Effectiveness of Thromboprophylaxis Agents Following Hip Fracture

A Systematic Review and Network Meta-Analysis

Ahmed M. Negm, MD, PhD, Lisa Yamaura, MKin, Ashley Clarke, MSc, Daniyya Chaudhry, BSc,
Tanya Cherppukaran, BSc, and Prism Schneider, MD, PhD, FRCSC

Investigation performed at the Department of Surgery, University of Calgary, Calgary, Alberta, Canada

Background: Multiple studies have compared different pharmacologic thromboprophylaxis agents after hip fracture surgery, including aspirin, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct oral antico-agulants (DOAC), and warfarin, resulting in variability in clinical practice. To guide clinical management, a systematic review and network meta-analysis (NMA), which enables the simultaneous assessment of the effects of multiple interventions for the same patient population, was performed. This study aimed to determine the comparative effectiveness of thromboprophylaxis in reducing venous thromboembolism (VTE) in patients with surgically treated hip fractures.

Methods: The primary outcome was the effect of the treatment on the VTE rate, and the secondary outcome was the treatment effect on the bleeding rate. Relevant studies were identified by a systematic search of Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) from January 2000 to February 2022. Title, abstract, and full-text screening; data extraction; and risk-of-bias assessment were performed. All studies examining thromboprophylaxis interventions (DOAC, LMWH, UFH, aspirin, and warfarin) in patients with a surgically treated hip fracture were included. Bayesian NMA was performed, and dichotomous outcome data were pooled using the odds ratio. Interventions were ranked using the surface under the cumulative ranking curve (SUCRA) for each outcome.

Results: A total of 19 studies were included after the screening of 466 citations and 77 full-text articles. Of the included studies, 15 studies had a high overall risk of bias. The NMA of the VTE outcome included 19 studies, 49,409 participants, and 6 thromboprophylaxis interventions. The NMA of the bleeding outcome included 3 studies, 18,163 participants, and 3 interventions. The mean age ranged from 43.5 to 86.2 years among the included studies. No thromboprophylaxis intervention was statistically different from any other intervention in its effect on the VTE or bleeding rate in hip fracture patients.

Conclusions: This NMA demonstrated that there was no difference between the thromboprophylaxis interventions in reducing VTE or bleeding rates in hip fracture patients. More robust randomized controlled trials are needed to determine the most effective thromboprophylaxis interventions for patients with hip fractures.

Level of Evidence: Therapeutic Level II. See Instructions for Authors for a complete description of levels of evidence.

More than 14.2 million hip fractures per year occur globally, and the incidence is projected to increase with our aging population[1]. Hip fractures place a considerable burden on society in terms of morbidity and mortality, with mortality rates up to 20% to 24% in the first year after a hip fracture[2].

Although hip fracture surgery is highly effective in improving functional status, it is associated with a substantial risk of developing a deep vein thrombosis (DVT) or pulmonary embolism (PE)[3]. Collectively referred to as venous thromboembolism (VTE), thromboses (blood clots) in the venous system are associated with substantial morbidity and mortality for patients, as well as substantial costs to the health-care system[3]. The incidence of DVT in patients after hip fracture surgery without thromboprophylaxis is as high as 50%[4]. Furthermore, a fatal PE is more likely to
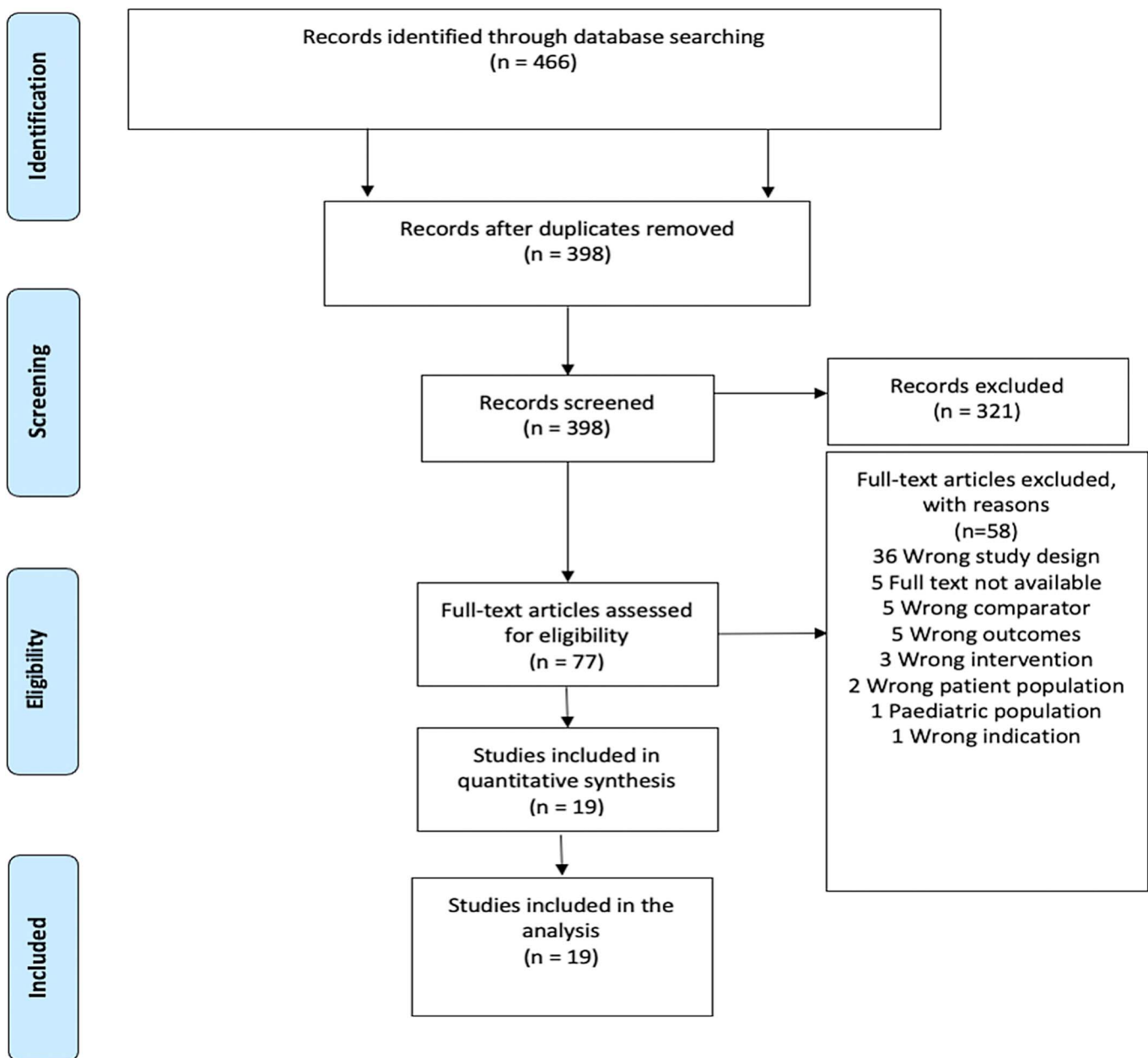
Fig. 1
Study flow diagram.

occur after hip fracture surgery than after elective hip surgery, which may be due to inherent physiological factors related to the patient population, the fracture, the required surgery, or a combination[4]. Despite this high morbidity, mortality, and cost, there is no consensus regarding the best pharmacologic thromboprophylaxis strategy after hip fracture surgery for VTE prevention.

Several pharmacologic thromboprophylaxis options (including aspirin, unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], direct oral anticoagulants [DOAC], and warfarin) have been recommended in national guidelines, resulting in substantial clinical practice variation that is often based on clinician bias and preference[5,6]. Multiple studies have compared pharmacologic thromboprophylaxis agents after hip fracture surgery.

For example, Drescher et al. performed a meta-analysis (8 studies and a total of 1,408 participants) comparing VTE and bleeding rates in patients receiving aspirin versus anticoagulants (UFH, LMWH, warfarin) after major lower-extremity orthopaedic surgery. They reported that aspirin might be associated with a higher risk of proximal DVT following hip fracture repair, although bleeding rates were substantially lower with aspirin[7]. Similarly, a recent randomized controlled trial

TABLE I Summary of Study Characteristics (N = 19)	
Characteristic	No. (%) of Studies
Study design	
RCT	9 (47.4%)
Observational	10 (52.6%)
Continent	
Europe	1 (5.3%)
North America	8 (42.1%)
Asia	6 (31.6%)
Australia/New Zealand	1 (5.3%)
Africa	0 (0%)
Multi-continent	3 (15.8%)
Site	
Multicenter	7 (36.8%)
Single center	12 (63.2%)
No. of participants	
<200	2 (10.5%)
200-500	11 (57.9%)
>500	6 (31.6%)
Funding source	
Government	3 (15.8%)
Private sector	2 (10.5%)
Not funded	4 (21.1%)
Not reported	10 (52.6%)

(RCT) conducted by Haac et al. compared the effectiveness of aspirin with LMWH with respect to VTE event rates in patients with an operatively treated extremity fracture or with a pelvic or acetabular fracture that was treated operatively or non-operatively. That trial found no evidence of superiority of either LMWH or aspirin for VTE prevention in patients with a fracture[8]. Similarly, a recent retrospective study compared DOAC (including dabigatran, apixaban, betrixaban, edoxaban, and rivaroxaban) and LMWH for thromboprophylaxis in 167,640 patients with lower-extremity fractures found no significant difference in VTE rates with either DOAC or LMWH[9].

The inconsistent results of these thromboprophylaxis interventions may be due, in part, to significant variations in study designs, patient populations, and intervention strategies (e.g., thromboprophylaxis duration) employed in the studies[10,11]. Large prospective clinical trials directly comparing different thromboprophylaxis regimens are lacking, and there is limited evidence to establish recommendations for optimal thromboprophylaxis for patients with hip fractures.

Conventional meta-analysis does not allow direct comparisons between >2 interventions unless head-to-head trials comparing each pair of interventions have been performed. Given the number of thromboprophylaxis agents of interest, as well as the variation in study designs and comparison groups, the use of network meta-analysis (NMA) methodology is necessary to permit synthesis of indirect as well as direct evidence, and thus allow for the comparison of treatments that have not yet been compared head-to-head in RCTs[12,13]. Such an NMA can effectively rank all existing interventions for VTE prevention and offer recommendations for optimal thromboprophylaxis strategies. Given the global burden of VTE after hip fractures and other lower-extremity fractures, an NMA is warranted to investigate the comparative effectiveness of thromboprophylaxis agents for hip fracture patients. The aim of the present systematic review and NMA of studies comparing different thromboprophylaxis interventions was thus to determine their comparative effectiveness in improving various outcomes in patients with hip fracture (see Appendix eTable 1, PICOT [patient, intervention, comparison, outcome, time] criteria).

Materials and Methods

Reporting of the methods and results of this systematic review and NMA was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions[14]. The protocol of the review was registered a priori at the Center for Open Science (osf.io/9xyg8).

Search Strategy
A search of the literature from January 2000 to February 2022 was performed to identify relevant studies. The search was conducted using Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials (CENTRAL) (see the eSearch Strategies in the Appendix).

Eligibility Criteria
All RCTs and retrospective and prospective studies comparing 1 or more thromboprophylaxis interventions (aspirin, UFH, LMWH, DOAC, warfarin) for postoperative VTE prevention in patients with traumatic hip fractures were included. Comparators were standard care, placebo, or another intervention. Studies including both hip and other fractures were included, given the relative novelty of DOAC and the scarcity of literature on this topic. Studies were excluded if the incidence of VTE was not reported.

Outcomes
The primary outcome was VTE, both symptomatic and asymptomatic. Secondary outcomes were bleeding events, including major bleeding, clinically relevant non-major bleeding, and minor bleeding[15,16].

Study Selection
The titles and abstracts of the identified articles were screened by 2 independent reviewers who were not blinded with respect to the authors, their country, and the journal. The full text of the potentially eligible studies was then assessed for eligibility by 2 independent reviewers. Any disagreement was resolved through consensus or by the senior reviewer.
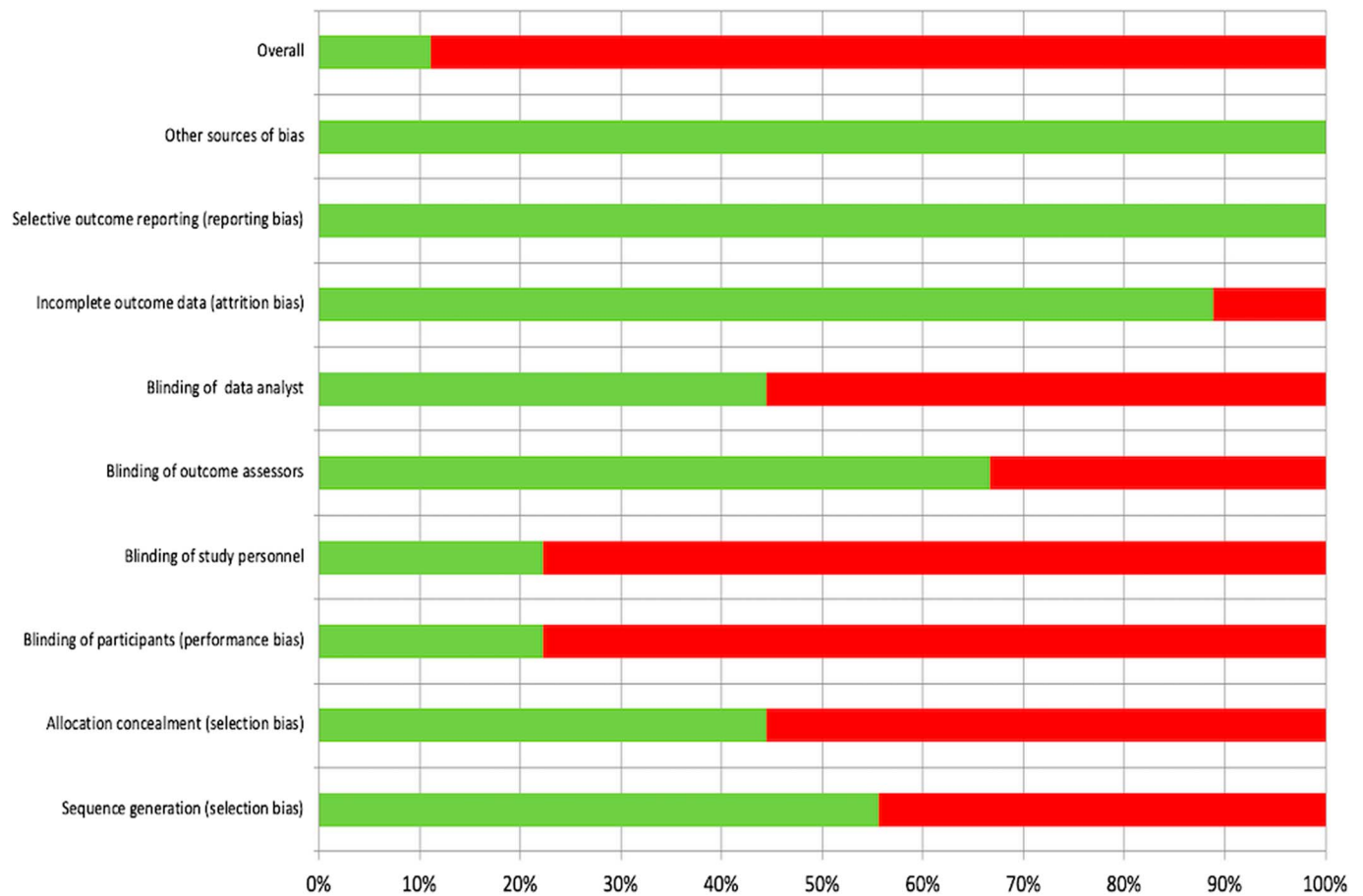
Fig. 2
Risk-of-bias assessment for the included RCTs.

Data Extraction

A previously developed and pilot-tested data extraction form was used for this review to ensure consistency of extraction[12]. Data were extracted by a reviewer and verified by the senior reviewer.

Risk-of-Bias Assessment

The risk of bias in each included RCT was assessed using the modified version of the Cochrane tool for assessing the risk of bias in RCTs[17]. The risk of bias in each observational study was assessed using the Clarity Group Risk of Bias Tool[18]. The overall risk of bias in a study was considered to be high if ≥1 of the domains was determined to have a high risk of bias. The risk-of-bias assessment was conducted by 2 independent reviewers. Any disagreements were resolved by consensus, or with assistance from the senior reviewer if necessary.

Data Synthesis and Statistical Analysis

Standard pairwise meta-analysis was initially performed using a frequentist random-effects model[19]. A model with random effects was selected because we expected that studies would differ both methodologically and clinically (between-study variability). The heterogeneity (between-study variability) of the treatment effects within each treatment comparison was

assessed by the I^2 statistic[20] and its 95% confidence interval. The magnitude of the between-study variance (τ^2) was estimated using the restricted maximum likelihood estimator and the Q-profile approach[21,22].

A Bayesian random-effects NMA was conducted for each outcome using Markov-chain Monte Carlo (MCMC) simulation. We assumed a common between-study variance (τ^2) across treatment comparisons within each network (VTE and bleeding rate), as clinically important differences in the magnitude of heterogeneity across treatment comparisons were not expected and as there were many treatment comparisons informed by a single study, so that τ^2 was not estimable.

For each NMA, we assessed the transitivity and consistency assumptions a priori[23-26]. Across all Bayesian NMA models, we assumed vague priors for all model parameters and a half-normal prior distribution for the between-study standard deviation ($\tau \sim N\ [0,1],\ \tau > 0$)[27,28]. A study with a markedly different intervention effect estimate compared with the remaining outcome data was defined as outlying[29]. We monitored comparison-adjusted funnel plots for extreme study effects (outlying studies). When obvious outliers were detected (effect size greater than log odds ratio of 2), these were excluded in a sensitivity analysis to assess the robustness of the results. Network
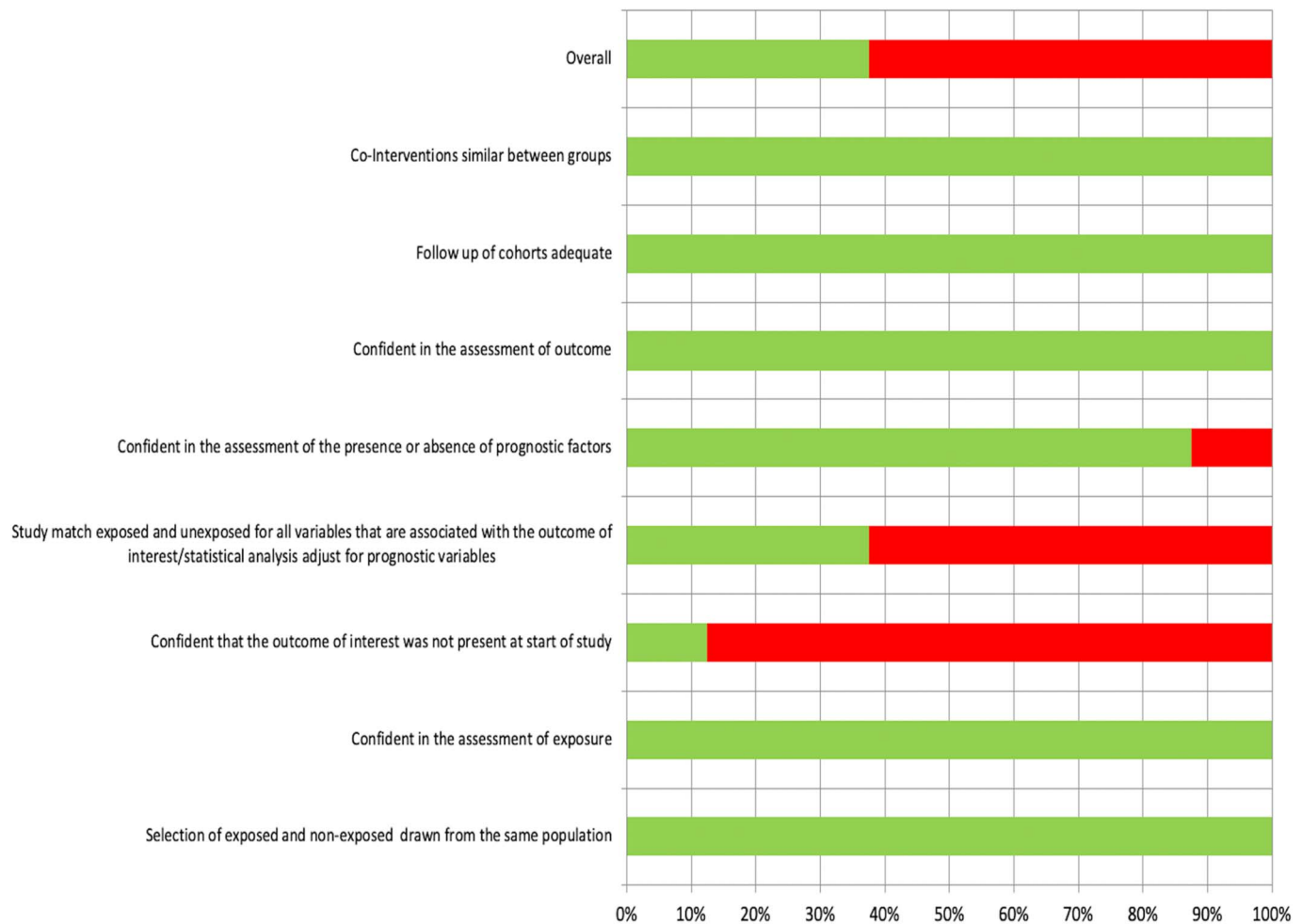
Fig. 3

Risk-of-bias assessment for the included observational studies.

meta-regressions and sensitivity NMAs were conducted for the primary outcome to assess potential modifiers of the treatment effect, which are age, sex, and overall risk of bias[30]. Two subgroup analyses were conducted to compare the treatment effects in (1) studies that included only patients with hip fracture versus studies that included participants with hip fracture or other orthopaedic surgical procedures, and (2) studies using observational versus RCT designs.

Lastly, the fit of the model was tested using a plot of the leverage values and a display of the corresponding effective number of parameters (pD), total residual deviance (Dres), and deviance information criterion (DIC). The DIC value is used to help determine or justify model choice when considering 2 or more competing models.

For each outcome, the interventions were ranked using the surface under the cumulative ranking curve (SUCRA)[31,32] and presented in a rank-heat plot (rankogram) (http://rh.ktss.ca/)[33]. SUCRA values can range from 0% to 100%. The higher the SUCRA value is, the higher the likelihood that a treatment is in the top rank or among the top ranks; the closer to 0 the SUCRA value is, the more likely that a treatment is in the bottom rank or among the bottom ranks (see the eMethods in the Appendix for more details about the data synthesis)[34].

Bayesian NMA models were run through the JAGS program[35] and conducted using the rjags package[36]. The shared-parameter modeling was conducted within BUGSnet[37,38]. Comparison-adjusted funnel plots were created, and heterogeneity was assessed using the metafor package[39]. All the analyses were conducted using R statistical software (version 4.2.2; R Foundation for Statistical Computing)[40].

Source of Funding

Results

A total of 19 studies met the eligibility criteria and were included for data extraction and analysis (Fig. 1).

Table I summarizes the study characteristics; additional details of the included studies are reported in Appendix eTable

TABLE II Summary of Patient Characteristics (N = 19)	
Characteristic	No. (%) of Studies
Mean age in yr	
<60	2 (10.5%)
60-69	4 (21.1%)
70-79	6 (31.6%)
80-89	2 (10.5%)
Not reported	5 (26.3%)
% male	
0-49.9%	13 (68.4%)
50-100%	3 (15.8%)
Not reported	3 (15.8%)
Body mass index in kg/m²	
20-24.9	6 (31.6%)
25-29.9	1 (5.3%)
30-34.9	1 (5.3%)
Not reported	11 (57.9%)

2. Of the included studies, 10 used an observational design and 9 were RCTs. The majority of the studies were conducted within a single center (n = 12, 63.2%) within North America (n = 8, 42.1%) or Asia (n = 6, 31.6%). The sample size of the included studies ranged from 92 to 17,413 participants, with the majority (n = 11, 57.9%) including between 200 and 500 participants.

Risk of Bias

Most studies (76.5%) had a high overall risk of bias. Of the included RCTs, only 1 had a low overall risk of bias. Most RCTs had a high risk of bias due to lack of participant blinding (77.8%) and study personnel blinding (77.8%). Similarly, most of the observational studies (62.5%) had a high overall risk of bias. Fig 2 and 3 illustrate the risk-of-bias results. Details of the risk-of-bias assessments are provided in Appendix eTable 3. All comparison-adjusted funnel plots suggested no evidence of publication bias (see Appendix eFig. 1). Visual assessment of funnel plots for the VTE and bleeding outcomes indicated the existence of studies with markedly different effects (outlying studies), and sensitivity analyses were conducted by excluding those due to outliers to check the robustness of the results.

Participant Characteristics

The mean age of the participants ranged from 40.6 to 84.3 years among the included studies (Table II); additional participant characteristics are provided in Appendix eTable 4. Most of the studies included in this systematic review included more females than males (n = 13, 68.4%), and the mean age most commonly fell between 70 and 80 years (n = 6, 31.6%).

Analysis of the Outcomes

Model Assumptions

The means of age and percentage male across studies were evenly distributed around the overall mean values of the included participants (red dotted line in Appendix eFigure 2). It appears that there is no meaningful heterogeneity in the distribution of the effect modifier within the networks.
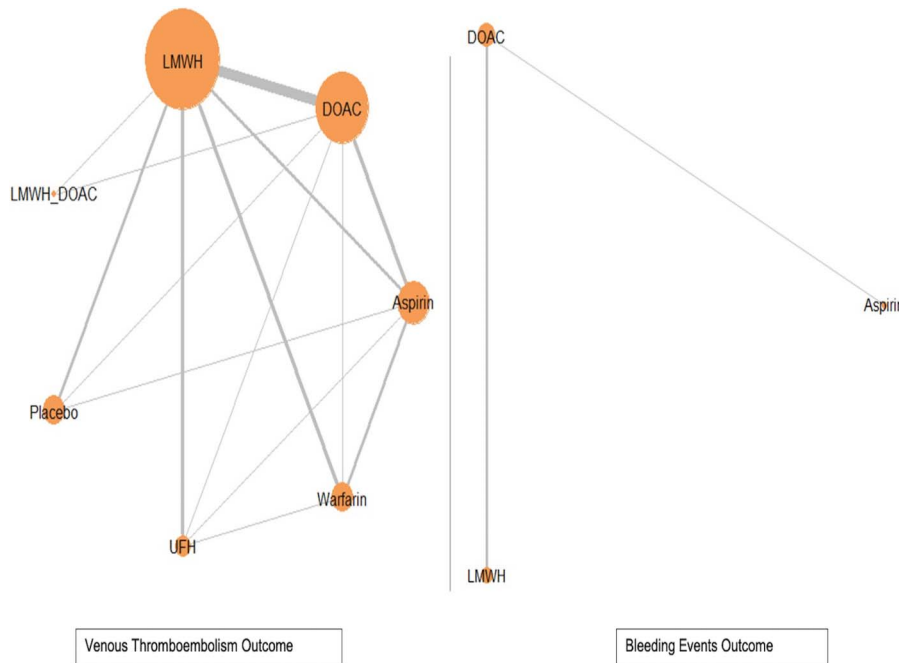

Fig. 4

Network geometry for the outcomes.

| | Treatment | | | | | |
	Placebo	Aspirin	Warfarin	UFH	LMWH_DOAC	DOAC	LMWH
Placebo		0.83 (0.24, 2.91)	0.46 (0.09, 1.84)	0.44 (0.09, 2.05)	0.36 (0.05, 2.80)	0.34 (0.10, 1.21)	0.34 (0.10, 1.07)
Aspirin	1.21 (0.34, 4.16)		0.55 (0.14, 1.78)	0.53 (0.12, 2.14)	0.43 (0.06, 3.07)	0.42 (0.15, 1.17)	0.41 (0.14, 1.11)
Warafarin	2.18 (0.54, 10.72)	1.82 (0.56, 7.34)		0.95 (0.24, 4.19)	0.78 (0.12, 6.31)	0.75 (0.26, 2.82)	0.74 (0.29, 2.23)
UFH	2.28 (0.49, 11.66)	1.90 (0.47, 8.44)	1.05 (0.24, 4.16)		0.82 (0.11, 6.55)	0.79 (0.23, 3.00)	0.78 (0.26, 2.39)
LMWH_DOAC	2.79 (0.36, 21.83)	2.30 (0.33, 16.82)	1.28 (0.16, 8.66)	1.22 (0.15, 8.99)		0.96 (0.17, 5.64)	0.95 (0.16, 5.25)
DOAC	2.90 (0.83, 9.67)	2.41 (0.85, 6.71)	1.34 (0.35, 3.91)	1.27 (0.33, 4.30)	1.04 (0.18, 5.78)		1.00 (0.45, 1.98)
LMWH	2.92 (0.93, 9.99)	2.44 (0.90, 7.06)	1.35 (0.45, 3.49)	1.28 (0.42, 3.81)	1.05 (0.19, 6.20)	1.00 (0.50, 2.25)	

(Comparator — row axis label)

Fig. 5

Network estimates of pairwise comparisons, venous thromboembolism outcome. CrI = credibility interval.

After comparing the fit of the inconsistency models against the consistency models for the 2 outcomes, we found that the DIC for the consistency model is smaller than for the inconsistency model. Overall, we concluded that there is a lack of evidence to suggest inconsistency within the network. The leverage plots with the DIC of inconsistency and the consistency models are illustrated in eFigure 3.

Primary Outcome: VTE

The NMA for VTE included 19 studies (9 RCTs and 10 observational studies with a total of 49,409 participants) with 6 interventions (Fig. 4). Of the included studies, 17 were 2-arm and the remaining 2 studies used multiple treatment arms. There was no significant heterogeneity or inconsistency in this NMA ($\tau^2 = 0.22$, $I^2 = 48.5\%$ [95% CI, 11.1% to 70.2%]), which increased the confidence in our results. Across all of the rele-

vant treatment effects from the NMA, all treatment comparisons were not significant from one another (Fig. 5). All 6 included interventions were not associated with a decrease in VTE compared with placebo (Fig. 6). According to SUCRA, thromboprophylaxis using DOAC or LMWH were probably the most effective interventions to reduce VTE events (SUCRA = 79.9% and 59.5%, respectively).

Meta-regression was used to determine if participant age, sex, and overall risk of bias modified the effect of the included interventions. We conducted 3 meta-regression analyses (Appendix eTable 5). The meta-regression for participant age included 15 studies (total of 23,885 participants) with 6 thromboprophylaxis interventions. There was no significant difference in the DIC of the models with or without age as a covariate (81.68 versus 81.49; eFigure 4), which suggests that the participants' mean age does not significantly impact the

Odds Ratio (95% CrI)

Compared with Placebo

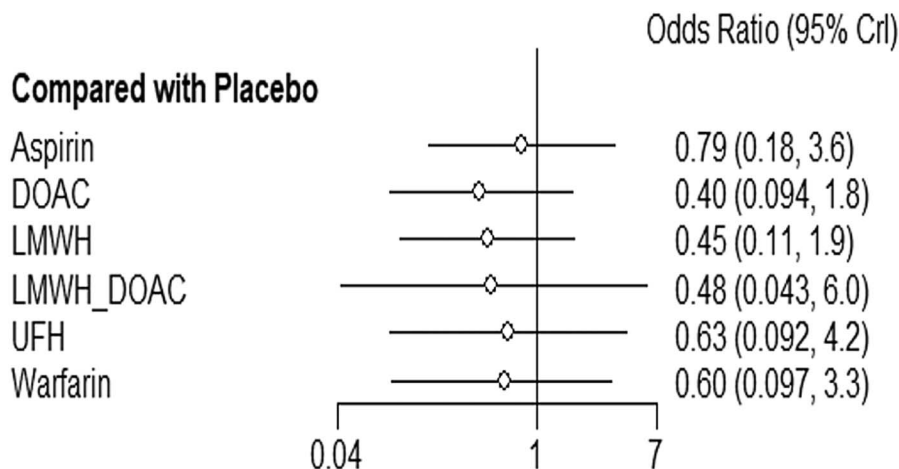|	Odds Ratio (95% CrI)
Aspirin	0.79 (0.18, 3.6)
DOAC	0.40 (0.094, 1.8)
LMWH	0.45 (0.11, 1.9)
LMWH_DOAC	0.48 (0.043, 6.0)
UFH	0.63 (0.092, 4.2)
Warfarin	0.60 (0.097, 3.3)

0.04   1   7

Fig. 6

Venous thromboembolism outcome of pairwise comparison of included interventions versus placebo.
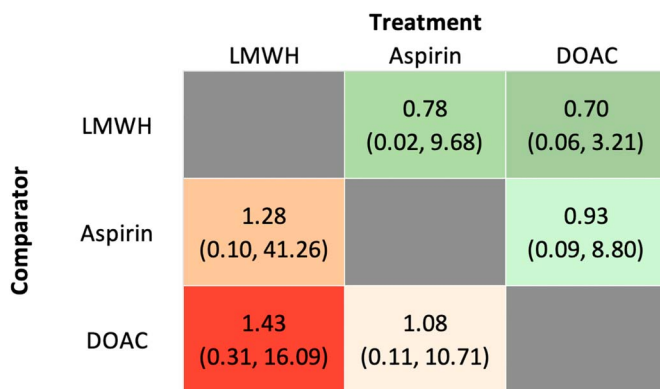
Fig. 7
Network estimates of pairwise comparisons, bleeding outcome.

effect sizes of the included interventions. The meta-regression for participant sex and risk of bias included 16 studies (31,479 participants) with 6 thromboprophylaxis interventions and 17 studies (31,679 participants) with 6 interventions, respectively. Similarly, sex and risk of bias did not significantly modify the interventions' effect across treatment comparisons (Appendix eTable 5 and eFigure 4).

After excluding the outlier study from the rest of the studies included in VTE outcomes analysis (eTable 6), sensitivity analysis showed that the effect estimates and intervention ranking did not significantly change compared with the main NMA analysis. Subgroup analysis showed that the effect estimates was not significantly different between studies with hip fracture participants only (n = 14) versus studies that included participants with hip fracture and other orthopaedic surgeries (n = 5) or studies with observational (n = 10) versus RCT (n = 9) designs (eTable 7).

Secondary Outcome: Bleeding Events
Three 2-arm observational studies (18,163 participants) using 3 different thromboprophylaxis interventions were included in the bleeding outcome network (Fig. 7). Aspirin and DOAC were not associated with decreased bleeding compared with LMWH (Fig. 8). Across all of the relevant treatment effects from NMA, all treatment comparisons were not significant (Fig. 7). Participants who received DOAC and aspirin had fewer

bleeding events (SUCRA = 60.2% and 52.8%, respectively) compared with LMWH. The rank-heat plot using the SUCRA values is presented in eFigure 5.

Discussion

This is the first systematic review and NMA to combine the direct and indirect evidence of 6 different thromboprophylaxis interventions, in order to compare their effect on VTE and bleeding events after hip fracture surgery. There were no significant differences found in VTE event or bleeding event rates between any of the included thromboprophylaxis interventions (DOAC, LMWH, UFH, aspirin, and warfarin) following hip fracture surgery. This analysis suggests that the effectiveness and safety of the included thromboprophylaxis interventions are comparable. Thus, thromboprophylaxis for trauma patients may depend on other factors that influence medication choice, such as patient tolerance, adherence, and preference, route of drug administration, drug availability, and cost.

Given the known low adherence and challenges with LMWH injections (only 1 in 5 hip fracture patients adhere to LMWH injection), oral thromboprophylaxis medications, such as DOAC and aspirin, are preferred by patients and potentially more effective[41]. The oral administration of DOAC and aspirin is convenient in both inpatient and outpatient settings because it is generally easier for patients to take an oral medication as opposed to a regular injection.

Strengths of this review include duplicate screening, data abstraction, risk-of-bias appraisal, and comprehensive search strategies. This review has its own limitations, such as the high risk of bias, small sample size of most of the included studies, and the considerable variability in the interventions of some of the individual nodes. For example, the LMWH and aspirin doses and durations were not consistent across studies, and there are differences in populations of the included studies, such as mean age and sex distribution. The primary efficacy outcome and detection of VTE varied between studies, with some reporting routine contrast venography results, while others were based on an ultrasound technique. Additionally, in some studies asymptomatic, distal DVT was the main contributor to the primary outcome, whereas others focused on clinically important, proximal

Fig. 8
Bleeding outcome of pairwise comparison of included interventions versus placebo. CrI = credibility interval.

DVT. Despite the variability of the included interventions, we found no significant heterogeneity in our traditional meta-analyses and no substantial inconsistency in our network meta-analyses.

Conclusions

There was not a significantly superior thromboprophylaxis intervention for VTE prevention, or reduction of bleeding events for patients requiring hip fracture surgery. Specifically, DOAC, aspirin, and LMWH are not statistically different in their effect on VTE event rate and bleeding event rate for hip fracture patients undergoing surgical treatment. Considering the high risk of bias in the current literature, more robust prospective trials, including well-designed RCTs, are needed to determine the most effective thromboprophylaxis agent for safe and efficacious VTE prevention after hip fracture surgery.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJSOA/A571). ∎

Ahmed M. Negm, MD, PhD[1]
Lisa Yamaura, MKin[1]
Ashley Clarke, MSc[1]
Daniyya Chaudhry, BSc[1]
Tanya Cherppukaran, BSc[1]
Prism Schneider, MD, PhD, FRCSC[1]

[1]Department of Surgery, University of Calgary, Calgary, Alberta, Canada

Email for corresponding author: ahmed.negm@ucalgary.ca

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