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**ORIGINAL ARTICLE**

# Efficacy and safety of low molecular weight heparin in patients with mechanical heart valves: systematic review and meta-analysis

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**Summary.** *Background:* Low molecular weight heparins (LMWHs) are not approved for patients with mechanical heart valves (MHVs). However, in several guidelines, temporary LMWH off-label use in this clinical setting is considered to be a valid treatment option. Therefore, we reviewed the efficacy and safety of LMWHs in patients with MHVs. *Methods:* MEDLINE and CENTRAL databases were searched from inception to June 2013. Review articles and references were also searched. We included experimental and observational studies that compared LMWHs with unfractionated heparin (UFH) or vitamin K antagonists (VKAs). Data were analyzed and pooled to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for thromboembolic and major bleeding events. Statistical heterogeneity was evaluated with the $I^2$-test. *Results:* Nine studies were included: one randomized controlled trial (RCT) and eight observational studies, with a total of 1042 patients. No differences were found between LMWHs and UFH/VKAs in the risk of thromboembolic events (OR 0.67; 95% CI 0.27–1.68; $I^2 = 9\%$) or major bleeding events (OR 0.66; 95% CI 0.36–1.19; $I^2 = 0\%$). *Conclusions:* The best evidence available might support the temporary use of LMWHs as a prophylactic treatment option in patients with MHVs. However, conclusions are mostly based on observational data (with large CIs), and an adequately powered RCT is urgently needed in this clinical setting.

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## Introduction

Patients with mechanical heart valves (MHVs) are at increased risk of experiencing thromboembolic events [1]. These patients require lifelong anticoagulant treatment, usually with vitamin K antagonists (VKAs), whose efficacy and safety depends on close monitoring of International Normalized Ratio (INR) levels. On some occasions, when the INR level is under the target range (e.g. immediately after valve implantation, when there is a low INR during routine monitoring, or during temporary interruption of oral anticoagulant therapy for invasive procedures), other anticoagulants should be temporarily used. Unfractionated heparin (UFH) has been recommended and used in this context [2–4]. However, low molecular weight heparins (LMWHs) have pharmacokinetic and pharmacodynamic properties (such as a more predictable dose–response relationship) that make this class a more attractive option for thromboprophylaxis [5].

The lack of randomized clinical trials (RCTs), together with some published reports with inconclusive and contradictory findings, have raised doubts about the safety and efficacy of LMWHs in patients with MHVs [6–10]. The European Society of Cardiology Guidelines consider both UFH and LMWHs as treatment options for postsurgery use in patients with MHVs and for those undergoing surgical or diagnostic procedures needing bridging anticoagulation. These recommendations were graded 'IIa' and were classified as 'level C' of evidence, reflecting the uncertainty of the recommendation but still favoring treatment [11,12].

In this study, we aimed to review and evaluate the efficacy and safety of LMWHs as compared with UFH or VKAs in patients with MHVs.

## Methods

### Eligibility criteria

We included RCTs and observational studies (cohort or case–control studies) comparing LMWHs with VKAs or UFH in patients with MHVs. Studies should report the incidence of thromboembolic events. We considered all patients with implanted MHVs, irrespective of the prosthesis position and model. LMWHs included the following drugs: enoxaparin, dalteparin, parnaparin, reviparin, nadroparin, ardeparin, and tinzaparin.

Studies without a control group were excluded.

### Database and search method

The MEDLINE and Cochrane Library (CENTRAL) databases were searched in October 2013 for eligible studies. The search strategy is detailed in Data S1. Studies were considered irrespective of publication language. We also evaluated PubMed's related citations, and hand-searched for other reviews and studies. References of obtained studies were systematically and comprehensively analyzed.

### Studies and data selection

Potential studies retrieved from the electronic search were screened independently by two authors (D.C. and A.T.S.), and this was followed by full-text assessment for inclusion in the systematic review according to the outlined criteria.

The primary outcome was overall incidence of thrombotic and thromboembolic events, defined as any of the following events: valvular thrombosis, stroke, transient ischemic attack, and peripheral arterial embolic events. The secondary outcome was overall incidence of major bleeding events, defined as those involving a critical organ, or requiring transfusion, surgical operation, or prolongation of hospitalization. Overall, we accepted each study definition for major bleeding. We extracted detailed data about populations, analyzed interventions, follow-up, and outcomes. Disagreements were resolved by consensus between the authors.

### Quality reporting assessment

Studies' reported quality was independently assessed by two authors (D.C. and A.T.S.). RCTs were evaluated with the Cochrane Collaboration's tool, which qualitatively stratifies the risk of bias as high, unclear, or low [13]. This tool evaluates the adequacy of the randomization method and allocation concealment, the blinding of participants and personnel, the selectiveness of outcome reporting, the completeness of withdrawals descriptions, and other biases deemed to be relevant. Observational studies were qualitatively assessed with the Newcastle–Ottawa Scale [14]. This instrument has nine different questions for cohort and case–control studies, and evaluates three parameters: selection of patients, comparability of study groups, and assessment of outcomes. For treatment arm comparability, the characteristics considered to be most important for data adjustment were age, gender, valve position, and other prothrombotic conditions, such as atrial fibrillation and deep vein thrombosis.

The quality of reporting was not used *a priori* as an exclusion criterion.

### Data synthesis

Primary and secondary outcomes were summarized as dichotomous data. To estimate the effect of treatment, we chose the relative measure odds ratio (OR), and its 95% confidence interval (CI), rather than an absolute measure to estimate the effect of treatment, because they are more applicable to comparisons across studies with different populations and lengths of follow-up [15]. The OR was also chosen in order to include estimates from case–control studies without losing data comparability.

All statistical analyses were performed with REVMAN version 5.2.6 (The Nordic Cochrane Center, The Cochrane Collaboration, 2012). This software calculates data from individual studies, and derives forest plots for the pooled analysis. Heterogeneity was assessed with the $I^2$-test, which measures the percentage of total variation attributable to interstudy heterogeneity rather than random factors [16,17]. The inverse of variance method with a random effects model was used by default, independently of the existence ($I^2 \geq 50\%$) or not of substantial heterogeneity between study results, because we expected to pool data from studies with different designs [16,17]. We planned to assess publication bias through visual inspection of funnel plot asymmetry and use of the Peters regression test [18,19]. The latter evaluates the linearity of the effect estimate with sample size.

## Results

After searching electronic databases, review articles, and references of the obtained studies, we were able to include nine studies (one RCT and eight observational studies) according to our eligibility criteria [20–28]. Figure S1 shows the studies' selection steps and the reasons for excluding studies.

### Description of studies and risk of bias

A total of 1042 MHV patients were evaluated in these nine studies [20–28].

The only RCT included had focused on VKA-treated patients undergoing tooth extraction [26]. There were 68 patients with prosthetic heart valves (31 in the LMWH arm vs. 38 in the VKA arm), and we confirmed with the

authors that all of these patients had MHVs. There were no thromboembolic or major bleeding events in any patients in either the LMWH arm or the non-bridged arm, which includes patients with MHVs.

The observational studies were two case–control studies [20,21] and six cohort studies (three of which were prospective cohort studies) [22–25,27,28]. Four studies evaluated LMWHs in pregnant patients with MHVs [22,23,27,28], two studies evaluated LMWHs in patients undergoing mechanical valve implantation [20,21], and the remaining three studies evaluated patients undergoing invasive procedures or non-cardiac surgery [24–26].

The sample size of the included studies varied between 24 and 342 patients. The control groups were VKAs in four studies, UFH in four studies (three with intravenous heparin and one with subcutaneous heparin), and both UFH and VKAs in one study. The reported mean follow-up varied between 14 days and after the delivery period of pregnancy.

Table 1 and Table S1 show the main characteristics of and data retrieved from the studies. The adjudicated events for the primary outcome and major bleeding definitions used in the studies are described in Table S2.

Overall, the methodological/reporting quality was low. The RCT of Bajkin *et al.* was considered to be at high risk for performance, detection, and reporting bias [26]. All observational studies are intrinsically prone to a high risk of selective reporting bias. Following the Newcastle–Ottawa scale for quality reporting, the most common flaw was the absence of adjustment for confounding factors (including those considered to be important by the authors). In case–control studies, the cases were not independently validated, and controls were all hospital-based. All of these aspects increase the risk of bias of the included studies. Figure S2 shows the risk of bias figures for all studies.

### *Effects of interventions*

*Thromboembolic events and major bleeding* Regarding the primary outcome, one study (the RCT) reported zero events in both treatment arms [26]. Thus, only eight studies contributed to the pooled OR estimate. The risk of thromboembolic events with LMWHs was not different from that with UFH or VKAs (OR 0.67; 95% CI 0.27–1.68). There was no significant statistical heterogeneity ($I^2$ = 9%) (Fig. 1).

Regarding our secondary outcome, in three studies there were no major bleeding events reported in either arm [22,23,26]. In the pooled analysis of the six included studies, LMWHs did not increased the risk of major bleeding (OR 0.66; 95% CI 0.36–1.19). No statistical heterogeneity was found among studies ($I^2$ = 0%) (Fig. 1).

Post hoc *subgroup and sensitivity analyses* Although no significant statistical heterogeneity existed in the pooled results from the included studies, we performed several subgroup and sensitivity analyses to explore the robustness of the results and to limit clinical heterogeneity. Pooled estimates were calculated according to the type of control group (LMWHs vs. UFH, and LMWHs vs. VKAs), indication for LMWH use (pregnancy, post-MHV implantation, post-procedure/non-cardiac surgery), and study design (prospective and retrospective). A sensitivity analysis was also performed by excluding from the analysis all case–control studies, which are known to be more prone to bias than cohort studies and RCTs. The overall results for both primary and secondary outcomes were consistent across all these analyses; that is, no differences existed between LMWH and control groups (Fig. 2).

Three studies used anti-factor Xa monitoring in the LMWH arm [20,27,28]. The incidence rates of thromboembolic events (OR 2.09; 95% CI 0.17–25.85; $I^2$ = 61%) and major bleeding events (OR 0.80; 95% CI 0.26–2.50; $I^2$ = 0%) were similar to those in controls.

*Analyses using Peto's ORs and risk difference measures* We also explored the impact of using different effect measurements on pooled estimates, because the event rates were low or null in some studies.

In circumstances of rare events, Peto's OR has been reported to be an adequate and more reliable effect measurement for dichotomous outcomes [29]. The results were similar to those of the primary analysis, with a Peto's OR of 0.62 (95% CI 0.25–1.57; $I^2$ = 55%). For major bleeding, Peto's OR was 0.64 (95% CI 0.34–1.21; $I^2$ = 0%).

Risk difference is a measure that can give inconsistent estimates in pooled analyses, mainly owing to the constraints of different baseline risks when results are applied across different groups and clinical settings [30]. However, it has the advantage of considering studies with zero events in both arms for meta-analysis estimates [30,31]. The risk differences between LMWHs and UFH/VKAs were − 1.0% (95% CI − 2.6% to 0.5%; $I^2$ = 0%) and − 0.1% (95% CI − 3.4% to 1.4%; $I^2$ = 0%) for thromboembolic and major bleeding events, respectively.

*Publication bias* Visual inspection of the funnel plot did not give conclusive results concerning the absence of publication bias (Fig. S3). The Peters regression test did not show evidence of publication bias ($P$ = 0.156).

## Discussion

VKAs are the oral anticoagulants of choice for patients with MHVs, and UFH (the only heparin approved for patients with MHVs) has been the most commonly used drug for bridging [2–4]. According to the present data, based on 10 studies and 1068 patients, LMWHs are effective and safe for temporary use in patients with MHVs in

**Table 1** Main characteristics of the included studies

| Study, year and design | Population Mean Age | Valve position and type | Interventions | LMWH | Obesity RD Pregnancy | AF LVD PTE | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|
| RCT | | | | | | | | |
| Bajkin *et al.* 2009 [26] RCT; subgroup of patients with valvular prostheses (MHV, confirmed by the author) | 69 patients treated with VKA requiring teeth extraction (without the need for a mucoperiosteal flap raise), with INR < 4.0, subgroup of patients with MHVs 61 years | NR | LMWH vs. VKA 31 vs. 38 | Periprocedural bridging Subcutaneous nadroparin 2.850–5.700 IU anti-FXa once or twice daily No anti-FXa monitoring reported | O: NR RD: NR P: NR | AF: NR LVD: NR PTE: NR | TE events and bleeding | 1 month |
| Cohort studies | | | | | | | | |
| Lee *et al.* 2007 [22] Retrospective cohort study | 31 pregnancies of 25 women with MHVs 25 years | Aortic position: 3 vs. 1 Mitral position: 15 vs. 6 Double prosthesis: 4 vs. 1 All BL valves | LMWH vs. VKA target INR 2.5–3.5 23 vs. 8 All had ASA 100 mg daily | Until 12 week of pregnancy (instead of VKA) and restarted before delivery in both groups Subcutaneous nadroparin 7.500 IU, 12/12 h No anti-FXa monitoring reported | O: NR RD: NR P: 100% | AF: NR LVD: NR PTE: NR | Fetal anomalies and losses, TE events, and bleeding | During pregnancy and after delivery |
| Shannon *et al.* 2008 [23] Prospective registry; subgroup analysis | 24 pregnant patients with MHVs included in the United Kingdom Heart Valve Registry Mean age not reported | Aortic position: 21 Mitral position: 15 Double prosthesis: 2 Valve types not reported | LMWH vs. UFH/ VKA (warfarin) 9 vs. 15 | Until 12 weeks of pregnancy (instead of VKA) Dalteparin 10.000–14.000 IU daily or enoxaparin 60 mg 12/12 h No anti-FXa monitoring reported | O: NR RD: NR P: 100% | AF: NR LVD: NR PTE: NR | Valve-related deaths, TE events, stroke, and bleeding | During pregnancy and after delivery |
| Spyropoulos *et al.* 2008 [24] Prospective registry; subgroup analysis | 245 patients from the REGIMEN registry with MHVs and temporary interruption of oral anticoagulation. 65 years | Aortic position: 92 vs. 34 Mitral position: 62 vs. 31 Double prosthesis: 17 vs. 8 BL: 116 vs. 32 ($P < 0.001$) TD: 10 vs. 6 CB: 2 vs. 0 | LMWH vs. UFH 172 vs. 73 | Periprocedural bridging Subcutaneous LMWH: enoxaparin 1 mg $kg^{-1}$ 12/12 h (76% of patients), dalteparin 100 IU $kg^{-1}$ 12/12 h (13% of patients), and tinzaparin 175 IU $kg^{-1}$ daily (4% of patients) No anti-FXa monitoring reported | O: NR RD: NR P: NR | AF: 45% LVD: NR HF: 26% PTE: stroke 6% | Mortality, TE events, stroke, and bleeding (major and all) | 1 month |

**Table 1** (Continued)

| Study, year and design | Population Mean Age | Valve position and type | Interventions | LMWH | Obesity RD Pregnancy | AF LVD PTE | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|
| McLintock *et al.* 2009 [27] Retrospective cohort study | 47 pregnancies in 31 women with MHVs 28 years | Aortic position: 4 BL Mitral position: 14; 8 CB, 5 BL, 1 tilt Double prosthesis: 13; 4 CB, 9 BL | LMWH vs. VKA (rarely UFH) 34 vs. 13 | Until 12 weeks or througout the entire pregnancy (instead of VKA) Subcutaneous enoxaparin 1 mg $kg^{-1}$ 12/12 h; then target levels of anti-FXa; trough levels should be 0.4–0.7 IU $mL^{-1}$ and 0.7–1.2 IU $mL^{-1}$ 4 h postdose | O: NR RD: NR P: NR | AF: 13% LVD: NR PTE: 40% | TE events and bleeding (maternal or feral) | > 3 months (83% of patients) |
| Daniels *et al.* 2009 [25] Prospective cohort study | 342 patients with MHVs referred to the Mayo Clinic Thrombophilia Center for periprocedural anticoagulation management 67 years | Aortic position: 372 Mitral position: 136 Double prosthesis: 48 | LMWH vs. UFH 243 vs. 99 | Periprocedural bridging Subcutaneous ardeparin 130 anti-FXa IU $kg^{-1}$ 12/12 h, or dalteparin 100 anti-FXa IU 12/12 h, enoxaparin 1 mg $kg^{-1}$ 12/12 h No anti-FXa monitoring reported | O: NR RD: 6% P: NR | AF: 37% LVD (LVEF < 40%): 6% PTE: NR | TE events and bleeding (major or minor) | 3 months |
| Basude *et al.* 2012 [28] Retrospective cohort study | 32 pregnancies in 15 women with MHVs 30 years | Aortic position: 14 Mitral position: 12 Double prosthesis: 2 | LMWH vs. VKA 4 vs. 22 | LMWH and aspirin throughout the entire pregnancy (mixed LMWH and VKA regimen was excluded from analysis) Subcutaneous enoxaparin 1 mg $kg^{-1}$ 12/12 h; then adjustments according to target levels of anti-FXa (1–1.2 IU $L^{-1}$) | O: NR RD: NR P: NR | AF: NR LVD: NR PTE: NR | TE events, deterioration of valve or ventricular function, significant bleeding and death | NR |
| Case–control studies | | | | | | | | |
| Montalescot *et al.* 2000 [20] Retrospective case–control study | 208 patients undergoing MHV implantation 58 years | Aortic position: 157 Mitral position: 29 Double prosthesis: 22 | LMWH vs. UFH All patients had UFH after surgery (approximatively during the first 2 days) 29 vs. 34 | Postsurgery bridging when no IV line was needed (~ 6 days postsurgery) Subcutaneous LMWH: enoxaparin 100 anti-FXa UI $kg^{-1}$ 12/12 h, or nadroparin 87 anti-FXa UI $kg^{-1}$ 12/12 h; adjustments to achieve anti-FXa target 0.5–1.0 IU $L^{-1}$ | O: NR RD: NR P: NR | AF: 20% LVD: 42 HF: 10% PTE: 3.5% stroke | Mortality, TE events, valve thrombosis, mechanical prosthesis failure, endocarditis, reintervention, and major bleedings | 14 days |

**Table 1** (Continued)

| Study, year and design | Population Mean Age | Valve position and type | Interventions | LMWH | Obesity RD Pregnancy | AF LVD PTE | Outcomes | Follow-up |
|---|---|---|---|---|---|---|---|---|
| Fanikos *et al.* 2004 [21] Retrospective case–control study | 63 patients undergoing MHV implantation that started warfarin and had subtherapeutic INR levels 56 years | Aortic position: BL 19 vs. 20; CB 1 vs. 0 Mitral position: BL 4 vs. 9; CB 1 vs. 1 Double prosthesis: BL 4 vs. 4 | LMWH vs. UFH 29 vs. 34 | Postsurgery bridging Subcutaneous enoxaparin 1 mg $kg^{-1}$ 12/12 h or lower dose if renal insufficiency Doses were rounded down to 40, 60, 80 or 100 mg twice daily No anti-FXa monitoring reported | O: NR RD: 35% P: NR | AF: 51% LVD: NR Congestive HF: 22% PTE: 10% DVT/stroke | Mortality, TE events, bleeding events, and 30-day readmission | 3 months |

AF, atrial fibrillation; ASA, acetylsalicylic acid; BL, bileaflleat valve; CB, caged-ball valve; DVT, deep vein thrombosis; HF, heart failure; INR, International Normalized Ratio; IU, International Units; IV, intravenous; LMWH, low molecular weight heparin; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; MHV, mechanical heart valve; NR, not reported; O, obesity; P, pregnancy; PTE, previous thromboembolic event; RCT, randomized controlled trial; RD, renal dysfunction; TD, tilting disk; TE, thromboembolic event; UFH, unfractionated heparin; VKA, vitamin K antagonist.

terms of thromboembolic risk, as compared with the 'reference' drugs. Subgroup and sensitivity analyses consistently showed no differences between LMWHs and the 'reference' drugs (VKAs/UFH). As compared with other reviews [10,32], this systematic review had the advantage of reviewing all clinical controlled studies and using a quantitative method to assess the benefit and harm of the intervention.

The data here presented are partially based on studies that used LMWHs as bridging agents. In this context, LMWHs offer some pharmacologic advantages over UFH: lower incidence rates of thrombocytopenia and osteoporosis, a predictable dose–response relationship, a decreased length of hospital stay, and reduced costs [21]. However, the dose–response relationship may be less predictable in patients with obesity [33], patients with renal dysfunction [34,35], and pregnant women [10,32].

Concerns have been raised about the thromboembolic risk during the periprocedural period. Impaired hemostasis related to the prothrombotic effect of 'switching on and off' of VKA, in addition to other patient thrombotic risk factors (e.g. atrial fibrillation), have highlighted the need for transitory antithrombotic treatment [36]. Nevertheless, Siegal *et al.* showed, in a systematic review, that periprocedural bridging is associated with an increase in bleeding risk [37]. Thus, considering the available data, VKA-treated patients receiving periprocedural heparin (UFH or LMWH) bridging appear to be at increased risk of overall and major bleeding as compared with non-bridged patients, with a similar risk of thromboembolic events [37,38]. Despite the absence of approval for use in patients with MHVs, LMWHs are considered to be a treatment option in guidelines for periprocedural bridging treatment [9]. These drugs should be given subcutaneously twice daily, with the use of body weight-adjusted therapeutic doses and anti-FXa activity monitoring, with target levels ranging from 0.5 to 1.0 U $mL^{-1}$ [8].

After MHV replacement, patients may also require heparin-based anticoagulation in order to avoid thromboembolic events associated with a delayed therapeutic effect and an early prothrombotic effect of VKAs [39]. Steger *et al.* followed a cohort of 256 patients who underwent MHV implantation and were treated with a fixed and a lower dose of enoxaparin (40 mg, twice daily, subcutaneously) [40]. In this study, with a mean follow-up of 38 days, LMWHs were shown to be safe, without prosthesis thrombosis and major bleeding [40].

Only three studies used anti-FXa monitoring to adjust LMWH anticoagulation [20,27,28]. No significant differences were found between UFH and VKAs, but the comparison was clearly underpowered. In fact, anti-FXa monitoring may optimize anticoagulation in some patients after surgery, not only because of the higher risk of bleeding [20], particularly in those for whom the dosage may be difficult to determine (e.g. patients with renal dysfunction or obesity), but also because of the lack of

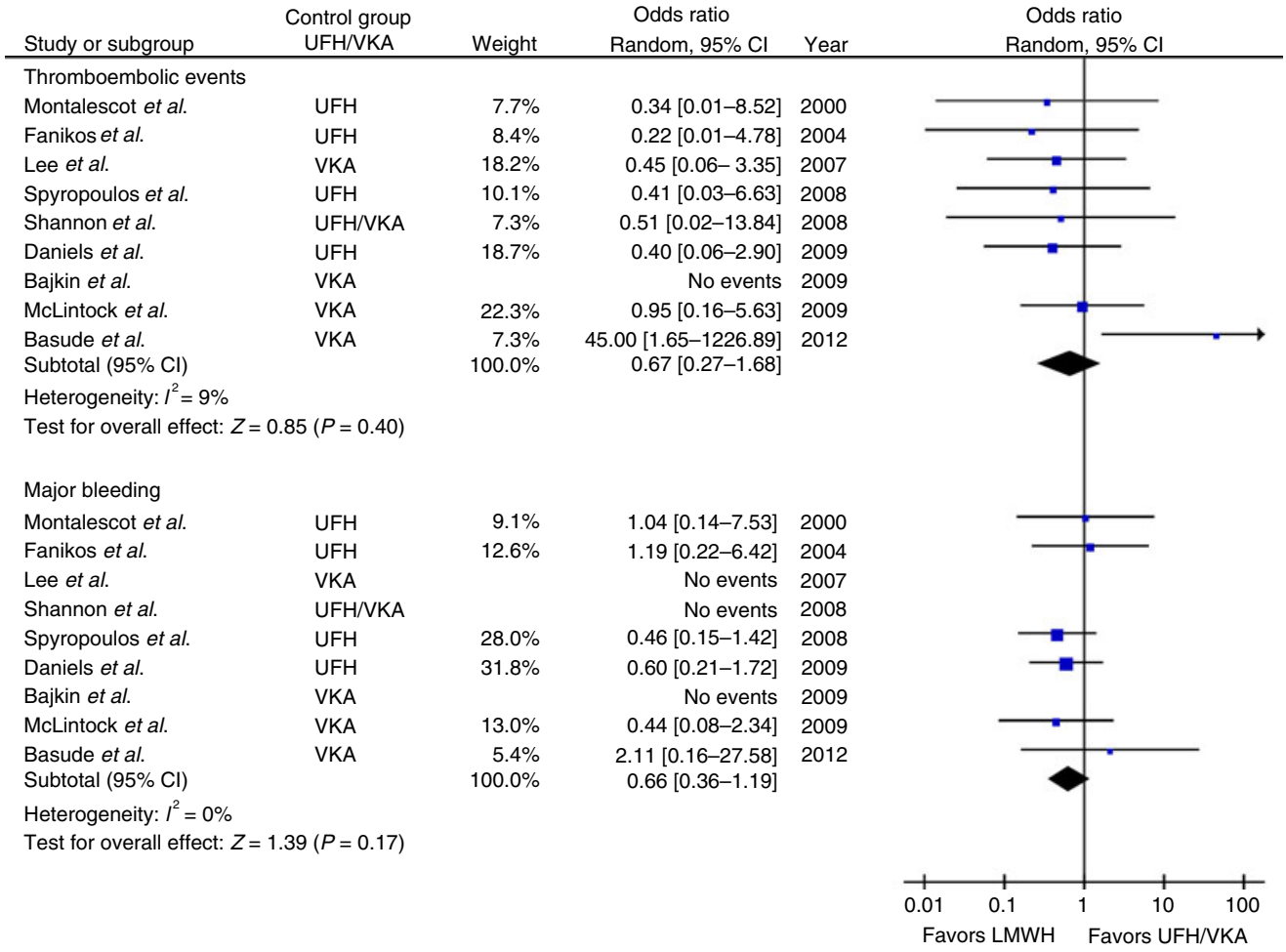


**Fig. 1.** Forest plots of primary and secondary outcomes. CI, confidence interval; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

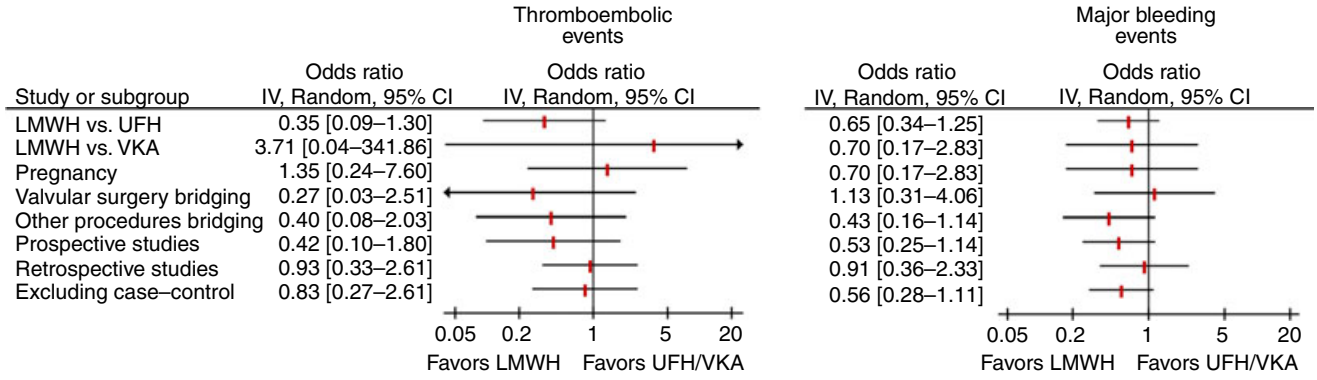


**Fig. 2.** Results of subgroup and sensitivity analyses. CI, confidence interval; IV, intravenous; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VKA, vitamin K antagonist.

full reversibility of LMWH effects by protamine, which is frequently insufficient to arrest bleeding [5,41].

In pregnant patients, VKAs cross the placenta, causing a teratogenic risk in the first trimester, and increasing the risk of fetal bleeding during delivery [32]. LMWHs do not cross the placenta and are not toxic to the fetus, but pregnant women have an increased risk of thromboembolic events, owing to pregnancy itself and to lower anti-FXa levels [42,43], probably related to erratic LMWH clearance and a higher volume of distribution [44,45].

Close monitoring is recommended, with target anti-FXa levels of 1.0–1.2U $mL^{-1}$ at 4–6 h after subcutaneous injection and 0.6–0.7 U $mL^{-1}$ before the next LMWH dose [46,47].

The use of LMWHs in MHV patients is associated with a low risk of events, similarly to what is seen in atrial fibrillation patients bridged with LMWHs [48]. This safety was also seen in case series and in prospective 'real-world' registries [39,49–51], but the absence of a control group limits their conclusions.

### *Limitations*

In this systematic review, we performed a meta-analysis of the best available evidence (mainly based on observational studies, and not patient-level data) in order to compensate for the scarcity of controlled studies in this area. The use of data from observational studies may raise methodologic and interpretational concerns [52]. Clinical decisions based exclusively on this type of evidence should be made with caution [53]. Nevertheless, these data are informative, and increase our knowledge concerning the use of LMWHs in patients with MHVs.

Other limitations should be taken into account in the interpretation of our findings. First, we pooled different studies with different indications, which cumulatively limit our conclusions. Second, we acknowledge that most of the evidence and estimates shown here were derived from observational study data. The only randomized study included was not considered in most of the quantitative analyses, owing to the lack of events, which suggests safety despite the underpowered nature of the study. Third, short-duration bridging treatment is different from the longer substitution of anticoagulants (as occurs in pregnant women with MHVs), as a residual effect of VKAs may still be present during the first days, causing a potentially higher risk of hemorrhagic events.

It should be acknowledged that outcomes were not systematically adjudicated, giving the potential for major imprecision in outcome rates, and that the definition of major bleeding was also different among studies (Table S2).

In a systematic review of non-randomized studies, the risk of selective reporting bias should be noted. Furthermore, we included studies based on the absence of events. Nevertheless, these studies did not contribute to the primary analysis of this review. Confounding factors were not considered in individual study estimates (e.g. a possible lack of therapeutic compliance or inadequate anti-FXa levels in some populations; the mechanical valve position and model), or taken into account in the quantitative analysis. As previously shown, there are two main effects of this limitation in a meta-analysis: a systematic bias overestimating the effect of the studied intervention, and an increase in between-study variability in the estimates with high statistical heterogeneity [54]. In opposition to such potential bias, the estimates obtained for LMWHs still have a large margin for remaining similar to UFH/VKAs, and there was no statistical heterogeneity in the meta-analysis results.

Pregnant women belong to a special population that requires special attention in terms of safety. The results here presented are limited by the low number of studies and the absence of RCTs.

### *Implications for clinical practice and research*

The temporary use of LWMHs appears to be as efficacious and safe as the use of VKAs or UFH in terms of thromboembolic and major bleeding risks in patients with MHVs. The higher predictability and greater ease of use of LMWHs, and the possibility of administration to outpatients, may decrease length of in-hospital stay and translate into both clinical and financial benefits [21]. Despite the absence of an association of LMWHs with increased thromboembolic risk, the data were mainly derived from observational studies. Therefore, an adequately powered multicenter RCT is urgently needed in this clinical setting, to definitely establish the true efficacy and safety of LMWHs in patients with MHVs.

## Conclusions

The temporary use of LMWHs does not seem to be associated with an increased risk of thromboembolic or major bleeding events as compared with the continued use of UFH or VKAs in patients with MHVs. The majority of the evidence comes from observational studies with large CIs, highlighting the need for larger and experimental studies to ensure safety and further evaluate efficacy.

## Addendum

D. Caldeira contributed to the concept and design, data acquisition, data analysis, and interpretation of the data, wrote the first draft of the manuscript, critically revised the manuscript, and gave final approval of the submitted manuscript. C. David contributed to the interpretation of the data, wrote the first draft of the manuscript, critically revised the manuscript, and gave final approval of the submitted manuscript. A. T. Santos contributed to data acquisition and data analysis, critically revised the manuscript, and gave final approval of the submitted manuscript. J. Costa contributed to data analysis and interpretation of the data, critically revised the manuscript, and gave final approval of the submitted manuscript. J. J. Ferreira contributed to interpretation of the data, critically revised the manuscript, and gave final approval of the submitted manuscript. F. J. Pinto: contributed to interpretation of the data, critically revised the manuscript, and gave final approval of the submitted manuscript.

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## Disclosure of Conflict of Interests

J. J. Ferreira has received speaker and consultant fees from GlaxoSmithKline, Novartis, TEVA, Lundbeck, Solvay, Abbott, Bial, Merck-Serono, Grunenthal, and Merck Sharp and Dohme. F. J. Pinto has received consultant and speaker fees from Astra Zeneca, Bayer, and Boehringhrer Ingelheim. The other authors state that they have no conflict of interest.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Fig. S1.** Flowchart of studies selection.
**Fig. S2.** Risk of bias of included studies.
**Fig. S3.** Funnel plot.
**Data S1.** MEDLINE search strategy.
**Table S1**. Primary and secondary outcomes.
**Table S2.** Major bleeding definitions.

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