10.3% VM • 3.2 DVT	Group a: 117 patients on long-term warfarin without interruption of warfarin		Group a: 2.2 ± 0.4 (target INR 2-3)	Group a: 9 (7.7%), and one required surgical revision (0.9%).	no thromboembolic event
		Group b: 38 patients who underwent interruption of warfarin therapy 5 days before and bridging with dalteparin (200U/kg SC OD) on days 3.2 and 1 before procedure	Group b: warfarin and dalteparin were restarted 24 h after surgery and cotinnuedntil INR was > 2	Group b: 1.2 ± 0.2	Group b: 9 (23.7%, $p = 0.012$); 3 of whom required reoperation (7.9%, $p = 0.046$).	
		Group c: 117 age and sex matched controls not taking warfarin		Group c: normal	Group c: 5 (4.3%), none of which required revision ($p = 0.41$).	

Table continued

Table I. *Continued.* Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patients with indication for OAC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under OAC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Tolosana et al, 2009 Prospective randomized study PE definition: a palpable mass that protrunded > 2 cm anterior to pulse generator Allocation sequence: yes Allocation concealed: yes Blinding: single Complete outcome data: yes Full reporting: yes	101/101	Group a: bridging from OAC to heparin infusion 51 pt. OAC was discontinued 4 days before and IV heparin was started at INR < 2 and stopped 6h before he implant Group b: maintenance of OAC	Group a: started 24h after implantation with bolus of 60 UI/kg and infusion rate with aPTT of 55-70 sec. OAC restart the night of the procedure. Heparin was stopped when INR > 2	Group a: 1.1 ± 0.2 Group b: 2 ± 0.3	Group a: 4/51 patients (7.8%) from heparin group developed pocket hematoma following implant. One hematoma required evacuation (1.9 vs. 2%, $p = 1.00$). Group b: 4/50 (8.0%) from the OAC group developed pocket hematoma following the implant ($p = 1.00$). One hematoma required evacuation (1.9 vs. 2%, $p = 1.00$).	No thromboembolic events Hospital stay: was longer in the heparin group [median of 5 (4-7) vs. 2 (1-4) days; $p < 0.001$].
Thal et al, 2010 Retrospective study PE definition: Not reported Selection:****; Comparability:*; Outcome:***;	200/58	Group a: Warfarin (53), Group b: ASA (82), Group c: clopidogrel (2) Group d: dual antiplatelet therapy (DAPT, 15 and 5 DAPT + Warfarin) Group e: control group 43		Group a: 1.9± 0.6	Group a: 1 (1.88%) Group b: 1 (1.21%) Group c: 0 (0%) Group d: 5 (25%) Group e: 0 (0%	No thromboembolic events

Table continued

Table I. *Continued.* Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patient with indication for AOC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under AOC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Ahmed et al, 2010	459/459 • 51.8% FA • 6.9% MV	Group a: 222 Continued warfarin group		Group a: 2.57 ± 0.49 (range 1.5-4.7)	Group a: 1 (0.45%) in the continued warfarin group	Group a: no complication
Retrospective study PE definition: a palpable tense swelling causing severe pain that required rolonged hospitalization and/or discontinuation of AOC or surgical evacuation or blood transfusion	• 5.8% DVT • 0.87% Left ventricular thrombus	Group b: 123 Bridging group. Warfarin was discontinued 3 to 5 days prior to the surgery or the INR was normalized by coagulation factors or vitamin K. Patients received bridging therapy when INR was expected to be subtherapeutic. Intravenous heparin was discontinued 4 to 6 hours prior to the procedure.	Group b: Intravenous heparin was restarted without bolus administration 12 hours after the procedure. The last dose of subcutaneous enoxaparin (1 mg/kg q12h) was given 12 to 18 hours prior to the procedure and restarted 24 hours after the procedure. Warfarin was reinstituted in the evening of the day of surgery. Bridging therapy was discontinued when INR reached the therapeutic range	Group b: 1.33 ± 0.20	Group b: 7 (5.7%) in the bridging group, and	Group b: one TIA within 3 days postoperatively (0.8%)
Selection:****; Comparability:*; Outcome:***;		Group c: 114 Anticoagulation withheld group. Warfarin was discontinued 3 to 5 days prior to the procedure or the INR was normalized by coagulation factors or vitamin K. Device procedure was performed when INR was < 1.5.	Group c: Warfarin was restarted in the evening of the day of surgery. Patients did not receive bridging therapy perioperatively.	Group c: 1.35 ± 0.32	Group c: 2 (1.75%) in the anticoagulation withheld group.	Group c: 4 TIA within 3 days postoperatively (3.5%) had anticoagulation withheld
Ghanbari et al, 2010 Retrospective study PE definition: a palpable mass that protrunded > 2 cm	123/49 • 90% FA • 10% MV	Group a: 29 had oral anticoagulants suspended 4 days before surgery and switched to heparin/LMWH. Therapy with IV heparin was interrupt at least for 4h, and LMWH for 12h suspended	Group a: intravenous heparin or low molecular weight heparin	INR 1.35 ± 0.27		
Selection:****; Comparability:*; Outcome:***;		Group b: 20 continued warfarin group	Group b: Warfarin continuation With INR target 2-3	INR 2.39 ± 0.29	Group b: 1	
		Group c: 74 control group	Group c: no anticoagulant	INR 1.12 0.14	Group c: 3	Hospital stay: Post operative days was longer in the bridge group in comparison with warfarin group and control group (3.7± 3.2 vs 2.9 ± 2.7 vs 1.6 ± 1.6; $p < 0.001$)

Table continued

Table I. *Continued.* Studies evaluating the occurrence of pocket hematoma post PM/ICD implantation in patients with indication for OAC.

Study and year Study type and PE definition Quality assessment of trials	Total Patients/ Patients under OAC (indication)	Preimplantation Treatment (n)	Postimplantation Treatment (n)	Procedural INR	Pocket hematoma (PE) n (%)	Thromboembolic complications and hospital stay
Tompkins et al, 2010	1388/450	Group a: 258 warfarin interrupted		INR < 1.5	Group a: 6	Group a: 1 stroke/TIA and 1 DVT
Retrospective study		Group b: 46 Warfarin continuation			Group b: 0	Group b: no thromboembolic event
PE definition: Not defined		Group c: 154 bridging therapy		INR > 1.5	Group c: 10	Group c: 1 stroke/TIA
Selection:****; Comparability:*; Outcome:***;		Group d: 255 control			Group d: 3	Group d: 4 DVT
		Group e: Aspirin 536			Group e: 17	Group e: 5 DVT
		Group f: 139 DAPT			Group f: 5	Group f: 1 stroke/and 1 DVT

p for heterogeneity = 0.49) despite statistical evidence of small study effect/publication bias (p = 0.01) (Figure 2 b).

Four studies[17,18,20,26] showed that heparin bridging significantly prolonged the duration of hospital stay (9.13± 1.94 days vs. 5.11±1.39 days), with a weighted mean difference (WMD) of 2.43 days (95% CI 1.79-3.08, $p < 0.00001$) (Figure 3).

Warfarin Continuation vs. no Warfarin Continuation

We have included in our meta-analysis 7 studies[2,22,23,26-29] comparing warfarin continuation vs. no warfarin continuation. These studies involved 970 patients (53% male) undergoing PM/ICD implantation while on anticoagulation and 1529 patients (55% male) not on anticoagulation. Indications for anticoagulation were: atrial fibrillation/flutter (79%), prosthetic heart valve (14%) and intracardiac thrombus/deep vein thrombosis/pulmonary embolism/stroke prophylaxis (9%). Of the 837 cases for which data was available, the, type of implant was PM in 54% (36% DDD, 8% VVI, 9% replacements), ICD in 44% (13% DDD, 31% single chamber ICD), and CRT in 2%. Our analysis showed that the rate of pocket hematoma did not significantly differ if warfarin was continued or not (2.68% vs. 2.03%, OR = 1.28, 95% CI 0.73-2.26, p = 0.38) (Figure 2 a). No significant heterogeneity among studies was detected (I^2 = 0%; p heterogeneity = 0.64) and no small study effect/publication bias was observed (Figure 2 b). We could not determine whether either strategy significantly prolonged the duration of hospital stay as only one study reported such data[26].

Warfarin Continuation vs. Heparin Bridging

We have analysed 5 studies comparing warfarin continuation with heparin bridging. These studies[24,25,27-29] involved 476 patients in whom anticoagulation was not stopped and 406 patients treated with heparin bridging. A significantly reduced risk of pocket hematoma with warfarin continuation was evident, with a cumulative OR of 0.37 (95% CI 0.2-0.69, p = 0.002), without significant heterogeneity among studies (I^2 = 42%; p for heterogeneity = 0.14) (Figure 2 a). Funnel plots and Egger test revealed no small study effect/publication bias (Figure 2 b). We could not determine whether either strategy significantly prolonged the duration of hospital stay as only three studies reported such data[24-26].

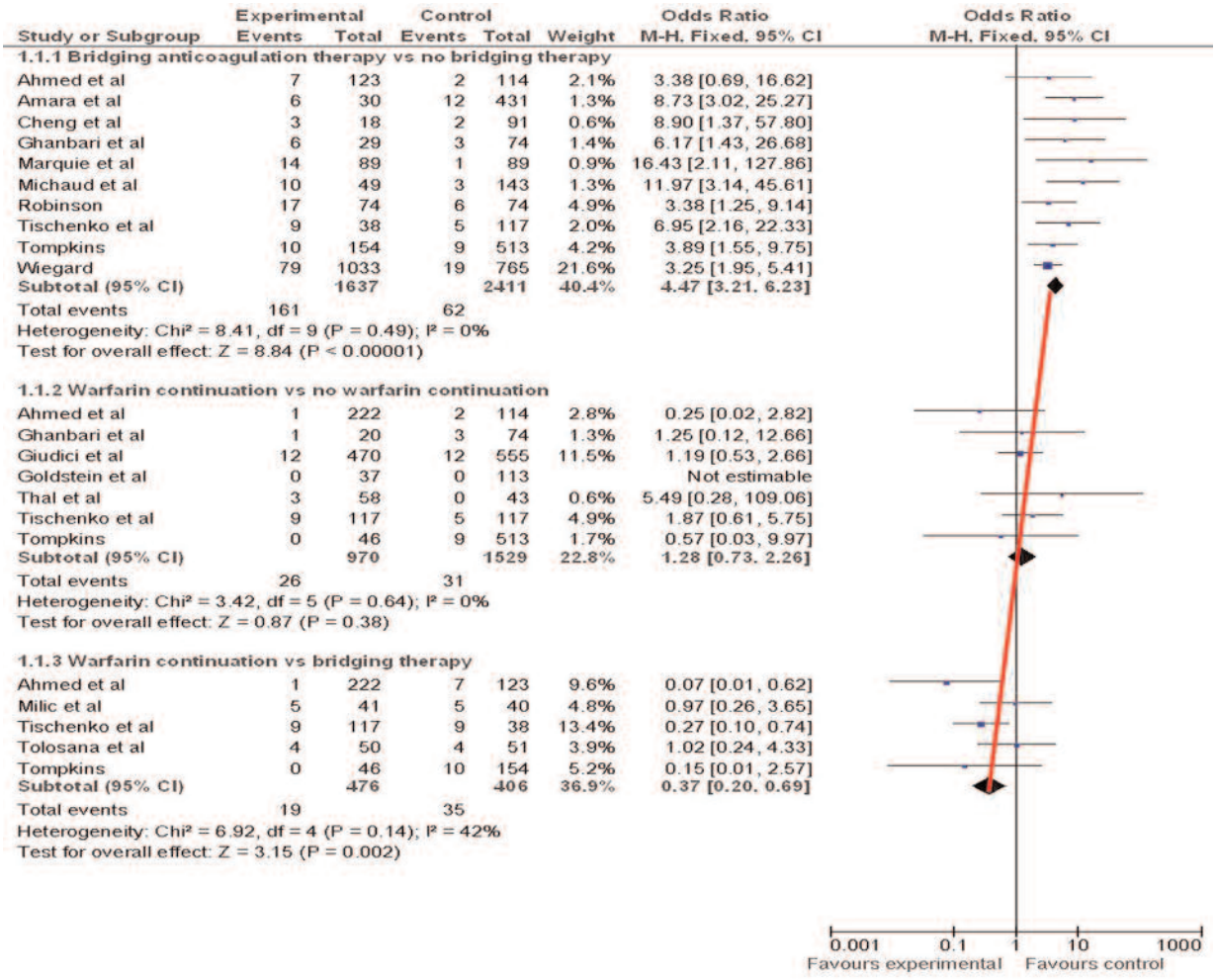

Figure 2A. Forest Plot for Odds Ratio of pocket hematoma associated with the use of different periproceduralstrategies.

Thromboembolic Complications

Fourteen[1,2,17-25,27-29] of the 15 studies included in this meta-analysis reported data about thromboembolic complications, which were rare in these studies. Among the 5780 patients included, the rate of perioperative stroke/transient ischemia was 0.40% (n = 23) and the rate of DVT was 0.42% (n = 24). There was a significant reduction in the thromboembolic complications end point with heparin bridging vs. no heparin (0.50% vs. 1.07%; OR = 0.39, 95% CI 0.18-0.85, $p = 0.02$) and a strong trend toward reduction in thromboembolic complications with warfarin continuation compared with no warfarin continuation (0% vs. 0.76%; OR = 0.21, 95% CI 0.04-1.14, $p = 0.07$) (Figure 4 a), mainly due to reduction in DVT rate (Figure 4 b). No significant differences in thromboembolic complications were reported between the groups of heparin bridging vs. warfarin continuation (0.21% vs. 0.49%; $p = 0.83$).

Multivariable Analysis

The meta-analytic computations using pooled multivariable adjusted estimates confirmed the above findings. Heparin bridging vs. no heparin was associated with a higher risk of pocket hematoma (OR 5.58, 95% CI 3.76-8.29, $p < 0.0001$). Warfarin continuation vs. heparin bridging was associated with a significantly reduced risk of pocket hematoma (OR 0.41, 95% CI 0.22-0.77, $p = 0.005$) (Figure 5). Moreover, this analysis also confirmed a significant reduction in thromboembolic complications with heparin

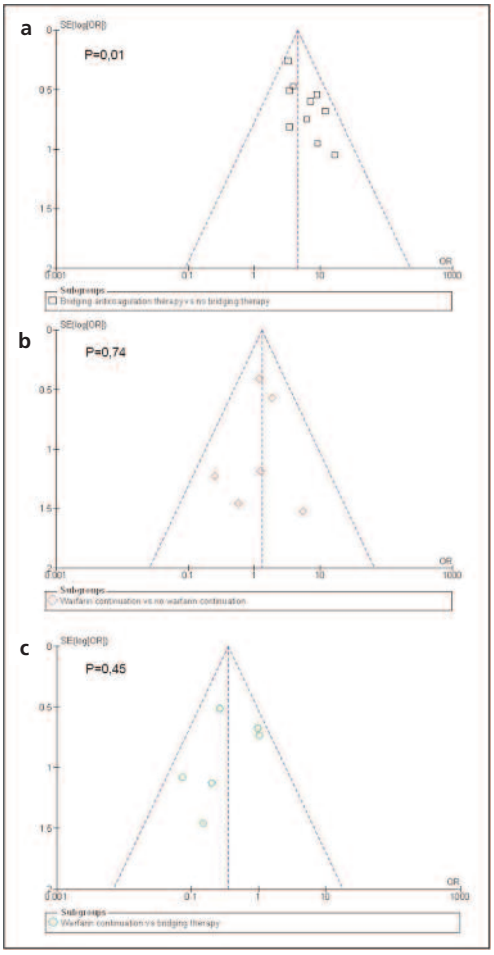

Figure 2B. Funnel plots of trials included in the meta-analysis. ***a,*** Bridging therapy vs control, ***b,*** warfarin continuation vs no warfarin continuation, ***c,*** warfarin continuation vs bridging therapy. *p* values are derived from Egger's test.

bridging vs. no heparin (OR 0.44, 95% CI 0.22-0.91, $p = 0.03$) and a trend toward a reduction in thromboembolic complications with warfarin continuation compared with no warfarin continuation (OR 0.26 95% CI 0.05-1.48, $p = 0.13$) (Figure 6).

Discussion

The perioperative management of patients on OAC who require PM/ICD implantation is still a matter of debate. European guidelines on non-cardiac surgery[30] and the American College of Chest Physicians guidelines on perioperative management of antithrombotic therapy (6) recommend discontinuation of OAC with heparin bridging at doses prolonging aPTT to 60 seconds in patients with a prosthetic valve and in patients considered at high risk of thromboembolic events. Nevertheless, several studies using different protocols have demonstrated that heparin bridging is associated with a higher risk of hemorrhagic complications[8,20,21,28,29]; some investigators have even recommended against this strategy because of higher perioperative bleeding risk[31]. The efficacy and low risk of warfarin continuation strategy was initially suggested by two previous small studies[22,28]. Goldstein et al[22] demonstrated the safety of outpatient PM placement in 37 patients on OAC (mean INR 2.5). Al-Khadra et al[33] reported no hematoma or other bleeding complications in 47 patients undergoing device implantation on OAC (mean INR 2.3).

In our meta-analysis, warfarin continuation did

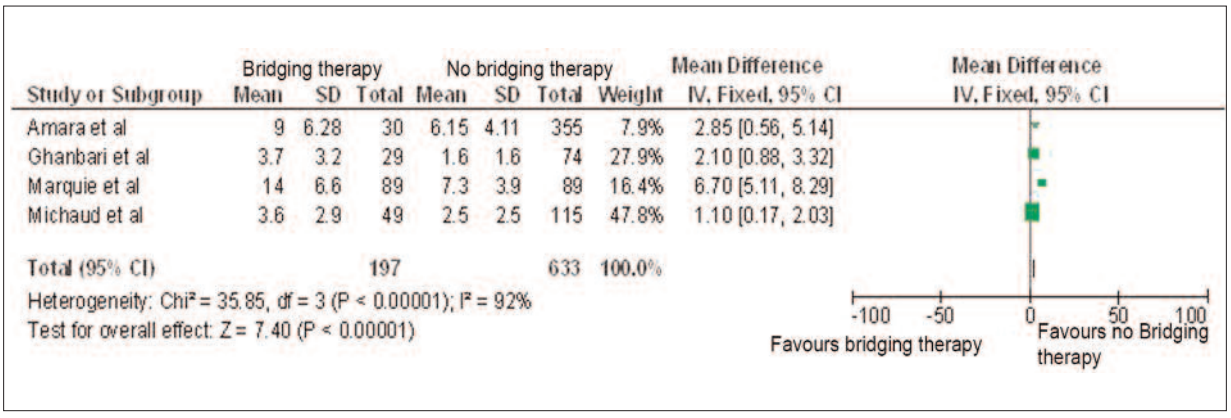

Figure 3. Hospital stay (days) - Forest Plot for weighted mean difference (WMD) of hospital stay (days) with the use of heparin bridging therapy vs no bridging therapy.

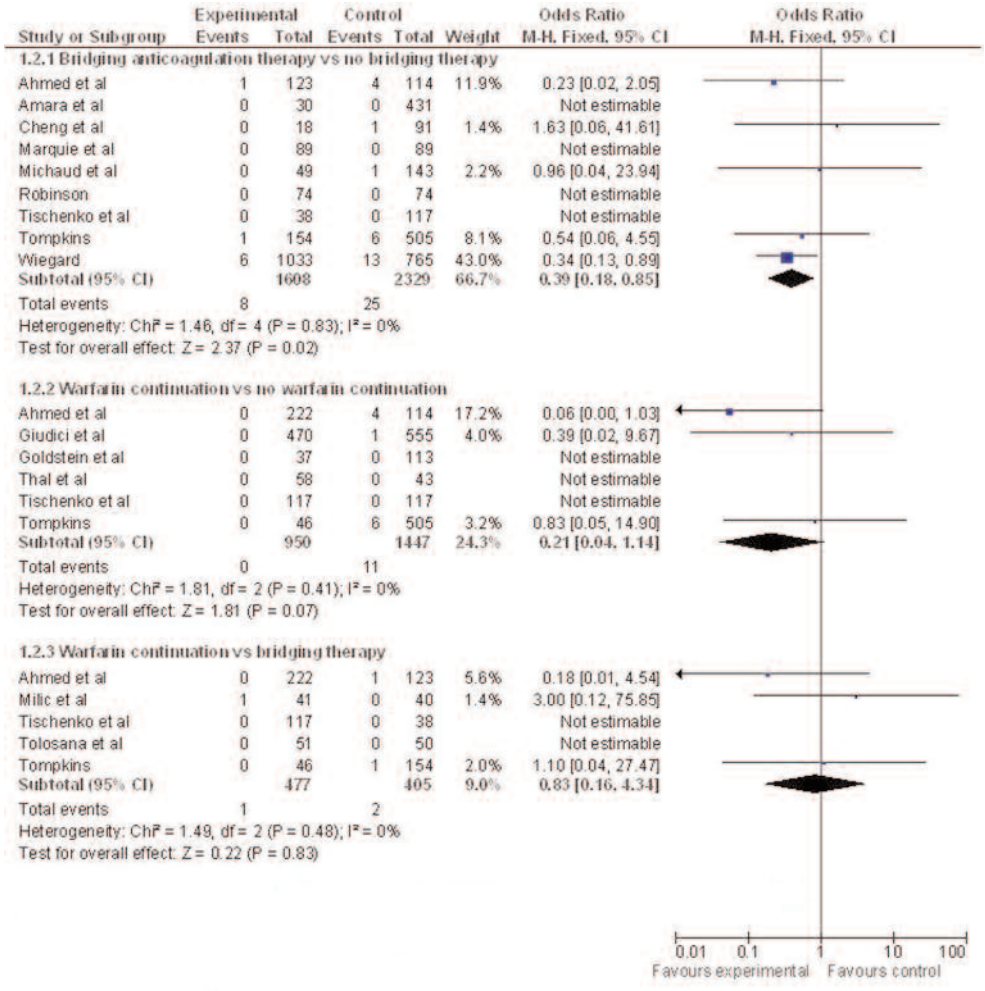

Figure 4A. Composite of Stroke/TIA and DVT - Forest Plot for Odds Ratio of composite of stroke/TIA and DVT with the use of different periprocedural strategies.

not increase the risk of bleeding compared with warfarin discontinuation (2.68% vs. 2.03%, p = 0.38). Furthermore, when compared to a heparin bridging strategy, warfarin continuation was associated with a 60% reduction in risk of pocket hematoma in patients who underwent PM/ICD surgery. The increased risk of hematoma with heparin was independent of the choice of unfractionated heparin vs. low molecular weight heparin, as previously suggested[18,32-34]. These findings were validated in the randomized BRUISE CONTROL trial that showed a significantly lower rate of device-pocket hematoma in patients undergoing PM/ICD surgery without interruption of warfarin therapy, as compared with bridging therapy with heparin (3.5% vs. 16.0%, p = 0.001)[10]. Of note, continued warfarin therapy was not associated with any major perioperative bleeding events.

Our meta-analysis showed no significant difference in thromboembolic complications between the groups of heparin bridging vs. warfarin continuation (0.21% vs. 0.49%; p = 0.83). In the BRUISE CONTROL study there were no thromboembolic events in the heparin-bridging group, while two patients with atrial fibrillation and high CHADS2 scores in the continued-warfarin group had embolic events (in the context of sub-therapeutic INRs). Importantly, our meta-analysis found that strategies involving complete interruption of anticoagulation (i.e. warfarin discontinuation without bridging vs. heparin bridging or continued warfarin) were associated with a greater than twofold risk of thromboembolism. This highlights the impor-

tance of avoiding interruption of anticoagulation particularly in patients at high risk of thromboembolism.

The analysis of the 4 studies that reported the length of hospital stay[17,18,20,26] showed that the heparin bridging also significantly prolonged hospitalization. These results confirm that continuation of warfarin without heparin bridging seems to offer the best compromise for minimizing perioperative bleeding without increasing thromboembolic risk.

Similar rates of pocket hematoma have been reported in patients with a wide range of procedural INR values from supra- to sub-therapeutic, suggesting that operator experience and intraoperative pocket management might play an important role[1]. Other methods of reducing pocket hematoma have been considered. Milic et al[25] reported that in 81 patients with an indication for OAC, a fibrin sealant prior to wound closure was associated with a 0% hematoma rate vs. 25% rate of hematoma in the control group ($p < 0.05$). A portable drainage device prior to wound closure was also reported to significantly reduce the risk of pocket hematoma also in the study by Wang et al[35].

Limitations

Our meta-analysis is a pooled analysis, not based on individual data, and a propensity score approach could not be used. Our study is mainly based on observational, non-random-

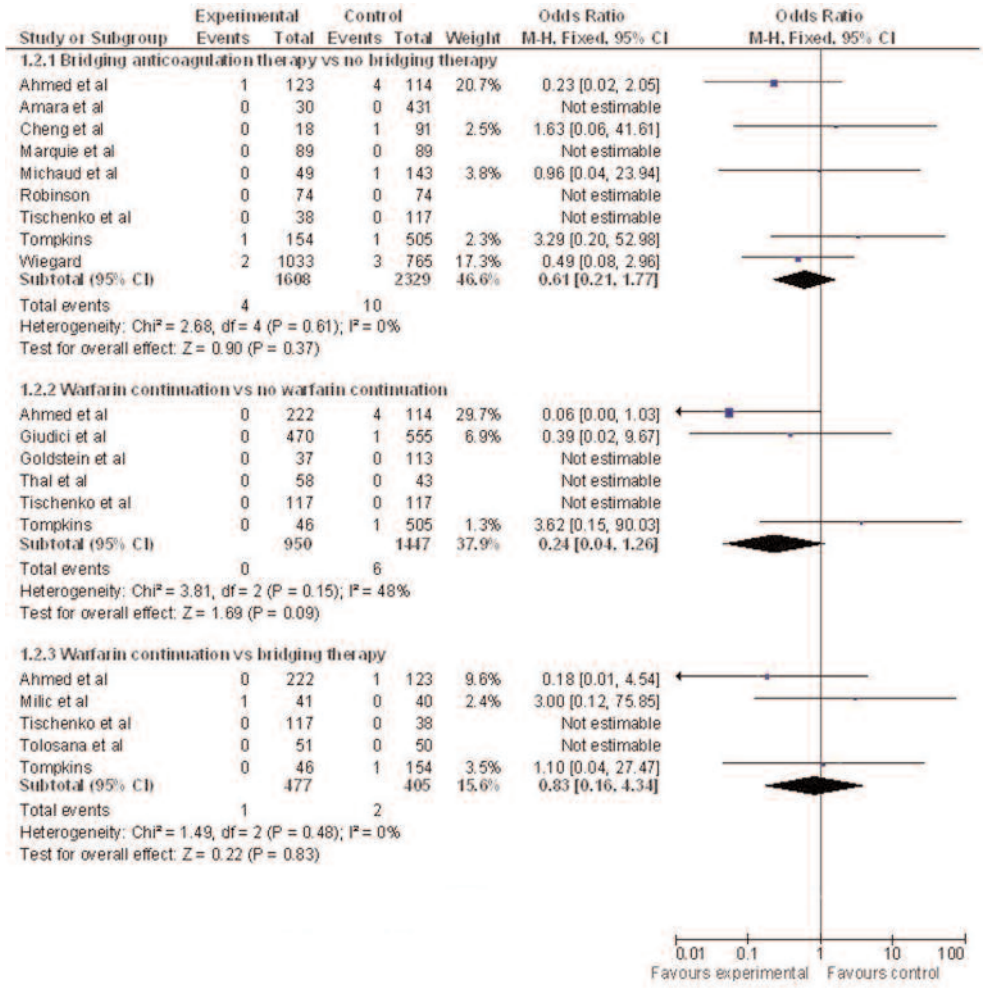

Figure 4B. Composite of Stroke/TIA - Forest Plot for Odds Ratio of stroke/TIA with the use of different periprocedural strategies.

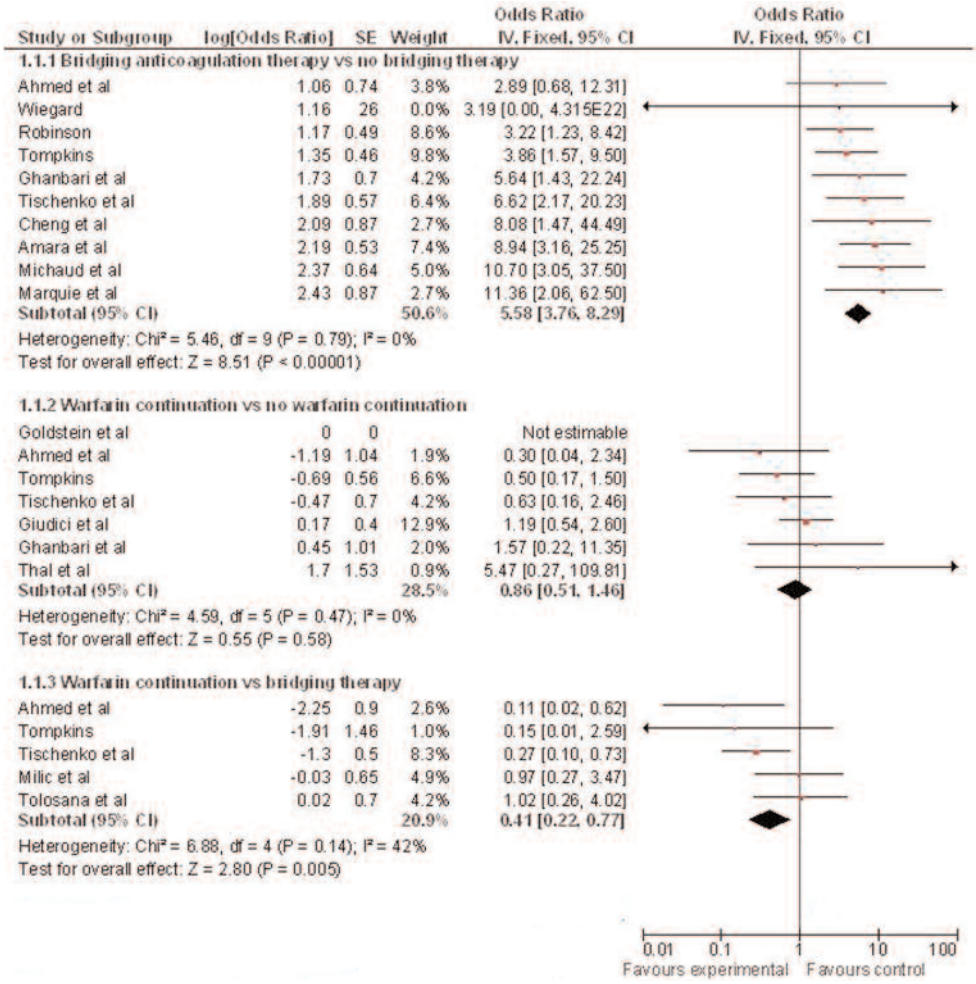

Figure 5. Forest Plot for Odds Ratio of pocket hematoma with the use of different peri-procedural strategy using pooled multivariable adjusted estimates.

ized data, and differences in baseline characteristics, drug therapies, procedural techniques and operator experience cannot be excluded. A small study effect/publication bias may be present.

Conclusions

Our analysis suggests an increased risk of pocket hematoma in patients requiring OAC who undergo electrophysiological device implantation with interruption of warfarin therapy and employment of a heparin bridging strategy. On the other hand, the perioperative continuation of warfarin reduces the occurence of clinically significant device-pocket hematoma and the duration of hospital stay, without any increase in thromboembolic events. These findings, based on observational studies and two underpowered negative randomized studies, were confirmed by the large multicentre randomized controlled BRUISE CONTROL trial. In light of evidence suggesting increased risk of thromboembolism when warfarin is discontinued without heparin bridging, continued warfarin with avoidance of post-operative heparin appears to be the safest strategy for patients at high risk of thromboembolism undergoing implantable cardiac electronic device procedures. Future guidelines should recommend favouring continuation of warfarin rather

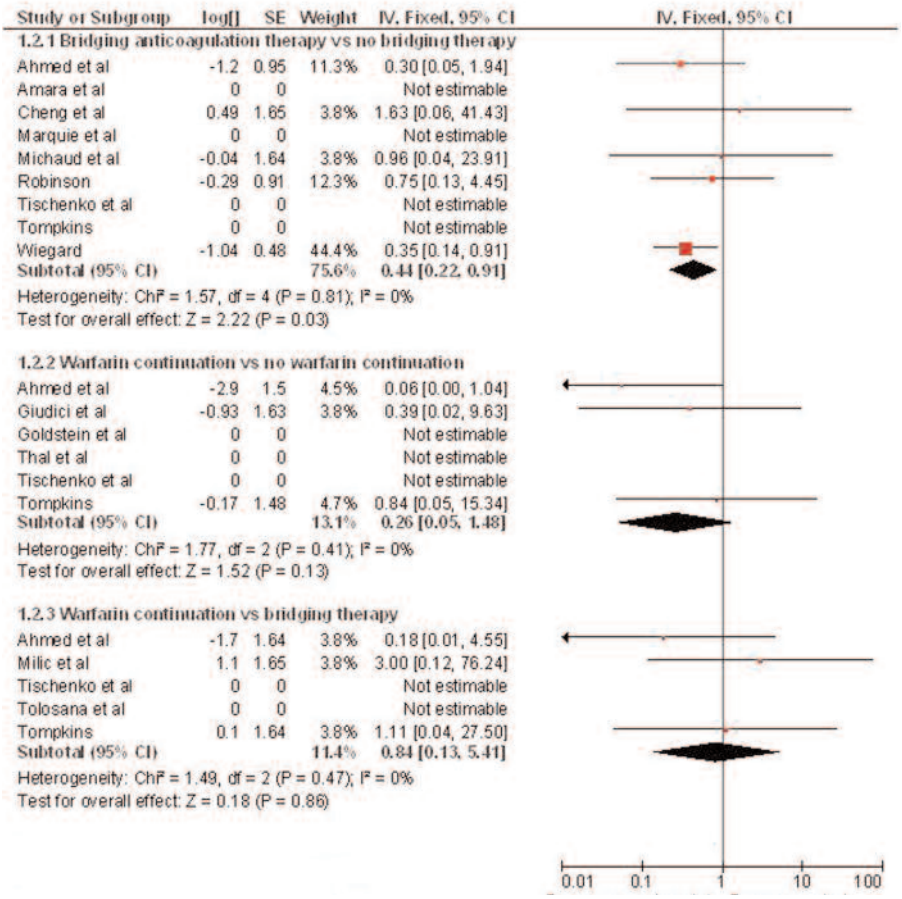

Figure 6. Composite of Stroke/TIA and DVT - Forest Plot for Odds Ratio of composite of stroke/TIA and DVT with the use of different periprocedural strategies using pooled multivariable adjusted estimates.

than post-operative heparin bridging and future clinical trials are required to guide optimal management of concurrent anti-platelet therapy or novel oral anticoagulants.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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