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The efficacy and safety of low-molecular-weight heparin in patients undergoing knee arthroscopic surgery and anterior cruciate ligament reconstruction☆

Hui-Min Li, Leyi Huang, Junwei Fu, Zhicheng Tong, Wei Wei, Chong Teng *

Department of Orthopedics, The Fourth Affiliated Hospital, Zhejiang University School of Medicine, Yiwu, 322000, China

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ABSTRACT

Purpose: To inveatigate how effective LMWH was at preventing venous thromboembolism (VTE), major bleeding events, and minor bleeding events after simple knee arthroscopic surgery and anterior cruciate ligament reconstruction (ACLR).

Methods: We conducted a comprehensive search of PubMed, EMBASE, Cochrane Library, and the CNKI database for potentially eligible articles. The outcomes were evaluated in terms of odds ratio (OR) and the associated 95% confidence intervals (CIs). Meta-analysis was performed using the Stata software and subgroup analyses were performed based on the surgical setting including ACLR and simple knee arthroscopic surgery.

Results: A total of eight studies with 2249 patients and 1794 controls were included in this meta-analysis. In patients undergoing simple knee arthroscopic surgery, LMWH prophylaxis did not bring a significant reduction in the risk of symptomatic deep venous thrombosis (DVT), symptomatic pulmonary embolism (PE), symptomatic VTE, and did not increase the risk of major bleeding events, but did have a higher risk of minor bleeding events (OR = 1.95, 95% CI 1.34–2.84, $P = 0.000$) and a lower risk of asymptomatic DVT (OR = 0.14, 95% CI 0.04–0.53, $P = 0.004$) in comparison with non-LMWH prophylaxis. In patients undergoing ACLR, LMWH prophylaxis did not bring a significant reduction in the risk of symptomatic DVT, symptomatic PE, symptomatic VTE, and did not increase the risk of major bleeding events and minor bleeding events, but did have a lower risk of asymptomatic DVT (OR = 0.43, 95% CI 0.23–0.78, $P = 0.006$).

Conclusion: When compared to a control group, this meta-analysis found that LMWH had little potential benefit in preventing major VTE (symptomatic VTE, symptomatic DVT, and symptomatic PE) after simple knee arthroscopy and ACLR. As a result, LMWH should not be considered routinely in patients undergoing knee arthroscopic surgery.

1. Introduction

With over 5 million patients undergoing knee arthroscopic surgery each year, it has become one of the most prevalent surgical

☆ **Level of Evidence:** Level I meta-analysis of Level I studies.

* Corresponding author. Department of Orthopedics, The Fourth Affiliated Hospital, Zhejiang University School of Medicine, Yiwu, 322000, China.

E-mail address: tengchong1984@zju.edu.cn (C. Teng).

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Table 1
Demographic characteristics of the included studies.

Study	Country	Study design	Operative Procedure	Age (year)		Treatment		Number		Follow-up
				Trial	Control	Trial	Control	Trial	Control	
Roth et al. (1995)	Germany	RCT	knee arthroscopic surgery (no anterior cruciate ligament reconstruction)	NA	NA	LMWH (Fraxiparine, 0.3 mL, once daily, for 4 d)	None	61	61	6–8 weeks
Wirth et al. (2001)	Germany	RCT	knee arthroscopic surgery (no anterior cruciate ligament reconstruction)	37.6	38.5	LMWH (Reviparin, 1750 IU, once daily, for 8 d)	None	117	122	7–10 days
Michot et al. (2002)	Switzerland	RCT	knee arthroscopic surgery (no anterior cruciate ligament reconstruction)	42.0	46.5	LMWH (Dalteparin, 2500 IU $\leq$ 70 kg or 5000 IU > 70 kg, once daily, for 30 d)	None	66	64	1 month
Canata and Chiey (2003)	Italy	RCT	anterior cruciate ligament reconstruction (100%)	29.6	32.5	LMWH (Enoxaparin, 4000 IU, once daily, for 6 d)	None	18	18	NA
Camporese et al.1 (2008)	Itlay	RCT	knee arthroscopic surgery, anterior cruciate ligament reconstruction (34.7%)	42.1	42.3	LMWH (Nadroparin, 3800 IU *anti*-Xa, once daily, for 7 or 14 d)	Placebo or Compression stocking	1101	660	3 months
Liu et al. (2016)	China	RCT	anterior cruciate ligament reconstruction (100%)	NA	NA	LMWH (Enoxaparin, 100 Axa u· kg^{-1}, once daily, for 7 d)	None	35	35	NA
Camporese et al.1 (2016)	Itlay	RCT	knee arthroscopic surgery, anterior cruciate ligament reconstruction (6.2%)	44.9	45.9	LMWH (Rivaroxaban, 10 mg, once daily, for 7 d)	Placebo	120	114	3 months
Van Adrichem et al. (2017)	Netherlands	RCT	knee arthroscopic surgery (no anterior cruciate ligament reconstruction)	48.1	49.1	LMWH (Nadroparin or Dalteparin, 2850 IU nadroparin or 2500 IU dalteparin, once daily for $\leq$100 kg and double dose for > 100 kg, for 8 d)	None	731	720	3 months

RCT, randomized controlled trial; NA, not applicable.

treatments for the knee [1]. When executing this surgical operation, however, an increased risk of venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), may occur [2,3]. Venous thromboembolism is a serious health issue that causes significant death, morbidity, and resource depletion [4]. Low-molecular-weight heparin (LMWH) is well suggested as thromboprophylaxis following most orthopaedic operations since it significantly reduces the risk of thrombosis while also increasing the risk of bleeding [5]. The use of this prophylactic in patients who have had knee arthroscopic surgery is, however, debatable. LMWH was found to minimize the risk of DVT in patients receiving therapeutic knee arthroscopy in several randomized controlled trials (RCTs) [6–9]. Another trial found that LMWH prophylaxis following knee arthroscopy was ineffective in preventing symptomatic VTE [10]. This could be attributable to a variety of factors, including sample sizes, race, surgery type, and other confounding variables.

Six meta-analysis studies were published in 2008, 2014, 2018, 2019, and 2020 to overcome the limitations of individual investigations. Ramos et al. [11] discovered that LMWH reduced the incidence of distal DVT diagnosed by sonogram, but no strong evidence was found to conclude that thromboprophylaxis is effective in preventing thromboembolic events and is safe in people undergoing knee arthroscopy who have unknown risk factors for thrombosis. Sun et al. [12] also discovered that LMWH lowers the risk of distal DVT. Chapelle et al. [13] observed that LMWH prophylaxis lowered the risk of significant VTEs, such as asymptomatic DVT, symptomatic VTEs, and VTE-related death. According to Huang et al. [14], the group treated with LMWH following knee arthroscopy had no effect on the rate of symptomatic VTE, symptomatic DVT, or symptomatic PE. Perrotta et al. [15] found no indication of benefit from the use of LMWH in reducing the minor risk of PE or symptomatic DVT. Furthermore, they stated that there was extremely low-certainty evidence that LMWH use could reduce the risk of asymptomatic DVT compared to no therapy. Only Zhu et al. [16] looked at the influence of various surgical procedures and reported that LMWH had no meaningful efficacy in avoiding VTE in patients undergoing basic knee arthroscopic surgery, although it did increase the risk of all bleeding events. LMWH, on the other hand, was found to be effective in avoiding VTE in patients having anterior cruciate ligament reconstruction (ACLR) and did not raise the risk of bleeding. The question of whether using LMWH following knee arthroscopy has a preventative effect is still being debated. The goal of this meta-analysis was to see how effective LMWH was at preventing VTE (symptomatic VTE, asymptomatic DVT, symptomatic DVT, symptomatic PE), major bleeding events, and minor bleeding events after simple knee arthroscopic surgery and ACLR compared to no LMWH medication. We hypothesized that LMWH after knee arthroscopy, including simple knee arthroscopy and ACLR, was ineffective.

2. Methods

The work has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [17].

2.1. Search trials

We searched PubMed, EMBASE, the Cochrane Library, and the CNKI database for RCTs comparing LMWH to placebo, no treatment, or alternative nonpharmaceutical therapy for the prevention of VTE following knee arthroscopic surgery. The search terms included "thromboembolism," "thromboembolization," "venous thromboembolism," "pulmonary embolism," "venous thrombosis," "heparin, low molecular weight," "low-molecular-weight heparin," "LMWH," "arthroscopic surgery," "arthroscopy," "feishuansezheng," "difenzigansu," "xiguanjiejing,". The detailed search strategy is reported in eTable 1. We did not limit the languages or publication date. The literature search was last updated on March 1, 2023. Two reviewers independently examined all of the titles, as well as the abstracts and references of relevant studies, for further relevant literature. If there was any doubt, full-text papers were obtained, and any discrepancies were handled by consensus among the reviewers.

2.2. Inclusion and exclusion criteria

The following criteria were used to select and exclude studies: (1) Patients who got LMWH following arthroscopy of the knee. (2) In the experimental group, the intervention was LMWH. (3) In the control group, there was no anticoagulant therapy. (4) Studies were considered valid if they included at least one of the following outcomes: VTE (symptomatic VTE, asymptomatic DVT, symptomatic DVT, and symptomatic PE), major bleeding, and minor hemorrhage. Venography or compression ultrasound were used to confirm DVT, both asymptomatic and symptomatic DVT. Pneumoangiography, ventilation-perfusion lung scanning, or helical computed tomography were used to confirm symptomatic PE. Symptomatic VTE (including symptomatic PE and proximal DVT), symptomatic DVT, and symptomatic PE were all examples of major VTE. (5) The study had to be a randomized controlled experiment. The following papers were excluded: cohort studies, case-control studies, case reports, retrospective studies, systematic reviews, and meta-analyses.

2.3. Risk-of-bias assessments

Two researchers assessed the methodological quality of the included RCTs using the Cochrane risk-of-bias criteria [18], which included seven items on randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Other biases were identified as company-sponsored trials and trials in which the baseline characteristics of distinct intervention groups differed. Each item was given a risk rating of low, high, or unclear. The quality of the trials included in this study was rated as poor, high, or moderate based on the

following criteria: 1) Trials were considered low quality if either the randomization or allocation concealment were assessed as having a high or unclear risk of bias, regardless of the risk of the other items; 2) trials were considered high quality when both randomization and allocation concealment were assessed as having a low risk of bias, and all other items in the trial were assessed as having a low or unclear risk of bias, except for the item of participant and personnel blinding; and 3) trials were considered of moderate quality if they did not meet the criteria for high or low risk.

2.4. Data extraction

Data was extracted from qualified papers by two reviewers separately. Any differences were resolved through conversation or consultation with a third reviewer. The essential study characteristics were retrieved, including the main author, publication year, country of origin, length of follow-up, sample size, experimental and control interventions, age, and outcomes. VTE (symptomatic VTE, asymptomatic DVT, symptomatic DVT, and symptomatic PE), major bleeding events, and minor bleeding events were the end measures of interest. Major bleeding is mainly defined as: (1) fatal bleeding, (2) symptomatic bleeding in critical areas or organs, (3) bleeding at the surgical site that results in a decrease in hemoglobin levels of $\geq$2.0 g/dL or transfusion of $\geq$1 U of whole blood or red blood cells, (4) bleeding at the surgical site that requires secondary intervention treatment, or joint hematocele that hinders recovery, or bleeding at the surgical site that requires transfusion, (5) joint hematocele with joint drainage exceeding 450 mL, or (6) obvious bleeding with a bleeding index $\geq$2. The bleeding index is calculated by subtracting the pre bleeding hemoglobin concentration (g/dL) from the post bleeding hemoglobin concentration (g/mL). Minor bleeding is defined as joint bleeding, with joint drainage of 100–450 mL, which is not life-threatening and does not require further intervention [7,19].

2.5. Statistical analysis

We estimated the odds ratio (OR) and its 95% confidence interval (CI) for dichotomous data in this meta-analysis. At a significance level of $P < 0.05$, statistical heterogeneity was examined using the I^2 and chi-squared tests. When there was no evidence of heterogeneity ($I^2 < 50\%$, $P > 0.05$) among the studies, a fixed-effects model was used [20–26]. Otherwise, a random-effects model was used. Based on the practice recommendation of Cochrane Handbook, trials with zero events in both the intervention and control groups when ORs were calculated were excluded from the meta-analysis.

To see if LMWH had a different effect on ACLR and simple knee arthroscopic surgery, all studies were divided into two groups based on the surgical setting: (1) ACLR group including ACLR in selected studies, and (2) simple knee arthroscopic surgery group only including meniscectomy, removal of loose bodies, or diagnostic arthroscopic surgery and no ACLR. Using the leave-one-out approach, we ran sensitivity analyses. We also used the funnel plot test to determine whether there was any publication bias. Revman 5.4 and Stata (version 14.0; TX 77845, USA) were used to conduct the statistical analysis. All tests were two-tailed, and statistical significance was defined as $P < 0.05$.

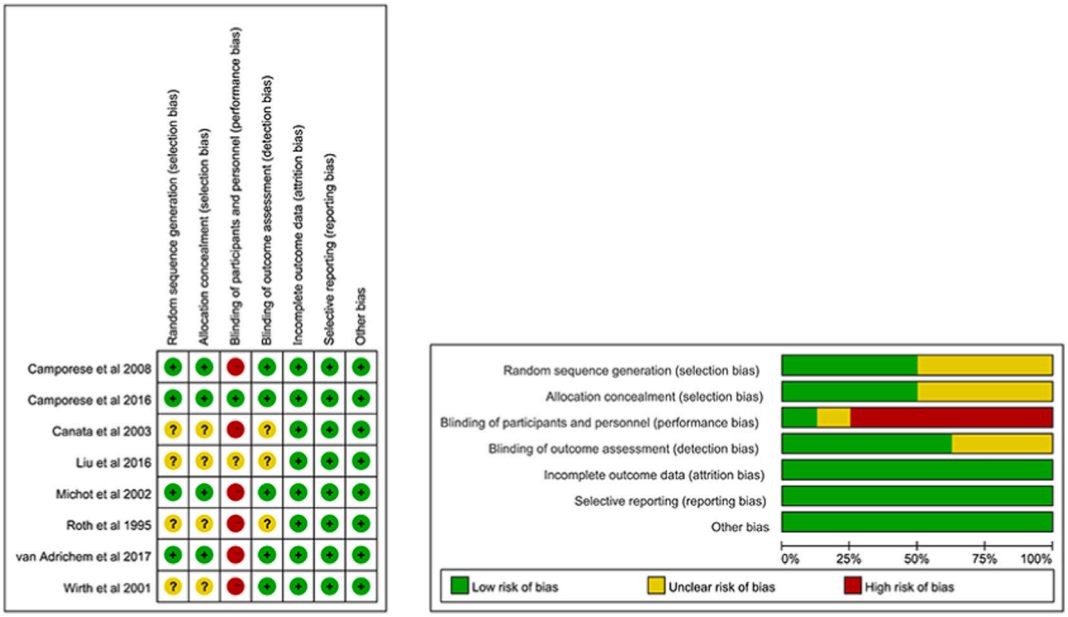

Fig. 1. Risk of bias summary. + indicates low risk of bias; -, high risk of bias; ? unclear risk of bias.

3. Results

3.1. Study search

A summary of the study selection process is shown in Supplementary Fig. 1. A total of 153 relevant studies were inspected via electronic search. A total of 53 studies were excluded because they were duplicates. After assessing the titles and abstracts, 70 studies were eliminated, because they did not meet the eligibility criteria. Besides, we also excluded one RCT study from Marlovits et al. because patients in both treatment arms received LMWH prophylaxis [19]. Finally, eight RCTs [6–10,27–29] with 2249 patients and 1794 controls were finally included in this meta-analysis.

3.2. Study characteristics

Table 1 summarizes the main characteristics of the studies included. The baseline information of the eight studies of the two groups was balanced and comparable. Among these studies, all studies were from a single-trial site. Among the eight studies, two studies [8,9] were conducted in Germany, one study [7] was conducted in Switzerland, three studies [27–29] were conducted in Italy, one study [6] was conducted in China, and one study [10] was conducted in Netherlands. All studies compared LMWH with no anticoagulant therapy. Four [6,27–29] of the 8 selected studies including ACLR were categorized into the ACLR group. Four studies [7–10] only included meniscectomy, removal of loose bodies, or diagnostic arthroscopic surgery and no ACLR were categorized into the simple knee arthroscopic surgery group.

3.3. Risk of bias in the included studies

The risk of bias in the included studies is presented in Fig. 1. Four studies [7,10,28,29] showed appropriate randomization, described the allocation concealment in detail, and thus, were regarded as high quality. Four studies [6,8,9,27] were regarded as low quality, because their randomization and allocation concealment were assessed as unclear risk of bias. Five studies [7,8,10,28,29] reported an adequate blinding of outcome assessment. In terms of incomplete outcome data, selective reporting, and other biased, eight studies [6–10,27–29] were deemed to have a low risk of bias.

3.4. Meta-analysis results

3.4.1. Major VTE

Symptomatic DVT Eight studies [6–10,27–29] provided data on symptomatic DVT. For knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 0.64, 95% CI 0.24–1.69, $P = 0.37$; $I^2 = 15\%$; Fig. 2). Besides, for simple knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.65, 95% CI 0.39–6.96, $P = 0.49$; $I^2 = 0\%$; Fig. 2). For

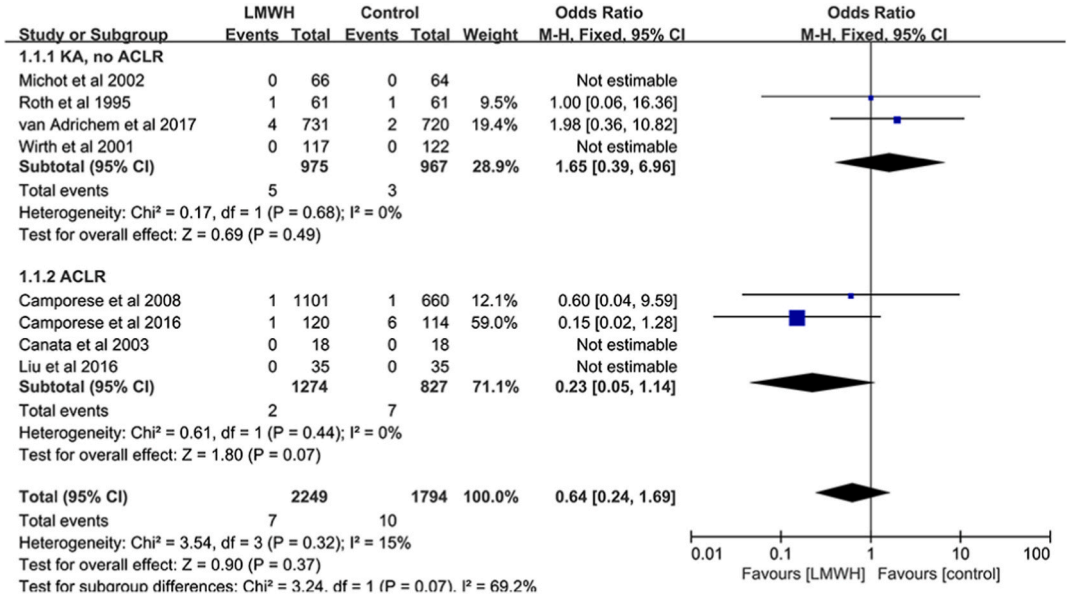

Fig. 2. Forest plot diagram showing symptomatic DVT compared between LMWH and non-LMWH prophylaxis for patients undergoing simple knee arthroscopic surgery and ACLR.

ACLR, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 0.23, 95% CI 0.05–1.14, $P = 0.07$; $I^2 = 0\%$; Fig. 2).

Symptomatic PE Eight studies [6–10,27–29] provided data on symptomatic PE. For knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.36, 95% CI 0.37–5.03, $P = 0.64$; $I^2 = 0\%$; Fig. 3). Besides, for simple knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.64, 95% CI 0.21–12.46, $P = 0.64$; $I^2 = 0\%$; Fig. 3). For ACLR, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.20, 95% CI 0.22–6.57, $P = 0.83$; Fig. 3).

Symptomatic VTE Seven studies [7–10,27–29] provided data on symptomatic VTE. For knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 0.84, 95% CI 0.39–1.80, $P = 0.66$; $I^2 = 0\%$; Fig. 4). Besides, for simple knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.65, 95% CI 0.51–5.33, $P = 0.40$; $I^2 = 0\%$; Fig. 4). For ACLR, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 0.47, 95% CI 0.16–1.38, $P = 0.17$; $I^2 = 53\%$; Fig. 4).

3.4.2. Asymptomatic DVT

Six studies [6–9,28,29] provided data on asymptomatic DVT. For knee arthroscopic surgery, the combined results demonstrated that the incidence of asymptomatic DVT was lower in the LMWH group compared with the control group (OR = 0.33, 95% CI 0.19–0.56, $P = 0.000$; $I^2 = 0\%$; Fig. 5). Besides, for simple knee arthroscopic surgery, the combined results demonstrated that the incidence of asymptomatic DVT was lower in the LMWH group compared with the control group (OR = 0.14, 95% CI 0.04–0.53, $P = 0.004$; $I^2 = 0\%$; Fig. 5). For ACLR, the combined results demonstrated that the incidence of asymptomatic DVT was lower in the LMWH group compared with the control group (OR = 0.43, 95% CI 0.23–0.78, $P = 0.006$; $I^2 = 0\%$; Fig. 5).

3.4.3. Major bleeding events

Eight studies [6–10,27–29] provided data on major bleeding events. For knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.44, 95% CI 0.26–08.06, $P = 0.68$; $I^2 = 0\%$; Fig. 6). Besides, for simple knee arthroscopic surgery, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 0.98, 95% CI 0.06–15.78, $P = 0.99$; Fig. 6). For ACLR, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.80, 95% CI 0.19–17.35, $P = 0.61$; Fig. 6).

3.4.4. Minor bleeding events

Eight studies [6–10,27–29] provided data on minor bleeding events. For knee arthroscopic surgery, the combined results demonstrated that the incidence of minor bleeding events was higher in the LMWH group compared with the control group (OR = 1.57, 95% CI 1.17–2.12, $P = 0.003$; $I^2 = 4\%$; Fig. 7). Besides, for simple knee arthroscopic surgery, the combined results demonstrated

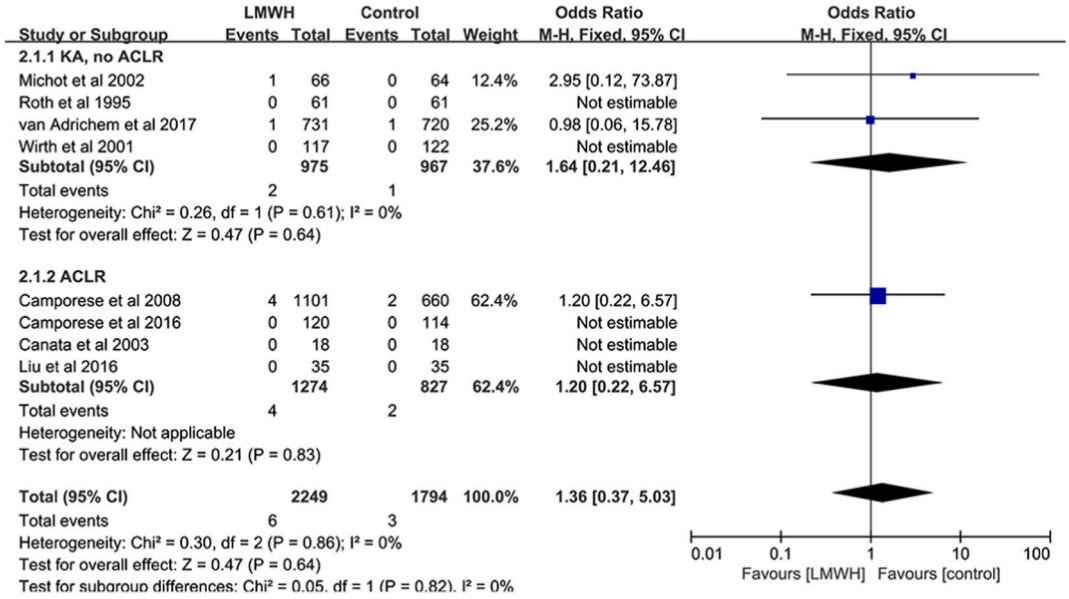

Fig. 3. Forest plot diagram showing symptomatic PE compared between LMWH and non-LMWH prophylaxis for patients undergoing simple knee arthroscopic surgery and ACLR.

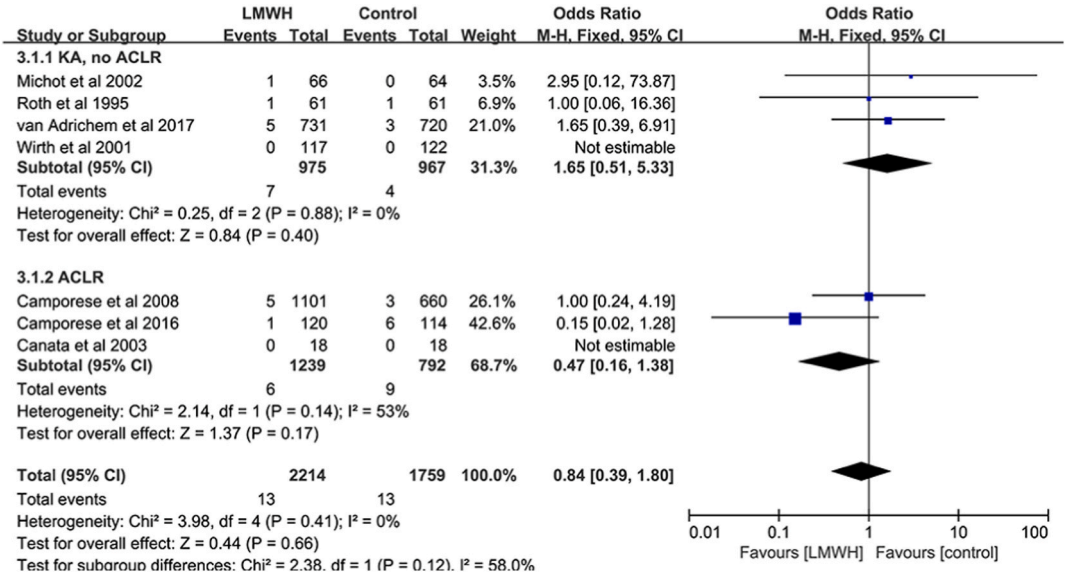

Fig. 4. Forest plot diagram showing symptomatic VTE compared between LMWH and non-LMWH prophylaxis for patients undergoing simple knee arthroscopic surgery and ACLR.

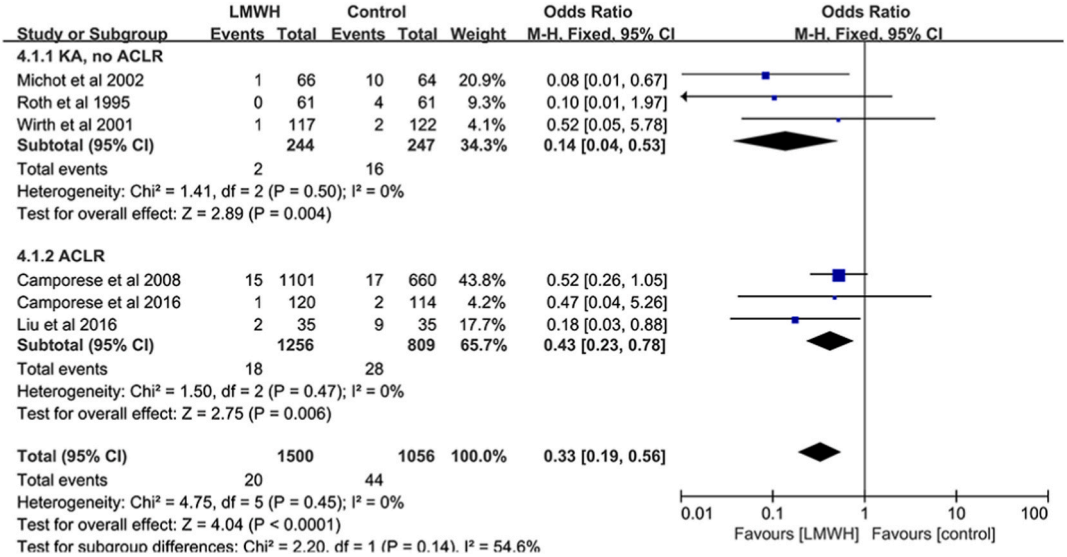

Fig. 5. Forest plot diagram showing asymptomatic DVT compared between LMWH and non-LMWH prophylaxis for patients undergoing simple knee arthroscopic surgery and ACLR.

that the incidence of minor bleeding events was higher in the LMWH group compared with the control group (OR = 1.95, 95% CI 1.34–2.84, $P = 0.000$; $I^2 = 0\%$; Fig. 7). For ACLR, the combined results demonstrated that there was no statistical difference between the LMWH group and the control group (OR = 1.07, 95% CI 0.65–1.75, $P = 0.80$; $I^2 = 0\%$; Fig. 7).

3.4.5. Sensitivity analyses and publication bias

Sensitivity analyses did not provide different results in terms of VTE (symptomatic VTE, asymptomatic DVT, symptomatic DVT and symptomatic PE), major bleeding events, and minor bleeding events by removing one study at a time (Supplementary Fig. 2). Besides, the funnel plot test showed that there was no publication bias in terms of VTE (symptomatic VTE, asymptomatic DVT, symptomatic DVT and symptomatic PE), major bleeding events, and minor bleeding events (Supplementary Fig. 3).

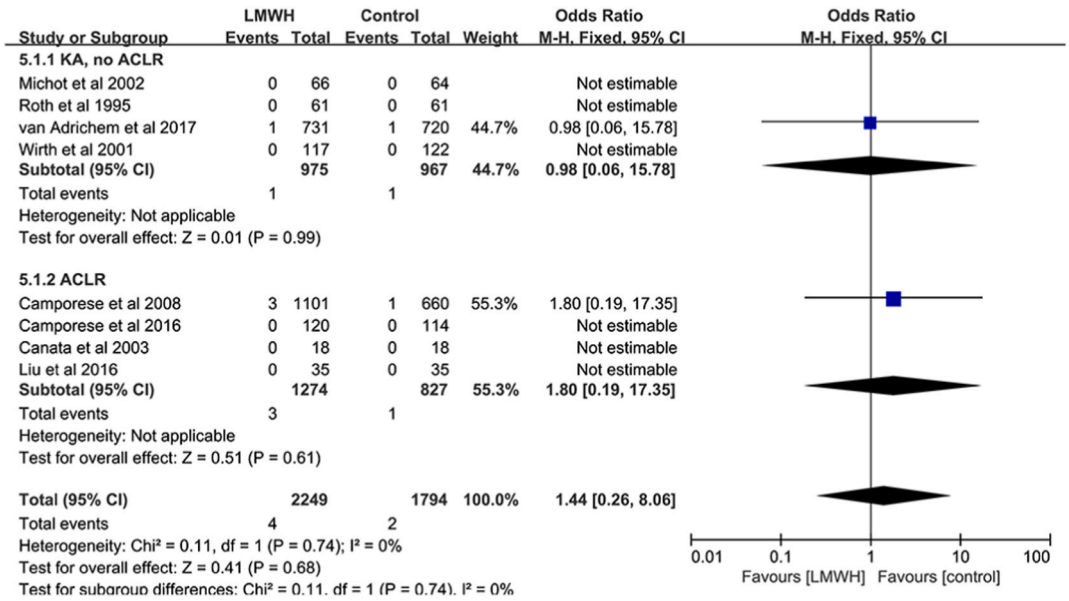

Fig. 6. Forest plot diagram showing major bleeding events compared between LMWH and non-LMWH prophylaxis for patients undergoing simple knee arthroscopic surgery and ACLR.

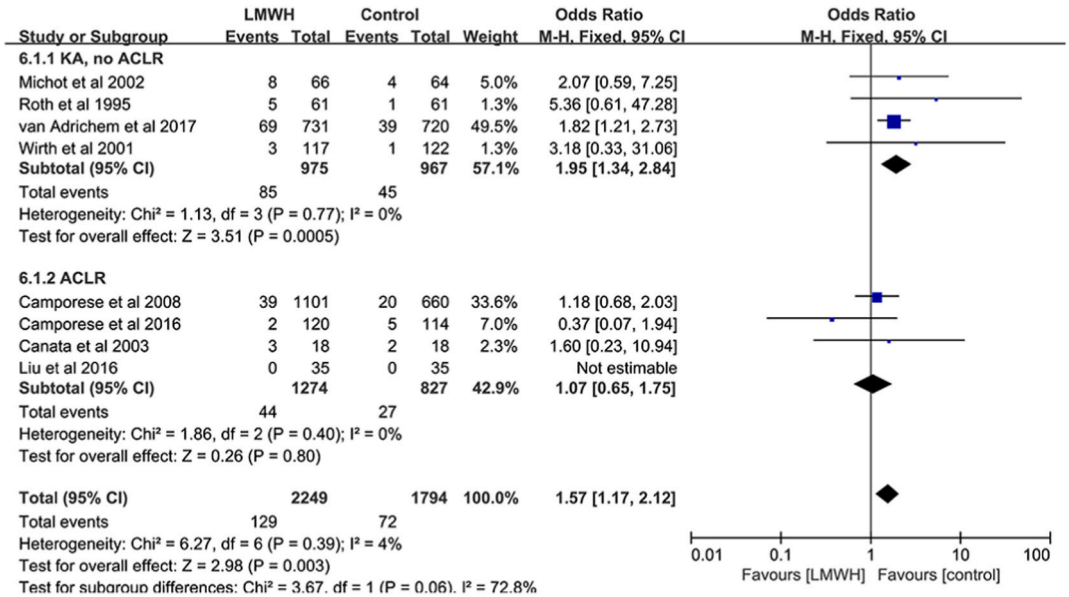

Fig. 7. Forest plot diagram showing minor bleeding events compared between LMWH and non-LMWH prophylaxis for patients undergoing simple knee arthroscopic surgery and ACLR.

4. Discussion

In patients undergoing simple knee arthroscopic surgery and ACLR, our meta-analysis found that LMWH prophylaxis did not reduce the incidence of major VTE (symptomatic VTE, symptomatic DVT, and symptomatic PE) and major bleeding events. In patients undergoing simple knee arthroscopic surgery and ACLR, however, LMWH prophylaxis reduced the chance of asymptomatic DVT. Furthermore, LMWH increased the incidence of minor bleeding events in individuals receiving simple knee arthroscopic surgery but had no effect on ACLR patients.

Previous meta-analysis studies on the prevention of VTE by LMWH have yielded conflicting results. In 2008, Ramos et al. [11] conducted the first meta-analysis in 2008, which included four RCTs [7–9,27] published before 2003 and a small sample size of 527 patients to explore the effectiveness and safety of LMWH in reducing the incidence of DVT in patients having knee arthroscopy. They

suggested that LMWH could minimize the incidence of distal DVT in this trial. In 2014, Sun et al. [12] reported that LMWH could lower the incidence of distal DVT in nine prospective uncontrolled studies and four randomized controlled trials [7–9,27]. However, the inclusion of major VTE in subsequent meta-analyses has been inconsistent. Major VTE was defined by Chapelle et al. [13] and Zhu et al. [16] as the cumulative incidence of all-cause death, symptomatic VTE, and asymptomatic proximal DVT over the follow-up period. Chapelle et al. observed that LMWH prophylaxis reduced the risk of serious VTE in patients having knee arthroscopy as compared to non-LMWH prophylaxis in 6 RCTs [7–9,19,27,29]. With 8 RCTs [7–10,19,27–29], Zhu et al. observed that the risk of significant VTE was not reduced in the LMWH group in patients undergoing simple knee arthroscopy. Huang et al. [14] stated that major VTE was characterized as symptomatic VTE, symptomatic DVT, and symptomatic PE in their study. They discovered that in patients undergoing knee arthroscopy, the risk of significant VTE was not reduced in the LMWH group when including 7 RCTs [7–10,19,27,29]. However, Marlovits et al.'s study [19] was included in all three investigations. In fact, after an initial treatment period of 3–8 days of inhospital prophylaxis with LMWH, Marlovits et al. randomized patients to extended prophylaxis with LMWH versus placebo. As a result, LMWH prophylaxis was given to patients in both therapy groups. Therefore, we excluded Marlovits et al.'s study [19] and included a new study of Liu et al. [6] Furthermore, as indicated in a previous study [30], anticoagulant efficacy in preventing asymptomatic VTE did not correlate with efficacy in preventing symptomatic VTE. As a result, we proposed that major VTE be classified as symptomatic VTE, symptomatic DVT, and symptomatic PE in our meta-analysis. In 2020, Perrotta et al. [15] found no evidence of benefit from the use of LMWH in reducing the small risk of PE or symptomatic DVT in a meta-analysis of 7 RCTs [7–10,27–29]. They also said that there was extremely low-certainty evidence that LMWH use could lessen the risk of asymptomatic DVT when compared to no treatment. Although arthroscopy patients are typically thought to be at low risk of VTE, risk factors such as advanced age or prolonged immobilization, as well as more difficult operations such as ACLR surgery, will put them at moderate or high risk, necessitating proper thromboprophylaxis [31]. As a result, we anchored our study subgroup analysis on simple knee arthroscopy and ACLR. To begin, we included two RCT trials by Camporese et al. [28,29], although the number of patients with ACLR was small, accounting for around 6% and 39% of the total included patients (15/241 and 681/1761 individuals, respectively). In patients undergoing knee arthroscopy, the risk of major VTE was not reduced in the LMWH group (Figs. 2–4). After that, we take two RCTs out of Camporese et al.'s study and perform subgroup analysis using simple knee arthroscopy and ACLR. LMWH prophylaxis did not reduce the incidence of major VTE (symptomatic VTE, symptomatic DVT, and symptomatic PE) in patients following simple knee arthroscopic surgery and ACLR. When two RCTs from Camporese et al. were combined, we discovered that LMWH administration could reduce the risk of asymptomatic DVT relative to no therapy in patients following knee arthroscopic surgery. Furthermore, even after excluding two RCTs from Camporese et al. we discovered that LMWH prophylaxis reduced the incidence of asymptomatic DVT in patients following simple knee arthroscopic surgery and ACLR (Supplementary Fig. 4).

When having moderate or high-risk surgery, LMWH has been widely used for VTE prevention; however, the risk of bleeding with LMWH is higher than with aspirin. As a result, the risks of LMWH treatment (such as severe and minor bleeding) must be considered. In the study of Huang et al. [14], they discovered that LMWH had no influence on major bleeding rates when compared to the control group, but that the control group had a lower frequency of minor bleeding than the LMWH group. In comparison to non-LMWH prophylaxis, Zhu et al. [16] observed that LMWH prophylaxis did not raise the risk of serious bleeding events but did increase the risk of all bleeding episodes in patients undergoing uncomplicated knee arthroscopic surgery. When compared to non-LMWH prophylaxis, LMWH prophylaxis did not increase the risk of major bleeding events or all bleeding episodes in patients receiving ACLR. When we included two RCTs from Camporese et al. in our meta-analysis, we observed that LMWH had no effect on major bleeding compared to the control group, but there was a reduced frequency of minor bleeding in the control group than in the LMWH group (Figs. 6–7). After deleting two RCTs from Camporese et al. we discovered that LMWH prophylaxis did not raise the risk of major bleeding events but did increase the risk of minor bleeding events in patients undergoing uncomplicated knee arthroscopic surgery. When compared to non-LMWH prophylaxis, LMWH prophylaxis did not enhance the incidence of major and mild bleeding events in patients receiving ACLR (Supplementary Fig. 4). In general, the risk of mild bleeding did not endanger the patient's life in most cases.

5. Limitations

This meta-analysis does have certain limitations. First, the patients' clinical state and intrinsic risk factors were not taken into account, which could have influenced the study's results. Second, the types and doses of LMWH used in this trial, as well as the use of varied periods for patients, were not taken into account. The research findings could have been influenced by the physician's experiences. Third, the low frequency of VTE makes it hard to draw to reliably identify a signal amongst the noisy data. In our study, we defined major VTE as symptomatic VTE, symptomatic DVT, and symptomatic PE. However, different conclusions can be made based on what trials are included and how VTE is defined. Last but not least, the intervention in the control group varied between trials, potentially introducing bias.

6. Conclusions

When compared to a control group, this meta-analysis found that LMWH had little potential benefit in preventing major VTE after knee arthroscopy, including simple knee arthroscopy and ACLR. In comparison to the control group, studies showed that LMWH had no influence on the major bleeding rate after simple knee arthroscopy and ACLR. In patients undergoing simple knee arthroscopy, the potential side effects of LMWH, such as minor bleeding, should be evaluated. As a result, prophylaxis with LMWH should not be considered routinely in patients undergoing knee arthroscopic surgery. There is a need for more high-quality RCTs comparing LMWH with placebo therapy.

Additional information

No additional information is available for this paper.

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Author contribution statement

Chong Teng; Hui-Min Li: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Junwei Fu; Hui-Min Li: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Leyi Huang; Hui-Min Li: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Wei Wei; Zhicheng Tong: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Hui-Min Li: Conceived and designed the experiments; Wrote the paper

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e19696.

References

[1] Falckytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Supplementary material : prevention of VTE in orthopedic surgery patients : antithrombotic therapy and prevention of thrombosis, ninth ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.

[2] R.A. van Adrichem, R.G. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter, Risk of venous thrombosis after arthroscopy of the knee: results from a large population-based case-control study, J. Thromb. Haemostasis 13 (2015) 1441–1448, https://doi.org/10.1111/jth.12996.

[3] R.V. Adrichem, J. Debeij, R. Nelissen, I.B. Schipper, F.R. Rosendaal, S.C. Cannegieter, Below-knee cast immobilization and the risk of venous thrombosis: results from a large population-based case-control study, J. Thromb. Haemostasis 12 (2015) 1461–1469.

[4] I.A. Naess, S.C. Christiansen, P. Romundstad, S.C. Cannegieter, F.R. Rosendaal, J. Hammerstrm, Incidence and mortality of venous thrombosis: a population-based study, J. Thromb. Haemostasis 5 (2010) 692–699.

[5] A. Gomez-Outes, A.I. Terleira-Fernandez, M.L. Suarez-Gea, E. Vargas-Castrillon, Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons, BMJ Br. Med. J. (Clin. Res. Ed.) 344 (2012), e3675.

[6] L. Liu, W. Cheng, Z. Pei, Q. Gui, F. Zhao, X. Zhang, [Rivaroxaban versus low molecular weight heparin in prevention of venous thromboembulism in patients undergoing arthroscopy knee multiple ligament reconstruction], Clinical Medication Journal 14 (2016) 4.

[7] M. Michot, D. Conen, D. Holtz, D. Erni, M.D. Zumstein, G.B. Ruflin, N. Renner, Prevention of deep-vein thrombosis in ambulatory arthroscopic knee surgery: a randomized trial of prophylaxis with low–molecular weight heparin, Arthroscopy 18 (2002) 257–263, https://doi.org/10.1053/jars.2002.30013.

[8] T. Wirth, B. Schneider, F. Misselwitz, M. Lomb, H. Tüylü, R. Egbring, P. Griss, Prevention of venous thromboembolism after knee arthroscopy with low-molecular weight heparin (reviparin): results of a randomized controlled trial, Arthroscopy 17 (2001) 393–399, https://doi.org/10.1053/jars.2001.21247.

[9] P. Roth, Thromboembolieprophylaxe bei ambulant durchgeführten arthroskopischen Meniskusoperationen, Orthopadische Prax. 5 (1995) 345–348.

[10] R.A. van Adrichem, B. Nemeth, A. Algra, S. le Cessie, F.R. Rosendaal, I.B. Schipper, R. Nelissen, S.C. Cannegieter, Thromboprophylaxis after knee arthroscopy and lower-leg casting, N. Engl. J. Med. 376 (2017) 515–525, https://doi.org/10.1056/NEJMoa1613303.

[11] J. Ramos, C. Perrotta, G. Badariotti, G. Berenstein, Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy, Cochrane Database Syst. Rev. (2008), Cd005259, https://doi.org/10.1002/14651858.CD005259.pub3.

[12] Y. Sun, D. Chen, Z. Xu, D. Shi, J. Dai, J. Qin, J. Qin, Q. Jiang, Deep venous thrombosis after knee arthroscopy: a systematic review and meta-analysis, Arthroscopy 30 (2014) 406–412, https://doi.org/10.1016/j.arthro.2013.12.021.

[13] C. Chapelle, N. Rosencher, P. Jacques Zufferey, P. Mismetti, M. Cucherat, S. Laporte, Prevention of venous thromboembolic events with low-molecular-weight heparin in the non-major orthopaedic setting: meta-analysis of randomized controlled trials, Arthroscopy 30 (2014) 987–996, https://doi.org/10.1016/j.arthro.2014.03.009.

[14] H.F. Huang, J.L. Tian, X.T. Yang, L. Sun, R.Y. Hu, Z.H. Yan, S.S. Li, Q. Xie, X.B. Tian, Efficacy and safety of low-molecular-weight heparin after knee arthroscopy: a meta-analysis, PLoS One 13 (2018), e0197868, https://doi.org/10.1371/journal.pone.0197868.
[15] C. Perrotta, J. Chahla, G. Badariotti, J. Ramos, Interventions for preventing venous thromboembolism in adults undergoing knee arthroscopy, Cochrane Database Syst. Rev. 5 (2020), Cd005259, https://doi.org/10.1002/14651858.CD005259.pub4.
[16] J. Zhu, L. Li, H. Jiang, J. Li, X. Tang, Low-molecular-weight heparin for the prevention of venous thromboembolism in patients undergoing knee arthroscopic surgery and anterior cruciate ligament reconstruction: response, Am. J. Sports Med. 47 (2019) Np72, https://doi.org/10.1177/0363546519873668.
[17] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, Int. J. Surg. 88 (2021), 105906, https://doi.org/10.1016/j.ijsu.2021.105906.
[18] J.P.T. Higgins, S. Green, Cochrane Handbook for Systematic Reviews of Interventions, 2011 [updated March 2011], Version 5.1.0.
[19] S. Marlovits, G. Striessnig, R. Schuster, R. Stocker, M. Luxl, S. Trattnig, V. Vécsei, Extended-duration thromboprophylaxis with enoxaparin after arthroscopic surgery of the anterior cruciate ligament: a prospective, randomized, placebo-controlled study, Arthroscopy 23 (2007) 696–702, https://doi.org/10.1016/j.arthro.2007.02.001.
[20] Y. Liu, H.M. Li, R. Wang, Effectiveness and safety of adding bevacizumab to platinum-based chemotherapy as first-line treatment for advanced non-small-cell lung cancer: a meta-analysis, Front. Med. 8 (2021), 616380, https://doi.org/10.3389/fmed.2021.616380.
[21] H.M. Li, Y. Liu, R.J. Zhang, J.Y. Ding, C.L. Shen, Vitamin D receptor gene polymorphisms and osteoarthritis: a meta-analysis, Rheumatology 60 (2021) 538–548, https://doi.org/10.1093/rheumatology/keaa644.
[22] L.P. Zhou, R.J. Zhang, H.M. Li, C.L. Shen, Comparison of cranial facet joint violation rate and four other clinical indexes between robot-assisted and freehand pedicle screw placement in spine surgery: a meta-analysis, Spine 45 (2020) E1532–E1540, https://doi.org/10.1097/BRS.0000000000003632.
[23] H.M. Li, R.J. Zhang, C.L. Shen, Accuracy of pedicle screw placement and clinical outcomes of robot-assisted technique versus conventional freehand technique in spine surgery from nine randomized controlled trials: a meta-analysis, Spine 45 (2020) E111–E119, https://doi.org/10.1097/BRS.0000000000003193.
[24] H.M. Li, R.J. Zhang, C.L. Shen, Differences in radiographic and clinical outcomes of oblique lateral interbody fusion and lateral lumbar interbody fusion for degenerative lumbar disease: a meta-analysis, BMC Muscoskel. Disord. 20 (2019) 582, https://doi.org/10.1186/s12891-019-2972-7.
[25] H.M. Li, R.J. Zhang, C.L. Shen, Radiographic and clinical outcomes of oblique lateral interbody fusion versus minimally invasive transforaminal lumbar interbody fusion for degenerative lumbar disease, World neurosurgery 122 (2019) e627–e638, https://doi.org/10.1016/j.wneu.2018.10.115.
[26] H.M. Li, R.J. Zhang, H. Gao, C.Y. Jia, J.X. Zhang, F.L. Dong, C.L. Shen, New vertebral fractures after osteoporotic vertebral compression fracture between balloon kyphoplasty and nonsurgical treatment PRISMA, Medicine (Baltim.) 97 (2018), e12666, https://doi.org/10.1097/MD.0000000000012666.
[27] G. Canata, A. Chiey, Prevention of venous thromboembolism after ACL reconstruction: a prospective, randomized study, in: Presented at the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine, 2003.
[28] G. Camporese, E. Bernardi, F. Noventa, M. Bosco, G. Monteleone, L. Santoro, C. Bortoluzzi, S. Freguja, M. Nardin, M. Marullo, G. Zanon, C. Mazzola, G. Damiani, P. Maniscalco, D. Imberti, C. Lodigiani, C. Becattini, C. Tonello, G. Agnelli, Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study, Thromb. Haemostasis 116 (2016) 349–355, https://doi.org/10.1160/th16-02-0118.
[29] G. Camporese, E. Bernardi, P. Prandoni, F. Noventa, F. Verlato, P. Simioni, K. Ntita, G. Salmistraro, C. Frangos, F. Rossi, R. Cordova, F. Franz, P. Zucchetta, D. Kontothanassis, G.M. Andreozzi, Low-molecular-weight heparin versus compression stockings for thromboprophylaxis after knee arthroscopy: a randomized trial, Ann. Intern. Med. 149 (2008) 73–82, https://doi.org/10.7326/0003-4819-149-2-200807150-00003.
[30] N.C. Chan, A.C. Stehouwer, J. Hirsh, J.S. Ginsberg, A. Alazzoni, M. Coppens, G.H. Guyatt, J.W. Eikelboom, Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials, Thromb. Haemostasis 114 (2015) 1049–1057, https://doi.org/10.1160/th14-12-1006.
[31] J.A. Caprini, J.I. Arcelus, J.J. Reyna, Effective risk stratification of surgical and nonsurgical patients for venous thromboembolic disease, Semin. Hematol. 38 (2001) 12–19, https://doi.org/10.1016/s0037-1963(01)90094-0.