



# Prevention of venous thromboembolism with aspirin following knee surgery: A systematic review and meta-analysis

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- Venous thromboembolism (VTE) is a well-known complication following orthopaedic surgery. The incidence of this complication has decreased substantially since the introduction of routine thromboprophylaxis. However, concerns have been raised about increased bleeding complications caused by aggressive thromboprophylaxis.
- Attention has grown for aspirin as a safer thromboprophylactic agent following orthopaedic surgery.
- A systematic review using MEDLINE, Embase and Web of Science databases was undertaken to compare the effectiveness of aspirin prophylaxis following knee surgery with the current standard prophylactic agents (low molecular weight heparin [LMWH], vitamin K antagonists and factor Xa inhibitors).
- No significant difference in effectiveness of VTE prevention was found between aspirin, LMWH and warfarin. Factor Xa inhibitors were more effective, but increased bleeding complications were reported.
- As evidence is limited and of low quality with substantial heterogeneity, further research with high-quality, adequately powered trials is needed.

**Keywords:** aspirin; thromboprophylaxis; VTE

Cite this article: *EFORT Open Rev* 2021;6:892-904.

DOI: 10.1302/2058-5241.6.200120

## Introduction

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a well-known complication following orthopaedic surgery. In the absence of thromboprophylaxis, incidences

up to 40% have been reported after major orthopaedic procedures.<sup>1–4</sup> However, most of these events are asymptomatic.<sup>5,6</sup> With the administration of chemical thromboprophylaxis, the incidence decreases considerably to 1–10%.<sup>3,5,7</sup> For this reason, the use of thromboprophylaxis following major orthopaedic surgery is recommended by most guidelines and is widely accepted as the gold standard.<sup>8,9</sup> The 2012 American College of Chest Physicians (ACCP) guideline suggests that low molecular weight heparin (LMWH), fondaparinux, vitamin K antagonists, non-vitamin K antagonist oral anticoagulants (NOACs), low dose unfractionated heparin and aspirin are valid options for thromboprophylaxis, with a preference for LMWH.<sup>8</sup> The 2011 guideline by the American Academy of Orthopaedic Surgeons (AAOS) states that there is insufficient evidence to make recommendations for or against any specific prophylactic agent, and the more recent NICE guideline from 2018 recommends aspirin, LMWH or rivaroxaban.<sup>10,11</sup> As there is no consensus on the optimal mode of thromboprophylaxis, with conflicting recommendations in different guidelines, the choice is often left up to the surgeon's preference.<sup>12</sup>

The objective of thromboprophylaxis is to prevent VTE events with a minimal risk of complications caused by the prophylactic agent itself, especially when used in low-risk patients.<sup>1</sup> However, some concerns have been reported about possible drawbacks of the anticoagulants that are currently recommended for prophylaxis. A number of studies have reported increased haematoma formation and prolonged wound drainage, which could increase the risk of periprosthetic infection.<sup>12–16</sup> Additionally, higher incidences of major bleeding complications such as gastro-intestinal or cerebrovascular haemorrhage

have been reported.<sup>1,2,17–19</sup> With this in mind, the number of studies reporting on the prophylactic use of aspirin following orthopaedic surgery has increased since the recent endorsement of aspirin by the ACCP guideline.<sup>8</sup> Possible advantages are its low cost and convenient, oral administration without need for routine blood monitoring.<sup>2,20–22</sup> Several systematic reviews have attempted to summarize the evidence on aspirin thromboprophylaxis following lower limb orthopaedic surgery.<sup>1,23–27</sup> However, these reviews focus on the use of aspirin following lower limb surgery in general, including studies about knee and hip surgery. There are no recent systematic reviews available focusing entirely on knee surgery. In our opinion, a distinction should be made between patients who have undergone hip arthroplasty versus knee surgery, including arthroplasty and arthroscopy.

The objective of this review was to compare the effectiveness of aspirin with other recommended anticoagulants in the prevention of VTE events following knee surgery.

## Methods

This systematic review and meta-analysis was conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>28</sup>

### Outcome measures

The primary outcomes of interest in this review were venous thromboembolisms (VTE), defined as deep venous

thrombosis (DVT) and pulmonary embolism (PE). Bleeding events were a secondary outcome.

### Search strategy

Regular electronic searches of the databases MEDLINE, Embase and Web of Science were conducted from August 2019 to February 2020. The last search was performed on 18 February 2020. A combination of controlled vocabulary and free text search terms were used (Table 1). Duplicate articles were removed and the remaining articles were screened by title and abstract. Potentially relevant articles underwent full-text review. Any disagreements were discussed between reviewers. The reference lists of all relevant articles were manually reviewed to identify additional relevant reports.

### Inclusion and exclusion criteria

Studies were included if: (1) patients had undergone knee surgery, (2) PE or DVT outcomes were reported, (3) aspirin prophylaxis was compared to other prophylactic agents, no prophylaxis or if different dosages of aspirin were compared. Both observational studies and randomized controlled trials (RCTs) were included. Only articles published in the last 30 years were included in order to reflect the current practice. Only English-language articles were included.

Studies were excluded if: (1) aspirin was compared with multiple anticoagulants but results were not reported for each comparison separately, (2) < 2% of the study population received aspirin, (3) other anticoagulants were used

**Table 1.** Search strategies

No.	PubMed (279 hits)	Embase (534 hits)	Web of Science (326 hits)
1	Venous Thromboembolism [Mesh] OR Thromboembolism [Mesh] OR Venous thromboembolism [Title/Abstract] OR VTE [Title/Abstract] OR Thromboembolism [Title/Abstract] OR Thromboembol* [Title/Abstract]	venous thromboembolism/exp OR thromboembolism/exp OR venous thromboembolism:ab,ti OR vte:ab,ti OR thromboembolism:ab,ti OR thromboembol*:ab,ti	TS=Venous Thromboembolism OR TS=thromboembolism OR TS=VTE OR TS=thromboembol*
2	Pulmonary Embolism [Mesh] OR Embolism [Mesh] OR pulmonary embolism [Title/Abstract] OR PE [Title/Abstract] OR Pulmonary embol* [Title/Abstract] OR embol* [Title/Abstract]	lung embolism/exp OR embolism/exp OR pulmonary embolism:ab,ti OR pe:ab,ti OR pulmonary embol*:ab,ti OR embol*:ab,ti	TS=Pulmonary Embolism OR TS=embolism OR TS=PE OR TS=Embol*
3	Venous Thrombosis [Mesh] OR Thrombosis [Mesh] OR Deep vein thrombosis [Title/Abstract] OR DVT [Title/Abstract] OR Vein thrombosis [Title/Abstract] OR Venous thrombosis [Title/Abstract] OR Thrombosis [Title/Abstract] OR Thrombo* [Title/Abstract]	vein thrombosis/exp OR thrombosis/exp OR deep vein thrombosis:ab,ti OR dvt:ab,ti OR vein thrombosis:ab,ti OR venous thrombosis:ab,ti OR thrombosis:ab,ti OR thrombo*:ab,ti	TS=deep venous thrombosis OR TS=vein thrombosis OR TS=thrombosis
4	Aspirin [MeSH Terms] OR Aspirin [Title/Abstract] OR Acetylsalicylic acid [Title/Abstract]	acetylsalicylic acid/exp OR aspirin:ab,ti	TS=aspirin OR TS=acetylsalicylic acid
5	Postoperative Complications/prevention and control [Mesh] OR Thromboprophylaxis [Title/Abstract] OR thromboprophyla* [Title/Abstract] OR Prophyla* [Title/Abstract] OR Prevention [Title/Abstract] OR Prevent* [Title/Abstract]	postoperative thrombosis/exp OR thromboprophylaxis:ab,ti OR thromboprophyla*:ab,ti OR prophyla*:ab,ti OR prevention:ab,ti OR prevent:ab,ti	TS=Thromboprophylaxis OR TS=prophyla* OR TS=prevention
6	Knee Joint [Mesh] OR Knee [Mesh] OR knee [Text word] OR TKA [Text word]	knee/exp OR knee surgery/exp OR knee:ab,ti	TS=knee
7	1 OR 2 OR 3	review:it	1 OR 2 OR 3
8	7 AND 4 AND 5 AND 6	1 OR 2 OR 3	7 AND 4 AND 5 AND 6
9	No limits were used	8 AND 4 AND 5 AND 6 NOT 7	No limits were used

simultaneously with aspirin. Studies reporting on the sequential use of other prophylactic agents aside from aspirin during the same postoperative time period were not excluded. VTE outcomes in studies including mixed hip and knee populations were not reported separately per joint. Studies were not excluded based on number of patients, patient characteristics (age, body mass index [BMI], sex, ethnicity. . .) or duration of follow-up. Abstracts, supplements, conference proceedings, case reports, reviews etc. were excluded. Studies were excluded from the meta-analysis if the number of PE or DVT events was not reported and could not be calculated or if only compound VTE data were reported.

#### Data collection

Data were collected using a piloted data extraction form including the following parameters: author, publication year, study design, type of procedure, type of thromboprophylaxis, number of patients, number of events, duration and dosage of aspirin, duration of follow-up.

#### Quality appraisal

The quality of individual studies was scored by two authors independently using the Methodological Index for Non-Randomized Studies (MINORS) scoring system.<sup>29</sup> As only comparative studies were included, all studies were scored on 12 items with a maximum of 24 points. Three quality subgroups were created around the mean MINORS score. The quality of the body of evidence for the outcomes 'DVT' and 'PE' was determined using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system.<sup>30</sup>

#### Data analysis

Statistical analysis was performed for our primary outcomes PE and DVT. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Heterogeneity between studies was assessed using the  $I^2$  statistic.<sup>31</sup> A random-effects model was used for meta-analysis in order to account for heterogeneity of design and interventions among the included studies. A priori defined subgroup analysis was planned for RCT vs. observational study designs, procedure type, dosage and duration of prophylaxis, risk stratification and quality appraisal. PE and DVT outcomes were stratified per comparator drug. Subgroup analyses were not stratified by prophylactic agent and for studies with multiple comparisons, the 'comparator value' is a compound value of the different comparator drugs included in that study. Potential for publication bias was assessed through visual inspection of the funnel plots. All analyses were conducted using Review Manager 5.3 (The Cochrane Collaboration, Copenhagen, Denmark). Statistical significance was defined as  $p < 0.05$ .

## Results

#### Literature search

The details of the study identification and selection process are shown in Fig. 1. The electronic database search yielded 1139 articles. Following removal of duplicates and application of inclusion and exclusion criteria, 32 articles were included in this systematic review. Four studies were excluded from the meta-analysis for reasons stated above.<sup>16,17,32,33</sup>

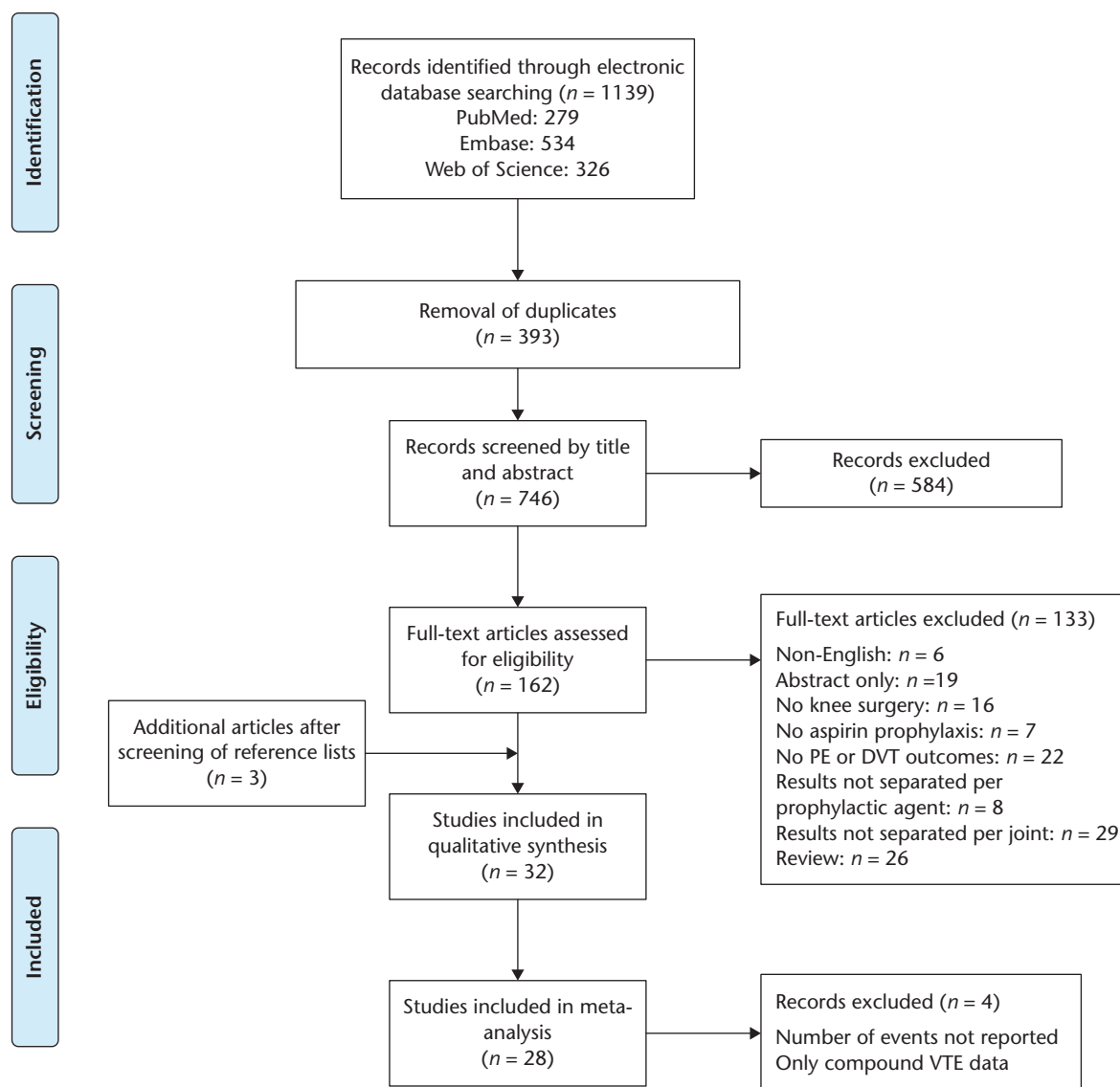
#### Study characteristics

The study characteristics of all individual studies are described in Table 2 and summarized in Table 3. Thirty-two articles were included in this systematic review (nine RCTs and 23 observational studies). Studies were published between 1996 and 2020. Meta-analysis of PE results included 23 studies<sup>3,6,19,20,22,34–49,50,52</sup> with 425,135 knee surgery patients (106,502 aspirin and 318,633 comparator) and meta-analysis of DVT included 24 studies<sup>3,6,19,20,22,34–38,43–56</sup> with 377,875 knee patients (90,637 aspirin and 287,238 comparator). Aspirin was compared to LMWH (11 studies),<sup>6,19,34,36,42,44,48,50,53,55,56</sup> factor Xa inhibitors (10 studies),<sup>35,36,38,41,45,48–51,56</sup> warfarin (10 studies)<sup>3,36,37,39,40,42,43,46,50,54</sup> and mechanical only prophylaxis (two studies).<sup>22,52</sup> Two studies compared the effectiveness of different dosages of aspirin.<sup>18,20</sup> Aspirin was studied as prophylaxis following TKA ( $n = 23$ ), unicompartmental knee arthroplasty (UKA,  $n = 2$ ), patellofemoral arthroplasty (PFA,  $n = 2$ ) and arthroscopy ( $n = 1$ ). The mean daily dosage of aspirin was 390 mg (range 81–650 mg). The mean duration of aspirin prophylaxis was 25 days (range 5–42 days). Seven studies used risk stratification for determining appropriate prophylaxis.<sup>3,37,39,43,44,46,53</sup> The criteria that were used to assign patients to a high-risk strategy in these articles are summarized in Table 4.

#### Primary outcomes

##### DVT and PE

Pooled data from 23 studies showed no difference in PE rate between LMWH and warfarin compared to aspirin (Fig. 2). There was a significantly lower incidence of PE with factor Xa inhibitors compared to aspirin (OR 2.05; 95% CI 1.45–2.88;  $P < 0.0001$ ). A similar trend was noted for the DVT outcome, with lower DVT rates using factor Xa inhibitors compared to aspirin; however, this result was not significant (OR 1.39; 95% CI 0.98–1.98;  $P = 0.06$ ). Pooled data of 24 studies showed no significant difference in DVT rates between LMWH, factor Xa inhibitors and warfarin compared to aspirin (Fig. 3). Low dose aspirin was not inferior to high dose aspirin in preventing PE and DVT (PE: OR 1.32; 95% CI 0.28–6.30;  $P = 0.73$  and DVT: OR 0.22; 95% CI 0.08–0.58;  $P = 0.002$ ). Meta-analysis could



**Fig. 1** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Note. PE, pulmonary embolism; DVT, deep venous thrombosis; VTE, venous thromboembolism.

not be performed for aspirin vs. mechanical only prophylaxis due to limited number of studies and events. However, one study showed significantly lower DVT and PE rates with aspirin compared to mechanical only prophylaxis.<sup>21</sup> Significant heterogeneity was present within the warfarin group for PE and DVT comparisons (PE:  $I^2 = 91\%$  with  $P < 0.001$  and DVT:  $I^2 = 69\%$  with  $P = 0.006$ ) and LMWH group for the DVT comparison ( $I^2 = 90\%$  with  $P < 0.001$ ).

#### Subgroup analysis

The heterogeneity within the warfarin and LMWH groups could not be explained by any of the subgroup analyses.

Subgroup analysis of RCTs showed significantly higher DVT rates and a trend for higher PE rates with aspirin compared to other anticoagulants (DVT: OR 1.51; 95% CI 1.04–2.18;  $P = 0.03$ ) (Fig. 4 and Fig. 5). Furthermore, aspirin was less effective than comparators in the prevention of DVT when used for  $< 2$  weeks (OR 2.04; 95% CI 1.15–3.62;  $P = 0.02$ ). The same trend was noted for prevention of PE. There was no significant difference between subgroups based on use of risk stratification, dosage of aspirin or quality appraisal of the studies. In the subgroup analysis based on procedure type, the number of studies on UKA, PFA and arthroscopy were too limited to generate valid conclusions.

**Table 2.** Study characteristics

Study	Study design	TKA patients (n)	Comparators	Procedure	Daily dosage aspirin (mg)	Duration aspirin prophylaxis	Risk stratification used? (Y/N)	Duration of follow-up (months)	MINORS score
Lotke 1996 <sup>54</sup>	RCT	179	Warfarin	TKA	650		N	6	20
Westrich 2006 <sup>55</sup>	RCT	275	LMWH	TKA	650	4 w	N	1.5	17
Lombardi 2007 <sup>44</sup>	R	423	LMWH, warfarin	UKA		6 w	Y	3	12
Callaghan 2008 <sup>37</sup>	R	423	Warfarin	TKA	650		Y	3	15
Cusick 2009 <sup>33</sup>	R	2050	Warfarin	TKA	150	6 w	N	3	15
Bozic 2010 <sup>17</sup>	R	93,840	LMWH, factor Xa, warfarin	TKA			N	1	14
Khatod 2012 <sup>42</sup>	R	30,020	LMWH, warfarin	TKA			N	3	18
Jameson 2012 <sup>6</sup>	R	156,798	LMWH	TKA, UKA, PFA			N	3	18
Levack 2012 <sup>43</sup>	R	131	Warfarin	PFA	325	2 w	Y	1.5	14
IJRCWC 2012 <sup>3</sup>	P	431	Warfarin	TKA	650	4 w	Y	3	21
Kulshrestha 2013 <sup>33</sup>	RCT	673	LMWH	TKA	650	4 w	Y	12	24
Gesell 2013 <sup>39</sup>	R	2017	Warfarin	TKA	650	6 w	Y	3	16
Jiang 2014 <sup>41</sup>	RCT	120	Factor Xa	TKA	100	2 w	N	1.5	18
Zou 2014 <sup>56</sup>	RCT	324	LMWH, factor Xa	TKA	100	14 d	N	1	19
Nam 2015 <sup>46</sup>	R	96	Warfarin	TKA	650	6 w	Y	3	15
Kaye 2015 <sup>52</sup>	RCT	170	Mechanical only	Arthroscopy	325	14 d	N	1	18
Radzak 2016 <sup>19</sup>	R	377	LMWH	TKA	650	4 w	N		11
Nielen 2016 <sup>32</sup>	R	3191	LMWH, factor Xa	TKA			N	>12	14
Bala 2017 <sup>50</sup>	R	18,288	LMWH, factor Xa, warfarin	TKA			N	3	14
Yhim 2017 <sup>48</sup>	R	261,260	LMWH, factor Xa	TKA			N	3	14
Cafri 2017 <sup>36</sup>	R	30,499	LMWH, Factor Xa, warfarin	TKA	325		N	3	16
Chung 2017 <sup>38</sup>	RCT	268	Factor Xa	TKA	100	5 d	N	3	22
Parvizi 2017 <sup>47</sup>	P	2356	Low-high dose	TKA	160/650	4 w	N	3	20
Anderson 2018 <sup>35</sup>	RCT	1620	Factor Xa	TKA	81	9 d	N	3	24
Colleoni 2017 <sup>51</sup>	RCT	32	Factor Xa	TKA	300	2 w	N	1	13
Goel 2018 <sup>40</sup>	R	18,951	Warfarin	TKA	162/650	4 w	N	3	14
Faour 2018 <sup>20</sup>	R	5666	Low-high dose	TKA	81/325	4 w	N	3	17
Hood 2019 <sup>22</sup>	R	41,537	Mechanical	TKA			N	3	17
Alamiri 2018 <sup>34</sup>	P	80	LMWH	TKA	325		N	1	17
Tan 2019 <sup>16</sup>	R	32,752	LMWH, warfarin	TKA	162/650	4 w	N	3	17
McHale 2019 <sup>45</sup>	R	218	Factor Xa	TKA	150	6 w	N	3	17
Yuenyongviwat 2019 <sup>49</sup>	R	155	Factor Xa	TKA	300	14 d	N	1.5	16

Note. R, retrospective study; P, prospective study; RCT, randomized controlled trial; TKA, total knee arthroplasty; LMWH, low molecular weight heparin; UKA, unicompartmental knee arthroplasty; PFA, patellofemoral arthroplasty; MINORS, Methodological Index for Non-Randomized Studies.

### Secondary outcome: bleeding events

Twenty-two studies included in this review reported on bleeding outcomes using aspirin thromboprophylaxis. However, the outcome measurements of these bleeding events were inconsistent between studies. Bleeding has been reported as incidence of major bleeding events (gastro-intestinal [GI] and cerebrovascular), decrease in haematocrit and haemoglobin levels, need for transfusion, wound drain output volume and prolonged drainage. Most studies found no significant difference in bleeding events between aspirin and comparators. Three studies reported increased bleeding events with LMWH compared to aspirin<sup>19,32,34</sup> and three studies reported increased blood loss or higher transfusion rates with factor Xa inhibitors.<sup>41,48,56</sup>

### Publication bias

Visual inspection of the funnel plot of studies on PE suggested some degree of publication bias in which small studies were more likely to be published when a positive

intervention effect was found. However, exclusion of these small studies in a sensitivity analysis resulted in little change to the overall results (Fig. 6).

### Quality appraisal

The mean MINORS score was 17 (range 11–24). Three groups were created around the mean quality score, with low quality defined as a score < 15 (seven studies), moderate quality as a score 15–19 (15 studies) and high quality as scores ≥ 20 (six studies).

## Discussion

This is the first systematic review and meta-analysis focusing on thromboprophylaxis after knee surgery. Previous studies have pooled patients following hip and knee surgery to evaluate the effectiveness of different thromboprophylactic agents and adverse events. In our opinion, a distinction should be made between both hip and knee patients as rehabilitation programmes after knee surgery

**Table 3. Summary characteristics**

Characteristic	DVT	PE
No. of studies	24	23
Study design		
RCT	8	4
Observational	16	19
Procedure		
TKA	23	
UKA	2	
PFA	2	
Arthroscopy	1	
No. of participants	377,875	425,135
Aspirin	90,637	106,502
Comparator		
LMWH	196,423	206,132
Factor Xa inhibitors	74,518	74,494
Warfarin	15,525	37,235
Mechanical only	772	772
Event rates, %		
Aspirin	0.8%	0.6%
Comparator		
LMWH	1%	0.6%
Factor Xa inhibitors	0.7%	0.4%
Warfarin	2.4%	1.2%
Mechanical only	2.2%	1.8%
Daily dosage aspirin, mean (range)	390 mg (81–650 mg)	
Duration aspirin, mean (range)	26 d (5–42 d)	
Duration follow-up, mean (range)	3 m (1–12 m)	
No. Studies using risk stratification	7 studies	

Notes. No., number of; RCT, randomized controlled trial; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; PFA, patellofemoral arthroplasty; DVT, deep venous thrombosis; PE, pulmonary embolism; LMWH, low molecular weight heparin.

**Table 4. Criteria used for allocation to high-risk cohorts**

High-risk criteria
Hypercoagulable disorders
History of VTE or stroke
Active cancer
Multiple comorbidities (heart, lung, diabetes)
Heart disease: congestive heart failure (CHF), atrial fibrillation
Delayed mobilization
Age > 70 years
Obesity (BMI > 40)

Note. VTE, venous thromboembolism; BMI, body mass index.

might impose prolonged periods of immobilization, limited ambulation and weight bearing restrictions.

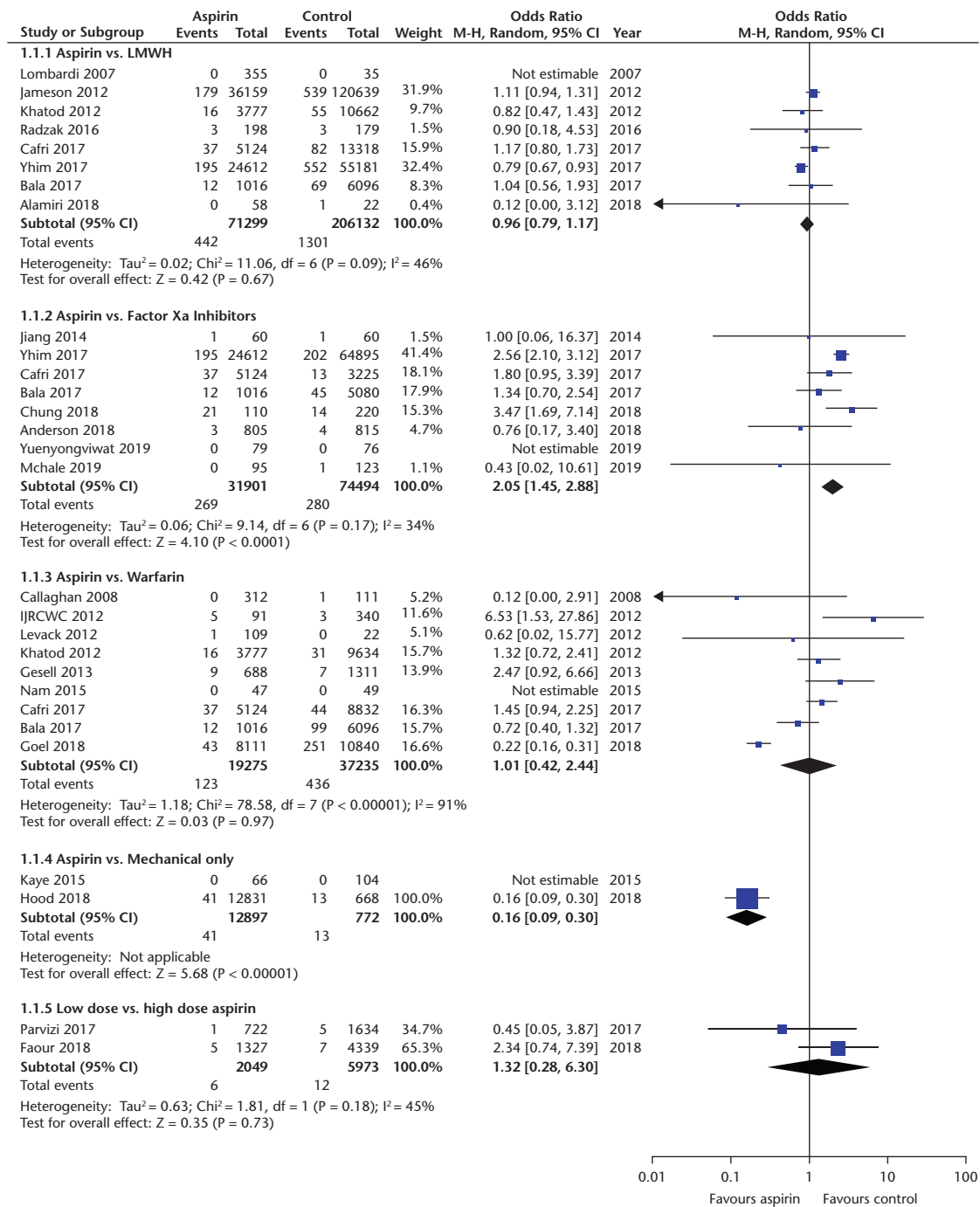
This study found that there was no statistically significant difference in the effectiveness of aspirin compared with LMWH and warfarin for prevention of VTE, including PE and DVT, following knee surgery. However, factor Xa inhibitors (rivaroxaban and fondaparinux) were found to be more effective than aspirin in preventing PE. Regarding adverse effects, only a few studies reported a significant difference in bleeding events, with three studies finding a higher bleeding risk with LMWH compared to aspirin and three studies reporting increased bleeding with factor Xa inhibitors. The number of studies focusing on knee surgery (UKA, PFA and arthroscopic procedures) was too limited to generate valid conclusions. Based on

this meta-analysis, aspirin appeared to be less effective when used for a duration shorter than two weeks. Furthermore, there was insufficient evidence for a significant difference in effectiveness between high or low dosages of aspirin. Subgroup analysis showed no advantage of risk stratification.

A high level of heterogeneity was present between the studies included. There was a considerable variability in the patients included in studies (age, sex, comorbidities. . .), dosages and duration of aspirin and comparators. Furthermore, there was a high level of inconsistency in the outcome measurements used in these studies. All studies assessed DVT, PE or combined VTE events as outcomes, which are objectifiable endpoints. However, some studies systematically screened all patients with radiographic examination or ultrasound on a set date, whereas other studies performed imaging based on clinical suspicion. This caused large discrepancies in reported VTE incidences between studies screening for asymptomatic or symptomatic DVTs. This heterogeneity was most notable for the DVT outcome, as radiographic examination for PE was almost always performed based on clinical suspicion. The clinical importance of asymptomatic DVT is still unclear, and both the ACCP and AAOS guidelines recommend against systematic screening.<sup>1,8,10</sup>

Our findings of a similar effectiveness of aspirin, LMWH and warfarin in VTE prevention are consistent with the conclusions of previous systematic reviews including both hip and knee surgery populations.<sup>1,23–27</sup> Increased bleeding with factor Xa inhibitors compared to aspirin and LMWH was also reported by Lindquist et al, and a meta-analysis by Venker et al reported a significantly higher risk of major bleeding events with factor Xa inhibitors compared to LMWH.<sup>57,58</sup> However, this is the first systematic review in which factor Xa inhibitors were found to be more effective than aspirin. This finding is also in contrast with a recent high-quality study by Anderson et al, in which no significant difference in VTE events between aspirin and rivaroxaban was found.<sup>35</sup> A possible explanation could be that this review included both RCTs and observational studies, while other reviews only included RCTs. This increased the number of patients in this study and power to detect differences substantially, especially since the incidence of VTE events is low. The number of adequately powered, high-quality RCTs on this topic is limited. Two large trials are currently being conducted: the CRISTAL trial, comparing VTE between aspirin and LMWH following hip and knee arthroplasty, and the PEPPER trial, comparing warfarin, rivaroxaban and aspirin following hip and knee arthroplasty.<sup>59,60</sup> Both studies aim to enrol > 15,000 patients and will be the largest prospective trials on aspirin prophylaxis including knee surgery patients.

Our subgroup analysis showed no advantage of risk stratification. However, due to uneven covariate distribution

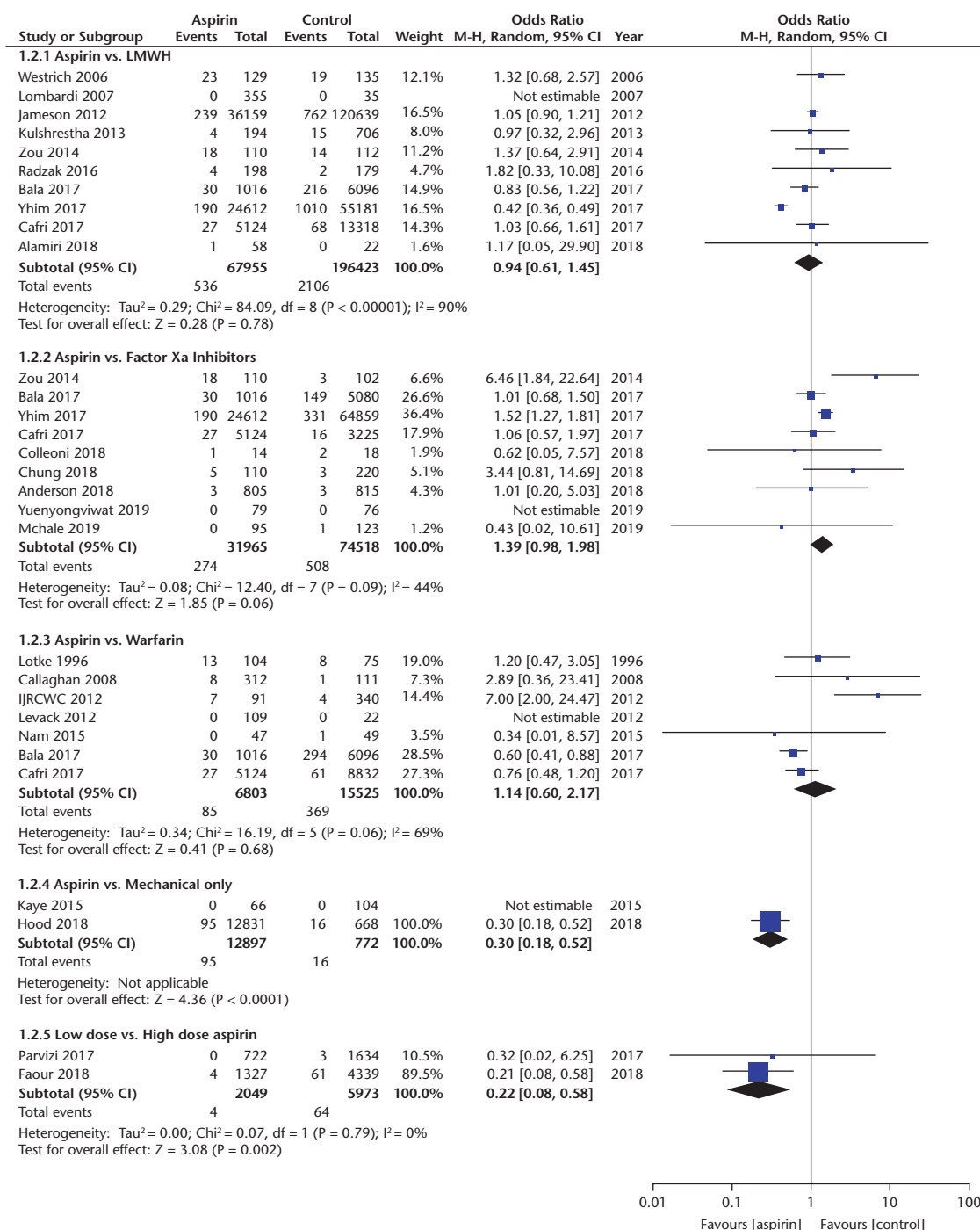


**Fig. 2 Forest plot of pooled PE rates of aspirin vs. comparators.**

Note. PE, pulmonary embolism; LMWH, low molecular weight heparin.

between subgroups and moderate heterogeneity within subgroups, these findings should be interpreted with caution.<sup>61</sup> Risk stratification for determining thromboprophylaxis has been recommended by guidelines.<sup>8,62</sup> Several studies have attempted to identify risk factors for VTE in orthopaedic surgery.<sup>15,63–67</sup> However, no risk stratification

protocol specifically for orthopaedic surgery has been validated yet.<sup>62,63,68,69</sup> The Caprini score, which has already been validated in other surgical disciplines, has been used in arthroplasty patients in multiple studies.<sup>70,71</sup> Bateman et al found no significant difference in scores between patients with and without VTE, and concluded that the Caprini



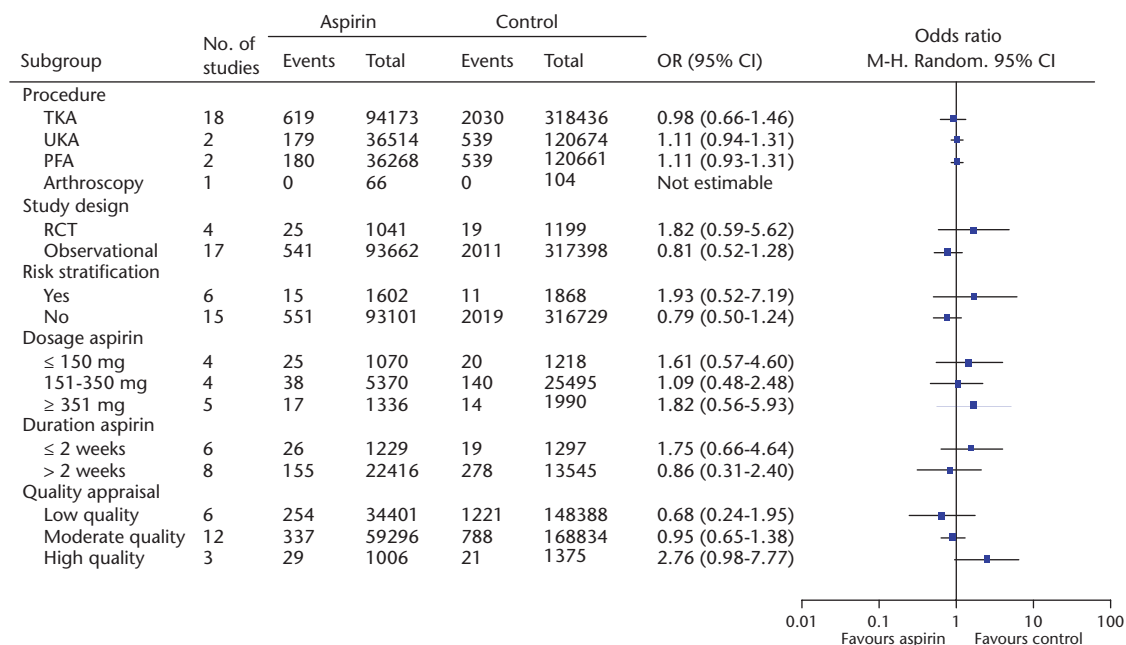
**Fig. 3 Forest plot of pooled DVT rates of aspirin vs. comparators.**

Note. DVT, deep venous thrombosis; LMWH, low molecular weight heparin.

score is not clinically useful in arthroplasty patients.<sup>72</sup> Tafur et al and Krauss et al found that the score was accurate in predicting VTE events following arthroplasty.<sup>73,74</sup> Most of the studies included in this review used own risk stratification models.<sup>3,37,40,53,69,75</sup> Risk factors that were used in most stratification strategies were active cancer, hypercoagulable

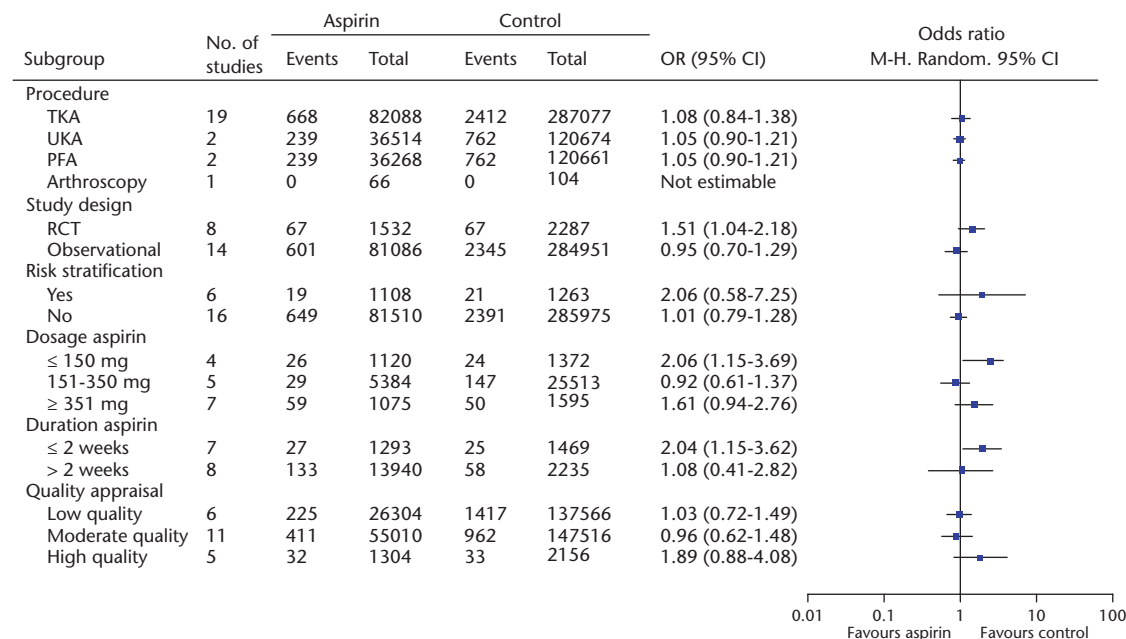
state, history of VTE or stroke, heart disease (such as congestive heart failure [CHF], atrial fibrillation), other important comorbidities (such as pulmonary disease or diabetes), obesity and age > 70 years.<sup>3,37,40,53,69,71,75</sup>

Another finding based on subgroup analysis was that aspirin is less effective when used for less than



**Fig. 4** Pooled results subgroup analyses PE.

Note. PE, pulmonary embolism; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; PFA, patellofemoral arthroplasty; RCT, randomized controlled trial.

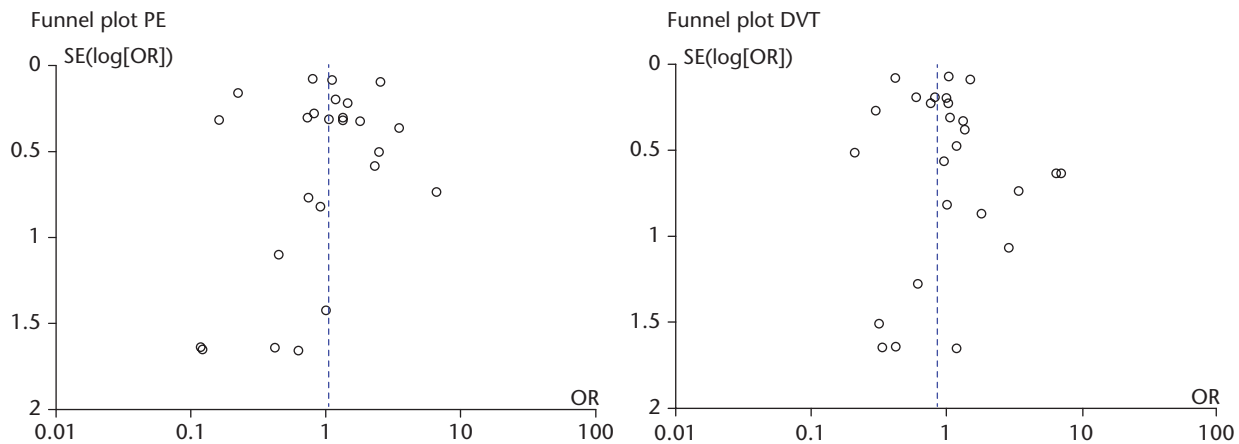


**Fig. 5** Pooled results subgroup analyses DVT.

Note. DVT, deep venous thrombosis; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty; PFA, patellofemoral arthroplasty; RCT, randomized controlled trial.

two weeks. The duration of aspirin prophylaxis in the studies included in this review ranged from five days to six weeks. The ideal duration of prophylaxis following knee surgery is still unclear.<sup>5</sup> In a recent study by Mula et al, the mean time to presentation of symptomatic PE

following TKA was nine days.<sup>76</sup> Given the low cost of aspirin, further research should compare the effectiveness of different durations of prophylaxis and determine the cost effectiveness of extending prophylaxis up to six weeks.



**Fig. 6** Funnel plots PE and DVT.

Note. PE, pulmonary embolism; DVT, deep venous thrombosis.

Furthermore, there was insufficient evidence for a difference in effectiveness of a low vs. high dosage of aspirin. This is accordance with a review by Azboy et al, in which low dose aspirin was found to be non-inferior to high dose aspirin for VTE prevention following total joint arthroplasty.<sup>77</sup>

The findings of this review must be interpreted in light of some limitations. First, as this is a pooled analysis of the existing literature, our study is inherently limited by the quality of the included studies. As most of the included studies are level 3 studies with a few level 2 studies, the quality of evidence of this review is moderate to low according to the GRADE scale.<sup>30</sup>

Second, we chose to include observational studies in this review in order to give a more complete summary of the current literature and to increase power of this study. This could have caused part of the heterogeneity between studies (for PE,  $I^2 = 45\%$ ,  $P = 0.16$  in RCTs and  $I^2 = 91\%$ ,  $P < 0.00001$  in observational studies; for DVT,  $I^2 = 0\%$ ,  $P = 0.64$  in RCTs and  $I^2 = 74\%$ ,  $P < 0.0001$  in observational studies). However, a significant level of heterogeneity was also noted in systematic reviews that included only RCTs.<sup>1,25,27</sup> In addition, with the inclusion of observational studies comes an inherent risk of selection bias. As some of the observational studies state that prophylaxis was selected based on the surgeon's preference, aspirin (which is perceived as a less potent prophylactic agent) could have been administered to patients who were perceived to be at a lower VTE risk.

Current evidence suggests that there is no statistically significant difference between the effectiveness of aspirin and LMWH or warfarin for the prevention of venous thromboembolism following knee surgery. However, the quality of the body of evidence in this review was moderate to low and there was substantial heterogeneity between

studies. Future research should ideally include large, adequately powered RCTs focusing on knee surgery. Efforts should be made to elucidate the most effective and safe dosing schedule for aspirin thromboprophylaxis and to validate risk stratification protocols for implementing thromboprophylaxis.

## Conclusion

Aspirin thromboprophylaxis following knee surgery seems promising because of the low cost and convenient administration without the need for routine blood monitoring. Evidence suggests a similar effectiveness of aspirin, LMWH and warfarin in preventing VTE. Factor Xa inhibitors may be more effective than aspirin in VTE prevention, but could increase bleeding following surgery. Current evidence is incomplete and further research is needed to strengthen recommendations.

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### ICMJE CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest relevant to this work.

### FUNDING STATEMENT

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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