

# A meta-analysis of bridging anticoagulation between low molecular weight heparin and heparin

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## Abstract

**Background:** Patients with mechanical heart valves (MHV) have an increased risk of thromboembolic complications. Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are often recommended for bridging anticoagulation; however, it is not clear which strategy is more beneficial.

**Methods:** The PubMed, EMBASE, and Cochrane databases were searched from January 1960 to March 2019. Randomized controlled trials and observational studies were analyzed. The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the studies. Stata 11.0 was used for the meta-analysis.

**Results:** A total of 6 publications were included; 1366 events were selected, involving 852 events with LMWH and 514 events with UFH. The thromboembolism risk of the LMWH group was lower than that of the UFH group (risk ratio [RR]=0.34, 95% confidence interval [CI] 0.12–0.95,  $P=.039$ ). The incidence of major bleeding was lower in the LMWH group than in the UFH group, albeit without statistical significance (RR=0.94, 95% CI 0.68–1.30,  $P=.728$ ), as was mortality (RR=0.52, 95% CI 0.16–1.66,  $P=.271$ ). Subgroup analysis showed that LMWH cardiac surgery patients had a higher risk of major bleeding compared with UFH cardiac surgery patients (RR=1.17, 95% CI 0.72–1.90,  $P=.526$ ); but among non-cardiac surgery patients, the LMWH group had a lower risk of major bleeding than the UFH group (RR=0.79, 95% CI 0.51–1.22,  $P=.284$ ), although the difference was not statistically significant.

**Conclusion:** Our meta-analysis suggests that LMWH not only reduces the risk of thromboembolism in patients with MHV but also does not increase the risk of major bleeding. LMWH may provide safer and more effective bridging anticoagulation than UFH in patients with MHV. It is still necessary to conduct future randomized studies to verify this conclusion.

**Abbreviations:** ACC/AHA = American College of Cardiology/American Heart Association, aPTT = activated partial thromboplastin time, AVR = aortic valve replacement, CI = confidence interval, ESC = European Society of Cardiology, INR = International Normalized Ratio, LMWH = low molecular weight heparin, MHV = patients with mechanical heart valves, MVR = Mitral valve replacement, NOS = Newcastle-Ottawa Scale, RR = risk ratio, UFH = unfractionated heparin, VKA = vitamin K antagonist.

**Keywords:** bridging, low molecular weight heparin, mechanical heart valve, meta-analysis, unfractionated heparin

## 1. Introduction

Patients with mechanical heart valves (MHVs) have an increased risk of thromboembolic complications, requiring long-term oral

anticoagulants, for example, vitamin K antagonists (VKAs). In cases of invasive procedures or sub-therapeutic International Normalized Ratio (INR) levels after heart valve replacement, heparin is used for short-term anticoagulation until and after the procedure. “Bridging” therapy with either unfractionated heparin (UFH) or low molecular weight heparin (LMWH) has evolved empirically to reduce thromboembolic events during temporary interruption of oral anticoagulation in high-risk patients, such as those with Mitral valve replacement (MVR) or aortic valve replacement (AVR) and additional risk factors for thromboembolism (e.g., AF, previous thromboembolism, hypercoagulable condition, older-generation mechanical valves, LV systolic dysfunction, or >1 mechanical valve).<sup>[1]</sup>

While both strategies reduce the risk of thrombus formation, they have distinct biomedical, financial, and logistical profiles. UFH is administered intravenously according to a nomogram and hence requires peri-procedural hospital admission and continuous monitoring of the activated partial thromboplastin time (aPTT). In contrast, LMWH has several potential advantages in patients with mechanical heart valves: a better safety profile, with less frequent thrombocytopenia and bleeding in pooled analyses; a more predictable and rapid anticoagulant effect; and the possibility of self-administration without daily laboratory monitoring.<sup>[2]</sup>

The limiting factors for the use of LMWH after mechanical valve replacement are the lack of randomized controlled trials,

Editor: Manal Elshmaa.

ET and YLL have contributed equally to this work.

The authors declare no competing interests.

The authors have no conflicts of interest to disclose.

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How to cite this article: Tao E, Luo YL, Tao Z, Wan L. A meta-analysis of bridging anticoagulation between low molecular weight heparin and heparin. *Medicine* 2020;99:3(e18729).

Received: 30 March 2019 / Received in final form: 30 November 2019 / Accepted: 13 December 2019

<http://dx.doi.org/10.1097/MD.00000000000018729>

concerns about pharmacokinetics in obese patients and target anti-Xa activity, and contraindication in the presence of severe renal dysfunction. The last dose of LMWH should be administered 12 hours before the procedure, whereas UFH should be discontinued 4 hours before surgery.<sup>[3]</sup>

The choice of heparin remains controversial. Some studies<sup>[4–8]</sup> found that LMWH was more feasible than UFH, but another report<sup>[9]</sup> found that LMWH was inferior to UFH. Caldeira et al<sup>[10]</sup> suggested that the temporary use of LMWH seemed to not increase the risk of thromboembolic or major bleeding events compared with the continued use of UFH in patients with MHV. However, another meta-analysis by Passaglia et al<sup>[9]</sup> suggested that early bridging therapy with LMWH appears to be associated with a higher rate of bleeding than UFH. The conclusions of the 2 meta-analyses were different and are outdated. After they were published, a new multicenter retrospective study was published. Therefore, we performed a meta-analysis with the available evidence to analyze the safety of LMWH compared with UFH in patients with MHV to assist clinicians in the selection of heparin.

## 2. Materials and methods

### 2.1. Literature search

We performed an electronic search with the terms “Low-molecular-weight heparin” or “unfractionated heparin” or “LMWH” or “UFH” or “heparin” or “bridging” or “postoperative anticoagulation,” and “mechanical” or “prosthesis,” and “valve” or “aortic” or “mitral” or “tricuspid” in the PubMed, EMBASE, and Cochrane databases to identify relevant studies published between January 1960 and March 2019 that compared outcomes between LMWH and UHF management for patients with mechanical valves. We also reviewed the references listed in the original studies to identify possible additional studies. To evaluate the quality of studies, we used the NOS. We assigned the studies of superior quality a score of 9 stars, and high-quality studies were assigned a score  $\geq 6$ . The results are shown in Table 1.

### 2.2. Eligibility criteria

Studies with the following criteria were eligible for inclusion: randomized controlled trials and retrospective or prospective observational studies; patients with implanted MHVs, irrespective of the prosthesis position; and publications dated between January 1960 and March 2019, including major bleeding, thromboembolic, mortality, or other related data. Studies without a control group were excluded.

### 2.3. Definitions

The MHV group was composed of patients with MHVs undergoing postoperative anticoagulation for heart valve replacement and noncardiac surgery.

Major bleeding events were defined as those involving a critical organ or requiring transfusion, surgical operation, or the prolongation of hospitalization.

Thromboembolic events were defined as any of the following events: valvular thrombosis, stroke, and peripheral arterial embolic events.

### 2.4. Data collection

All the data were extracted independently by 2 reviewers (EDT and YLL). Any initial disagreement was reviewed and resolved by consensus. The background and characteristics of the studies (author, publication date, age of patients, study design, number of cases, and major bleeding, thromboembolism, and death events) were extracted from each study. (This study is a meta-analysis and therefore does not involve ethics).

### 2.5. Statistical analysis

The relative risk (RR) was used as the combined effect, and the effects are expressed with the 95% confidence interval (CI). Stata 11.0 (Texas, USA) software was used for the data analysis and synthesis. Heterogeneity analysis was assessed with the Cochrane  $Q$  statistic for all clinical trials.  $I^2$  values of 25%, 50%, and 75% indicated low, moderate, and high levels of heterogeneity, respectively. If the heterogeneity was low or  $P > .1$ , the fixed effect model was used; if the heterogeneity was high or  $P < .1$ , the random effects model was used. Sensitivity analyses and subgroup analyses were used to explore the sources of heterogeneity among studies. Funnel plots and Egger regression test were used to evaluate publication bias. A  $P$  value  $< .05$  was considered statistically significant.

## 3. Results

### 3.1. Study characteristics

As shown in the flow chart (Fig. 1), the search strategy initially included 628 publications. After the title and abstracts were retrieved, 586 publications were excluded. A total of 42 articles were reviewed in detail. Finally, 6 publications met the eligibility criteria, which were determined after reading the article. A total

**Table 1**  
Characteristics of studies included in the meta-analysis.

Study	Country	Study design	n	L	U	Age, y		L (events)			U (events)			NOS (stars)
						L	U	MB	TE	Death	MB	TE	Death	
Hart et al (2017)	Netherlands	Retrospective cohort	238	154	84	62.3 ± 10.6	61.4 ± 11.7	29	1	3	16	2	1	9
Daniel et al (2009)	America	Retrospective cohort	342	243	99	-	-	9	2	-	6	2	-	7
Spyropoulos et al (2008)	America Canada	Prospective cohort	233	165	68	65.4 ± 1	66 ± 1	7	1	1	6	1	1	8
Puri et al (2008)	India	Prospective cohort	282	159	123	43.7 ± 16.1	44.7 ± 13.5	29	1	-	19	2	1	8
Fanikos et al (2004)	America	Case-control study	63	29	34	52.9 ± 14.6	58.7 ± 12.6	3	0	1	3	2	4	6
Montalescot et al (2000)	France	Comparative study	208	102	106	59.8 ± 1.4	55.3 ± 1.5	2	0	-	2	1	-	8

L = low molecular weight heparin, MB = major bleeding, NOS = Newcastle–Ottawa Scale, TE = thromboembolism, U = unfractionated heparin.

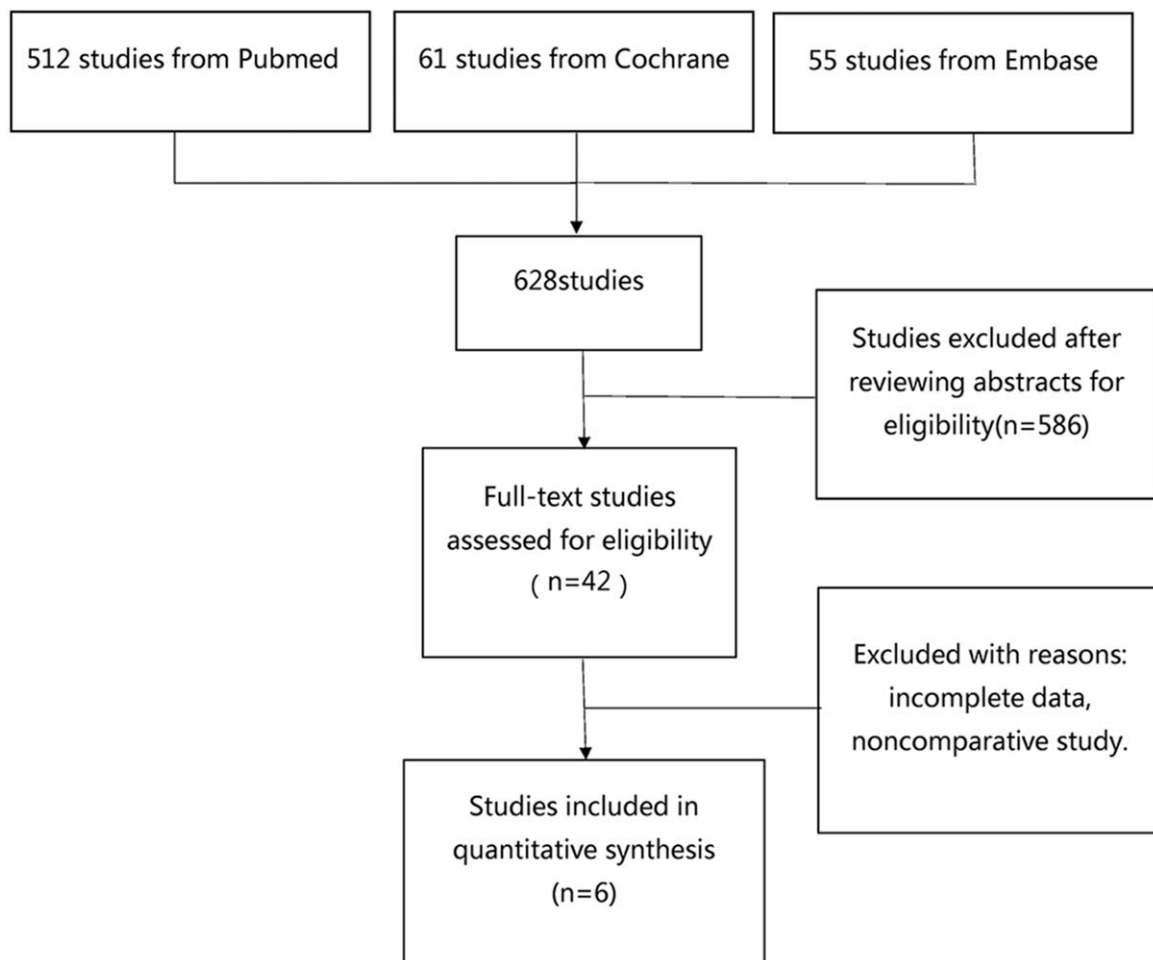


Figure 1. Flow chart.

of 1366 patients receiving bridging anticoagulants after mechanical valve implantation, including 852 cases in the LMWH group and 514 cases in the UFH group were included in the meta-analysis. The basic information is shown in Table 1 and Table 2.

### 3.2. Major bleeding events

Major bleeding events were mentioned in 6 studies. In the LMWH group, the risk of major bleeding was lower than that in the UFH group, but this difference was not statistically significant ( $RR=0.94$ , 95% CI 0.68–1.30,  $P=.728$ ) (Fig. 2A). No

Table 2

#### Characteristics of studies included in the meta-analysis.

Study	Patient	Date	Strategy
Hart et al (2017)	Non-cardiac surgery	January 2010–January 2015 Followed up 30 days	LMWH: once/twice daily; UFH: maintain APTT 1.5–2.0 times (3–5 days prior to the procedure)
Daniel et al (2009)	Non-cardiac surgery	January 1, 1997–December 31, 2003 Followed up 3 months	LMWH: twice daily; UFH: maintain APTT 1.5–2.0 times (4–7 days prior to the procedure)
Spyropoulos et al (2008)	Non-cardiac surgery	July 1, 2002–December 31, 2003 Followed up 30 days	LMWH: once/twice daily; UFH: maintain APTT 1.5–2.0 times (bridging therapy for $\geq 2$ days in the preoperative and/or postoperative period)
Puri et al (2008)	Cardiac surgery	July 2001–October 2006 Followed up 6 months	LMWH: once daily; UFH: maintain APTT 1.5–2.0 times (6–12 hours after surgery)
Fanikos et al (2004)	Cardiac surgery	June 1999–November 2001 Followed up 3 months	LMWH: twice daily; UFH: maintain APTT 1.5–2.0 times (discontinued after 2 consecutive therapeutic INRs were achieved)
Montalescot et al (2000)	Cardiac surgery	-	LMWH: twice daily (anti-Xa 0.5–1 IU/mL); UFH: maintain APTT 1.5–2.5 times (about 2 days after surgery)

LMWH=low molecular weight heparin, UFH=unfractionated heparin.

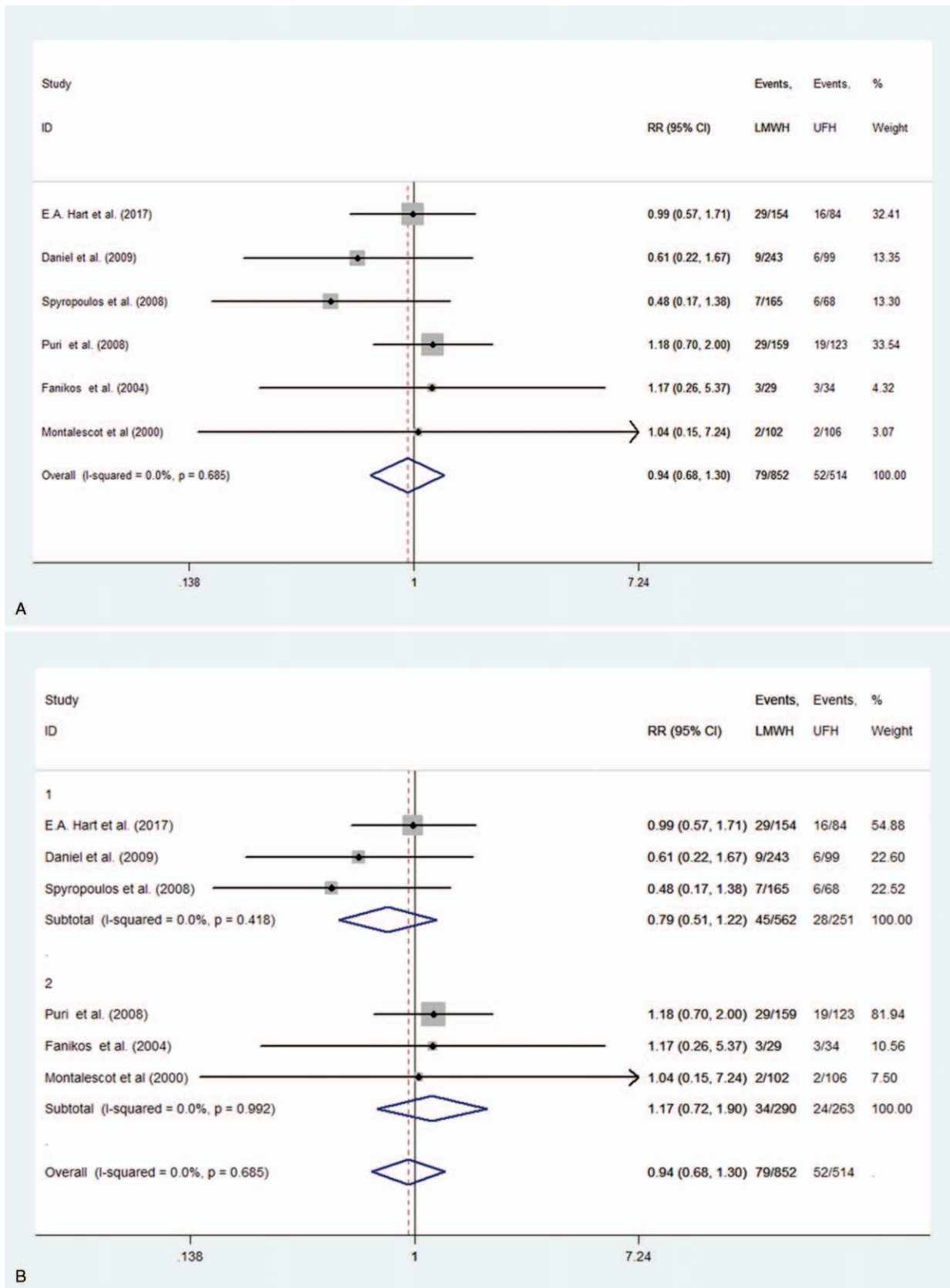


Figure 2. A: Major bleeding events. B: Subgroup analysis of major bleeding events.

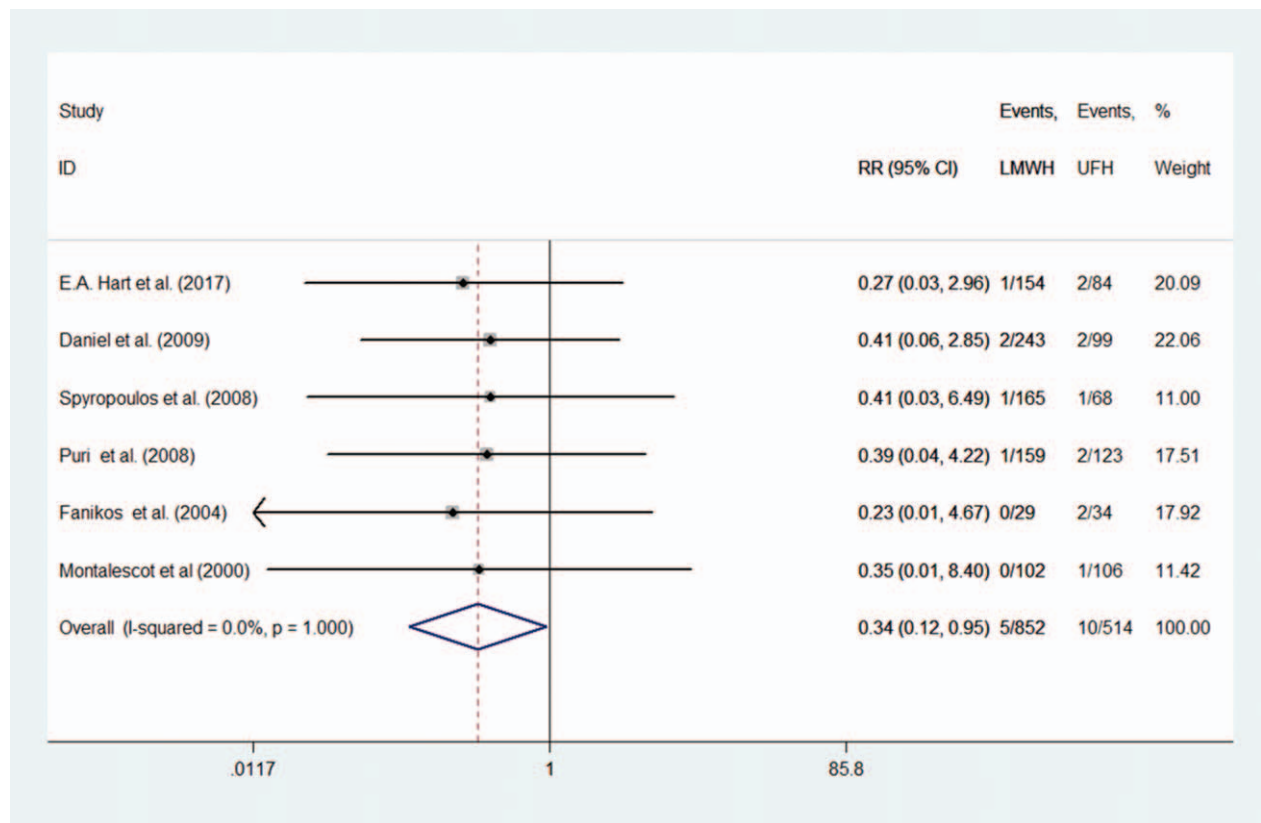


Figure 3. Thromboembolic events.

significant heterogeneity was found among the included studies ( $I^2=0.0\%$ ).

Because 3 studies included postoperative patients after valve replacement, we divided the studies into a noncardiac surgery group and a cardiac surgery group to perform a subgroup analysis. The subgroup analysis showed that the LMWH group had a higher risk of major bleeding compared with the UFH group during early anticoagulation after mechanical valve implantation (RR=1.17, 95% CI 0.72–1.90,  $P=.526$ ); the risk of LMWH-associated major bleeding was lower in the noncardiac surgery group than in the cardiac surgery group (RR=0.79, 95% CI 0.51–1.22,  $P=.284$ ), but these differences were not statistically significant. There was no heterogeneity among the included studies ( $I^2=0.0\%$ ) (Fig. 2B).

### 3.3. Thromboembolic events

Six studies reported thromboembolic events at follow-up (Fig. 3), and no statistical heterogeneity was found ( $I^2=0.0\%$ ). The thromboembolism risk of the LMWH group was significantly lower than that of the UFH group (RR=0.34, 95% CI 0.12–0.95,  $P=.039$ ).

### 3.4. Mortality

Four studies reported mortality (Fig. 4). The mortality rate of the LMWH group was lower than that of the UFH group, although the difference was not significant (RR=0.52, 95% CI 0.16–1.66,  $P=.271$ ). There was no heterogeneity among the included studies ( $I^2=0.0\%$ ).

### 3.5. Publication bias

Risk ratio (RR) results were used to produce a funnel plot; the result showed that both sides are symmetrical, and it could be concluded that the possibility of publication bias was small (Fig. 5A). Egger regression test was used to test bias, and the result showed that the value of  $t$  was  $-0.91$  ( $P=.414 > .05$ , 95% CI  $-2.28058-1.153898$ ). In the figure, we found the intercept at 0 points, which indicated no statistical significance (Fig. 5B).

## 4. Discussion

Patients with MHV require lifelong anticoagulation with a vitamin K antagonist to prevent thromboembolic complications. Warfarin treatment is usually initiated within 48 hours (h) of valve replacement surgery but takes 4 to 5 days to reach therapeutic levels. During this time, many cardiac surgeons bridge their patients with a rapidly acting parenteral anticoagulant.<sup>[11]</sup> However, there is no consensus regarding the ideal strategy, and prospective studies are lacking. Current European Society of Cardiology (ESC) guidelines state that “UFH remains the only approved heparin treatment in patients with mechanical prostheses; intravenous administration should be favored over the subcutaneous route (Level of evidence C II a).”<sup>[13]</sup> In contrast, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines advocate for the following: “bridging anticoagulation with either intravenous UFH or subcutaneous LMWH is recommended during the time interval when the INR is subtherapeutic preoperatively in patients who are undergoing invasive or surgical procedures with a mechanical aortic valve replacement (AVR) and any thromboembolic risk factor, older

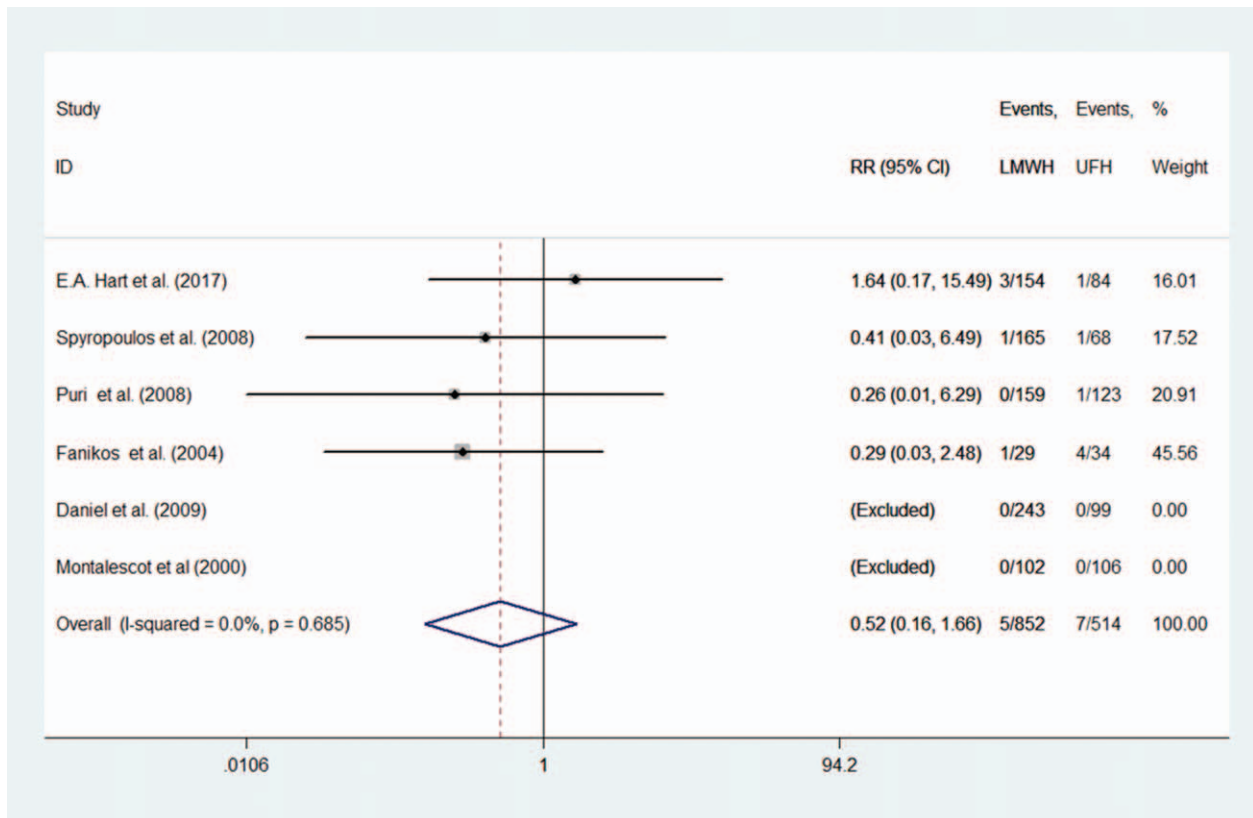


Figure 4. Death events.

generation mechanical AVR, or mechanical mitral valve replacement (MVR) (Level of Evidence: C-LD IIa).<sup>12</sup>

The primary finding was that LMWH could reduce the incidence of thromboembolism while not increasing the risk of major bleeding. This finding was different from that of another meta-analysis by Caldeira et al.<sup>10</sup> Caldeira's meta-analysis comparing LMWH and UFH/VKA found that there were no significant differences in the incidences of thromboembolism and major bleeding between the 2 groups. The meta-analysis included 4 studies comparing LMWH and UFH, and the subgroup analysis also showed no significant difference. Although statistically insignificant, the author suggested that LMWH was effective and safe for temporary use in patients with MHVs in terms of the thromboembolic risk compared with UFH/VKA. The reason for the difference between that study and the present study may be the inclusion of 2 new studies.<sup>14,13</sup> One of them was a recent retrospective multicenter study by E. Hart, which included 238 bridging episodes, and showed that there were 16 (19%) major bleeding events in the UFH group compared with 29 (19%) events in the LMWH group ( $P = .97$ ). The number of incidents of thromboembolism was 2 (2.4%) versus 1 (0.6%).<sup>14</sup> The author proposed that anticoagulant bridging in patients with high-risk MHVs should be applied based on the patient's individual risk profile and may be left to the physician's discretion. He also suggested that patients with mechanical heart valves can be bridged with LMWH.

This finding was consistent with the results of the study by Passaglia et al.<sup>9</sup> The meta-analysis by Passaglia et al.<sup>9</sup> assessed anticoagulation in cardiac surgery patients. It included 23 studies

comparing OAC and LMWH or UFH. Among them, only 3 studies compared LMWH and UFH. The author found a higher incidence of bleeding in the LMWH group (5.5%) than the OAC group (1.8%) and the UFH group (2.2%) ( $P = 0.042$ ); however, the incidences of thromboembolic events in the LMWH group and the UFH group were the same (1.1%). The author compared the total incidence of early postoperative bleeding and thromboembolic events; however, 3 separate studies comparing LMWH and UFH did not carry out subgroup analyses. By analyzing 3 studies, we found that the risk of bleeding in the LMWH group was higher than that in the UFH group in the early postoperative period, but the difference was not significant ( $RR = 1.17$ , 95% CI 0.72–1.90,  $P = .526$ ). The risk of thromboembolic events in the LMWH group was significantly lower than that in the UFH group (0.34% vs 1.9%). Only one case of thromboembolism occurred in the study by Puri et al.<sup>13</sup> Meanwhile, 3 studies involving patients undergoing noncardiac surgery showed no significant differences in the risk of bleeding between the LMWH group and the UFH group.

Our meta-analysis suggested that non-cardiac surgery patients receiving LMWH had a relatively lower risk of major bleeding ( $RR = 0.79$ , 95% CI 0.51–1.22,  $P = .284$ ). This might be related to the fact that non-cardiac surgery patients did not undergo extracorporeal circulation and their levels of clotting factors and platelets were normal, with no heparinization or endocardial injury, highlighting the LMWH advantage of a low bleeding risk.

The subgroup analysis of patients undergoing cardiac surgery revealed that the LMWH group had a higher risk of major bleeding ( $RR = 1.17$ , 95% CI 0.72–1.90,  $P = .526$ ). This might be

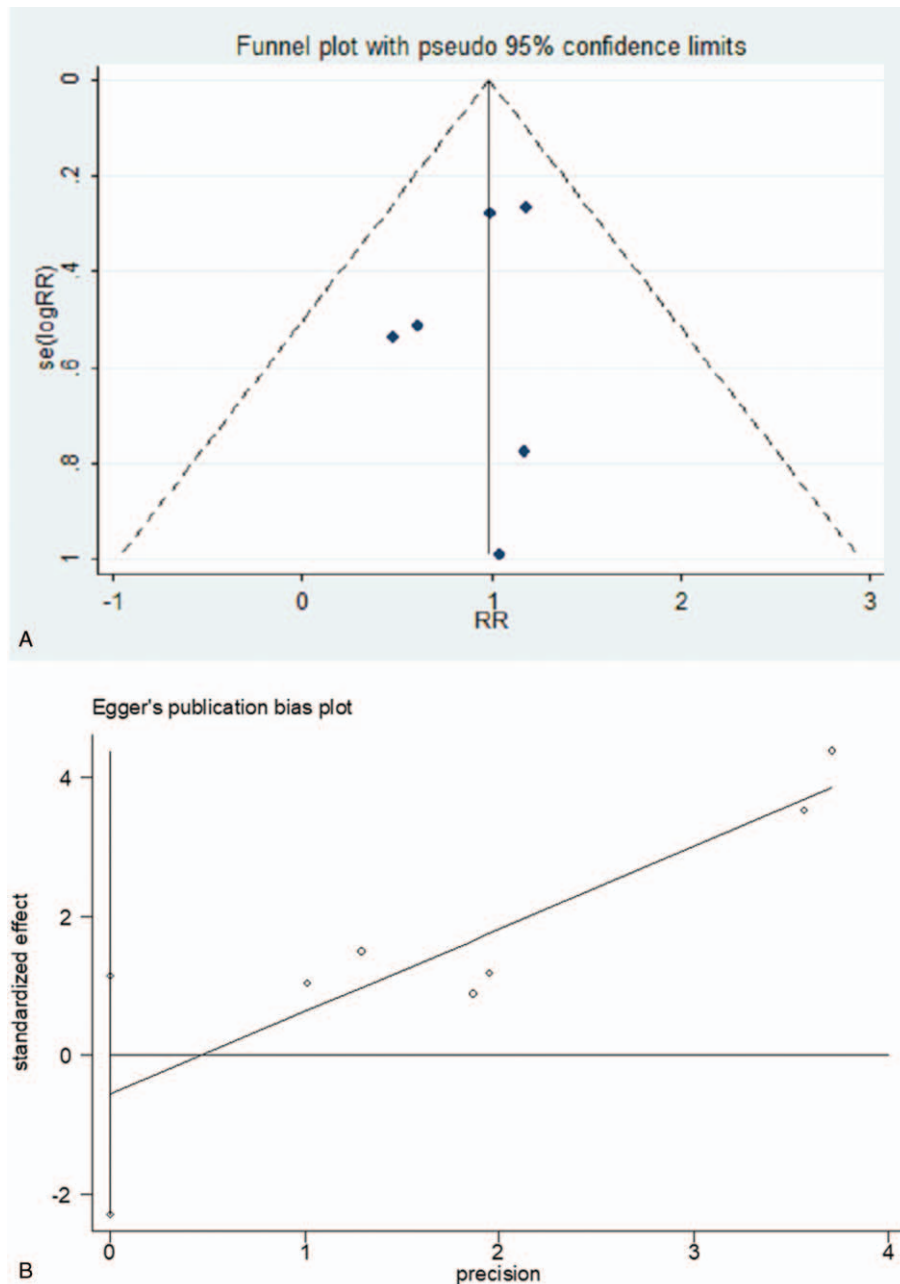


Figure 5. A: Funnel Plot. B: Egger regression test.

related to LMWH having a longer half-life than UFH and the different doses used. The half-life of LMWH is generally 5 to 7 hours, while the half-life of UFH is 1 to 2 hours. Some studies included preventive strategies, while others used therapeutic strategies. For patients with a high risk of bleeding, a reduced dose of LMWH can be used to bridge anticoagulation. In a study that was published in 2013 by Weiss et al<sup>[14]</sup> with 402 patients after cardiac surgery (24.9% with mechanical heart valve replacement), LMWH was administered at the full dose (FD) (1 mg/kg body weight twice daily) and a half dose (HD) (0.5 mg/kg body weight twice daily). The author observed more bleeding events (11 vs 5,  $P = .126$ ) but fewer thromboembolic events (5 vs 9,  $P = .277$ ) in the FD group than in the HD group.

## 5. Limitation

Our study has several limitations. First, our research consists of prospective or retrospective studies and no randomized studies. Additionally, the number of studies included was small. Moreover, several studies with small sample sizes raised some concerns regarding the reliability of their results. Second, the definition of major bleeding events and thromboembolic events may be different in different studies.

## 6. Conclusion

LMWH could significantly reduce the risk of thromboembolism without increasing the incidence of major bleeding in patients

with MHVs. LMWH might provide a safer and more efficient method of bridging anticoagulation than UFH. Further randomized studies are needed to verify the conclusions.

### Author contributions

**Conceptualization:** Ende Tao.

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**Formal analysis:** Ende Tao, YunLong Luo.

**Funding acquisition:** Li Wan.

**Methodology:** Ende Tao.

**Project administration:** Li Wan.

**Software:** YunLong Luo, Zhe Tao.

**Writing – original draft:** Ende Tao.

**Writing – review & editing:** Ende Tao, YunLong Luo, Zhe Tao, Li Wan.

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