Standard Review Article

Qualitative analysis of randomized controlled trials informing recommendations for venous thromboembolism prophylaxis after distal lower extremity injuries

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Abstract

Purpose: The purpose of this study is to assess the quality of evidence to stratify recommendations for chemoprophylaxis following distal lower extremity trauma.

Methods: Literature review identified primary studies investigating venous thromboembolism (VTE) chemoprophylaxis following traumatic injury distal to the knee. Inclusion criteria were randomized controlled trials in adult patients treated with and without operative intervention. Each primary study was assessed by the Consolidated Standards of Reporting Trials 2010 checklist and Modified Coleman methodology score.

Results: Literature review resulted in 462 studies, of which 9 met inclusion and exclusion criteria. All studies included low molecular weight heparin as a treatment group with 2 (22%) also including a treatment group with a direct factor Xa inhibitor. Five studies (56%) used placebo as a control group. The mean Modified Coleman Methodology score was 63% (range 51%–72%), a categorical rating of Fair. The mean Consolidated Standards of Reporting Trials score was 78% (range 56%–97%). Most studies (89%) screened all asymptomatic subjects for deep venous thrombosis. Statistical significance in VTE incidence among prophylactic treatment groups was not achieved in 78%.

Conclusions: Development of consensus for VTE prophylaxis recommendations following traumatic injury distal to the knee is complicated by heterogenous study populations, low incidence of VTE in study populations, and inconsistent definitions of clinically important VTE. Low molecular weight heparin is not consistently superior for preventing VTE. Chemoprophylaxis should be considered on an individual basis in the presence of additional risk factors, although an externally validated, evidence-based risk assessment tool does not currently exist.

Level of Evidence: IV, therapeutic

Keywords: aspirin, lower extremity fracture, prophylaxis, venous thromboembolism

1. Introduction

Traumatic injuries of the lower extremity often meet all 3 components of Virchow's triad—endothelial damage occurring during trauma and any subsequent surgery, hypercoagulability due to release of tissue factors, and stasis due to immobilization required to allow fracture and soft tissue healing.[1] Surgeons have mitigated the risk of venous thromboembolism (VTE), either deep vein thrombosis (DVT) or subsequent pulmonary embolism (PE), with a variety of mechanical and chemoprophylactic regimens. Unlike total hip arthroplasty (THA), total knee arthroplasty (TKA), or hip fracture, limited evidence-based guidance exists for VTE prophylaxis following isolated lower extremity injury.[2] Modern THA, TKA, and hip fracture implants permit early weight-bearing and mobilization after surgery, which minimizes the contribution of stasis in developing VTE. In contrast, lower extremity injuries treated with immobilization and protected weight-bearing with or without operative fixation limit mobilization to facilitate venous return. Multiple guidelines with disparate quality of supporting evidence have led to variability in clinical practice.[3]

Secondary studies on chemoprophylaxis following traumatic injury distal to the knee have a small number of prospective

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studies from which to draw conclusions. Although prospective randomized controlled trials (RCTs) represent the highest level of evidence, Cowan et al demonstrated that reliance on Oxford levels of evidence to assess study quality can yield a false strength of evidence.[4] The purpose of the present study is to provide a summary of the strength of distal lower extremity injury VTE prophylaxis recommendations based on a qualitative assessment of published primary studies. We also provide a review of the literature specific to traumatic injury distal to the knee with recommendations for risk-stratifying patients in considering VTE chemoprophylaxis.

2. Materials and methods

2.1. Literature search

A comprehensive review of 3 online databases (PubMed, Cochrane, Embase) was performed. The MeSH search terms were "prophylaxis," "thromboprophylaxis," "chemoprophylaxis," "venous thrombosis," "venous thromboembolism," "pulmonary embolism," "vte," "bones of lower extremity," "fractures, bone," "lower extremity," and "fracture." Additional terms were "aspirin" and "antiplatelet."

2.2. Study selection

The identified abstracts were analyzed to assess relevance to VTE chemoprophylaxis following lower extremity injury per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Inclusion criteria were prospective randomized controlled studies comparing chemoprophylaxis regimens following traumatic lower extremity injuries distal to the knee in adults treated with and without operative intervention. Articles were excluded if the study population included pathologic fractures, pediatric patients, polytrauma including spinal injury, knee arthroscopy, THA, TKA, fractures proximal to the knee, hip arthroscopy, knee arthroscopy, unspecified injuries about the lower extremity, and exclusively Achilles tendon pathology. Arthroscopy, arthroplasty, and Achilles tendon articles were excluded for differences in postoperative weight-bearing protocols and degree of tissue disruption based on thromboembolism pathophysiological theories. Articles which contained insufficient detail to ensure all fractures were distal to the knee, or > 50% soft tissue injuries were also excluded. References were reviewed to identify any additional articles, including those of systematic reviews and meta-analyses for additional primary studies.

2.3. Qualitative analysis

Similar to Cowan et al investigating the quality of evidence of RCTs,[4] each of the selected studies were assessed according to the most recent Consolidated Standards of Reporting Trials (CONSORT) checklist[5] and a Modified Coleman Methodology Score.[4,6] The updated CONSORT 2010 checklist consists of 37 items designed to improve the reporting of RCTs.[5] Each item was equally weighted, and inapplicable items recorded to facilitate an aggregate percentage of total applicable CONSORT criteria achieved. Categorical ratings for the CONSORT checklist were: Excellent from 81% to 100% of applicable criteria adequately reported, Good from 60% to 80%, Fair from 35% to 59%, and Poor if less than 35%. As CONSORT 2010 focuses on providing readers with sufficient information to critically appraise reported results, a well-designed and executed trial can be weakened by suboptimal reporting of methodology and results. The Modified Coleman Methodology Score complements CONSORT 2010 by evaluating study design to minimize chance, bias, and confounding factors.[4] The Modified Coleman includes weighted categories with brief descriptions for each point designation (Supplement 1, http://links.lww.com/OTAI/A40). Each study was designated a percentage based on points achieved out of a maximum possible 96 points. Categorical ratings for the Modified Coleman Methodology Score were: Excellent if greater than 88%, Good from 73% to 88%, Fair from 57% to 72%, and Poor if less than 57%. Two independent reviewers graded each of the 13 studies, and a third reviewer provided consensus if scores differed categorically.

2.4. Statistical analysis

Interobserver consistency was determined by percent agreement and Cohen kappa values.[7]

Any investigation involving human subjects or the use of patient data for research purposes was approved by the committee on research ethics at the institution in which the research was conducted in accordance with the Declaration of the World Medical Association (www.wma.net) and any informed consent from human subjects was obtained as required.

3. Results

After search, 462 unique articles were identified. Nine articles met inclusion and exclusion criteria for quality of evidence assessment with a total of 5106 patients (Fig. 1). Demographics, study design, VTE chemoprophylaxis, VTE incidence, author recommendations, and quality of evidence scores were recorded (Table 1). All studies included a low molecular weight heparin (LMWH) as a treatment group with 2 (22%) also including a treatment group with a direct factor Xa inhibitor.[8,9] Five studies (56%) used placebo as a control group.[10–14] There was heterogeneity in study population (e.g., fracture, operative management), exclusion criteria, duration of immobilization, duration of follow-up, and indication for VTE diagnostic work-up (e.g., symptomatic vs all subjects).

The mean Modified Coleman Methodology score was 63% of applicable criteria (range 51%–72%), a categorical rating of Fair (between 57% and 72%, Table 2). The mean CONSORT score was 78% of applicable criteria adequately reported (range 56%–97%, Table 3).

Interobserver consistency for Modified Coleman was 85% agreement with a Cohen kappa value of 0.82 (95% confidence interval [CI] 0.61–1.04, standard error 0.11), which corresponds to a Strong level of agreement. Interobserver consistency for CONSORT was 92% agreement with a Cohen kappa value of 0.85 (95% CI 0.56–1.13, standard error 0.15), which corresponds to an Almost Perfect level of agreement.

The qualitatively analyzed studies demonstrated some strengths in CONSORT scoring. Hundred percent of studies (9/9) adequately reported specific objectives, eligibility criteria, explanation of interim analysis/stopping guidelines, description of statistical methods, participant flow, reason study was stopped, demographic data table, and author recommendations. Eighty-nine percent of studies (8/9) additionally reported background and objectives, description of intervention, blinding details, subgroup analyses, dates of recruitment, details of sample size analyzed, and harms observed.

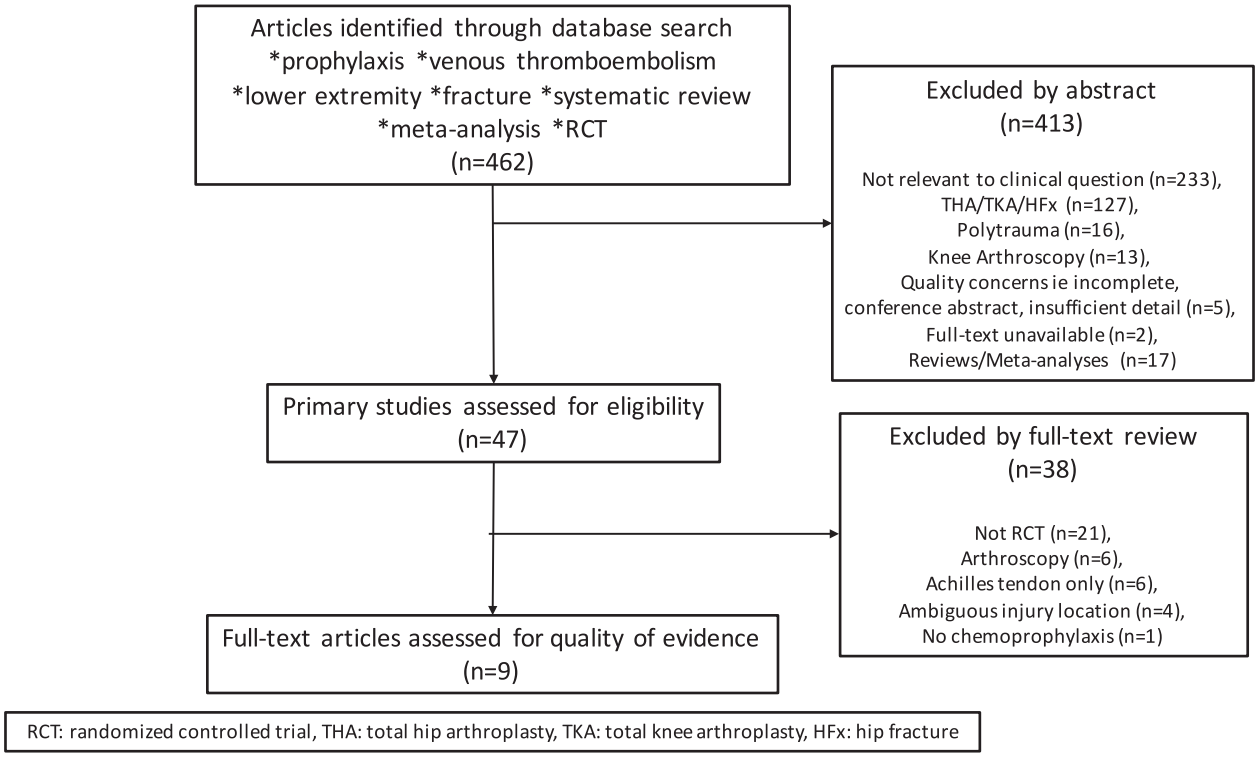

Figure 1. PRISMA 2009 flow diagram of study inclusion.

Consistent weaknesses in CONSORT scores included reporting of the location of full protocol (only 2/9 studies), trial registration information (3/8), details of randomization implementation (4/9), and inclusion of "Randomized" in article title (4/9). Only 22% of studies (2/9) reported both absolute and relative effect size, important for assessing intervention effectiveness.

Strengths on the Modified Coleman scale included sample size (average score 9.0/9 possible points), description of treatment (5.7/6), group comparability (5.7/6), randomization (7.6/8), power (5.0/6), and intention-to-treat patient analysis (5.0/6).

Weaknesses as determined by the Modified Coleman included both statistical and methodological shortcomings. Number needed to treat was only reported by 1 study[15] (11%), and 22% of studies (2/9) provided no clinical effect measure of any kind. All studies provided an a priori power analysis; however, 56% of studies (5/9) cited lack of power as a limitation of their study,[8,10,11,15,16] and 23% of studies (2/9) were stopped before reaching the intended sample size.[8,13] The average blinding score was only 2.9/6 possible points, as 33% of studies (3/9) were designed open label. Inclusion criteria lacked enrollment rates in 89% (8/9) studies. Similarity in treatment scores averaged 2.7/6 possible points. Rehabilitation protocol was only reported by 1 study.[13] Follow-up scores averaged 2.7/8 points.

Eighty-nine percent of studies (8/9) conducted ultrasound-based or venography VTE screening on all asymptomatic subjects, in addition to those presenting with VTE complaints before designated screening follow-up. Only 1 study[15] methodologically excluded asymptomatic VTE by restricting outcomes to symptomatic events.

There was heterogeneity in study population with variable inclusion of patients with fractures and operative management. Fifty-six percent of studies (5/9) included patients with fractures and excluded patients with only soft tissue injuries.[8,10,11,13,14] Of the 44% of studies (4/9) including both fractures and soft tissue injuries, fractures constituted between 73% and 90% of the population.[9,12,15,16] Forty-four percent of studies (4/9) included patients treated operatively and excluded patients treated nonoperatively.[10,11,13,14] For articles including both operative and nonoperative management, operative management was performed in less than 20% of the study population in 22% of studies (2/9),[15,16] and less than 60% of the study population in 11% of studies (1/9).[12] Twenty-two percent of studies (2/9) excluded surgical patients.[8,9]

There was no significant difference in DVT, PE or overall VTE incidence between groups in 78% of studies (7/9). No study reported a significant difference in PE incidence among treatment and control groups. One study reported an odds ratio favoring LMWH for overall DVT risk (odds ratio 0.45, 95% CI [0.24,0.82]), but the fracture-specific odds ratio was not statistically significant.[12] One study found a statistically significant difference for DVT risk favoring a factor Xa inhibitor to no treatment (relative risk 10.8, 95% CI [1.4,80.7]) as well as LMWH to no treatment (relative risk 5.4, 95% CI [1.2,23.6].[8] Another favored factor Xa inhibitors to LMWH for overall VTE risk (odds ratio 0.30, 95% CI [0.15–0.54]), but determined symptomatic VTE were not statistically significant.[9]

4. Discussion

The purpose of this study is to evaluate the strength of evidence informing recommendations for venous thromboembolism prophylaxis following traumatic injuries distal to the knee. The key findings are: (1) current recommendations are based on a small number of prospective studies with low methodological

Table 1

Summary of study characteristics.

Study	Design	Population (Mean, SD) *Inclusion criteria*	Injury (n) *Orthopaedic treatment*	Intervention, dose, and average duration (number of patients analyzed), % Adherence	VTE outcome measurement (length of follow-up)	VTE incidence, OR/RR [95% CI] DVT, *PE*	Bleeding incidence*	Author recommendation; Notes	CONSORT 2010 (%)	Modified Coleman (%)
Bruntink, 2017	RCT, SB	Mean 47 ±17 yo; 42% male *≥18 yo, fracture of foot or ankle requiring below-knee plaster cast for ≥4 wks w/in 72 h of injury*	Unspecified foot or ankle fracture (278) *SLC, mean 40± 9 d 100% nonoperative*	Nadroparin, 2850 IU/d, 40.2 d (n=92), ~100%	DVT on duplex sonography at SLC removal Symptomatic PE verified by CT angiography (until SLC removal, mean 40 ±9 d)	DVT 2.2% (2/92), RR 5.4 [1.2,23.6] *PE 0*	None	Routinely prescribe nadroparin or fondaparinux for ankle/foot fractures conservatively treated with SLC; Planned sample size not met because terminated early	94	59
				Fondaparinux, 2.5 mg/d, 38.0 d (n=92), ~100%		DVT 1.1% (1/92), RR 10.8 [1.4,80.7] *PE 0*	None			
Goel, 2009	RCT, DB	Mean 41±15 yo; 62% male *18–75 yo, unilateral isolated fracture below tie knee and above tie foot treated surgically w/ in 48 h*	Tibial plateau fracture (30), Tibial shaft fx (39), Ankle fx (150), Pilon fx (15), Other fx between knee/ foot (3) *SLC, below knee splint or light dressing, duration NR 100% operative*	No tx, 40.3 d (n=94) Dalteparin, 5000 IU/d, 14 d (n=127), >95%	DVT on bilateral venography at 14 d, clinically thereafter Standard protocol for PE (3 mo or until complete healing)	DVT 11.7% (11/94), *PE 2* DVT 8.7% (11/127), Not stat sig *PE 0*	None None	LMWH may be beneficial as thromboprophylaxis for DVT after isolated trauma below the knee. Future studies should investigate incidence and risk factors; Planned sample size not met because funding terminated	74	67
				Placebo, 14 d (n=111), > 95%		DVT 12.6% (14/111), Not stat sig *PE 0*	None			
Jorgensen, 2002	RCT, OL	Mean 47 yo, Range 18–93 yo; 57% male *> 18 yo, planned LE plaster cast for ≥3 wks*	Fracture distal to knee (220), Tendon rupture distal to knee (61), Other injury distal to knee (19) 73% fractures *SLC mean 5,5 wks, range NR 12% operative*	Tinzaparin 3500 IU/d, 5.5 wks (n=99), NR No tx, 5.5 wks (n=106)	DVT on unilateral venography at SLC removal (until SLC removal, mean=5.5 wks)	DVT 10% (10/99), Not stat sig *PE 0* DVT 17% (18/106), Not stat sig	None None	LMWH may be beneficial for patients with plaster cast of the lower extremity;	56	51
Lapidus, 2007	RCT, DB	Mean 48±14 yo; 46% male *18–75 yo, surgically treated ankle fracture w/ in 72 h of injury*	Ankle fracture Unimalleolar (103), Bimalleolar (95), Trimalleolar (74) *SLC (222), SLC then orthosis (47), orthosis only (3), mean 44± 2 d 100% operative*	Dalteparin, 5000 IU/d, 1 wk before randomization +5 wks (n=101), 94.6%	DVT by unilateral venography after cast removal or compression sonography if venography failed Spiral CT or scintigraphy for suspected PE (6 wks, mean 35±5 d, range 2–40 d)	*PE 0* DVT 21% (21/101) Not stat sig *PE 0*	None	Prolonged thromboprophylaxis for DVT with Dalteparin during immobilization after ankle fracture surgery is not recommended;	70	63
				Dalteparin, 5000 IU/d, 1 wk before randomization + Placebo for 5 wks (n= 96), 94.6%		DVT 28% (27/96), *PE 0*	None			
Lassen, 2002	RCT, DB	Median 47 yo, Interquartile Range 37–56 yo; 52% male *≥18 yo, leg fracture/ Achilles rupture requiring SLC/Brace for ≥5 wks w/in 96 h of injury*	Tibial fracture (28), Patellar fx (15), Ankle (malleolar) fx (282), Foot fx (28), Achilles tendon rupture (88) 80% fractures *SLC (371) or ankle brace (67), mean 44 d, range NR, all patients PWB 56% operative*	Reviparin 1750 IU/d, 43 d (n= 217) ~1/3 received other LMWH for ≤ 4 d before randomization, ~100%	DVT by unilateral venography w/in 1 wk of cast/brace removal or sooner if clinical suspicion Scintigraphy or pulmonary angiography for suspected PE (by telephone at 3 mo)	DVT 9% (17/183) OR 0.45 [0.24,0.82] Fx-specific OR not stat sig *PE 0*	<1% (2/217) Not stat sig	Reviparin given once daily appears to be effective and safe in reducing the risk of DVT follow leg injury requiring prolonged immobilization; Sponsor performed statistical analysis	76	64

(*continued*)

Table 1
(continued).

Study	Design	Population (Mean, SD) *Inclusion criteria*	Injury (n) *Orthopaedic treatment*	Intervention, dose, and average duration (number of patients analyzed), % Adherence	VTE outcome measurement (length of follow-up)	VTE incidence, OR/RR [95% CI] DVT, *PE*	Bleeding incidence*	Author recommendation; Notes	CONSORT 2010 (%)	Modified Coleman (%)
				Placebo, 44 d (n = 221) ~1/3 received other LMWH for ≤ 4 d before randomization, ~100%		DVT 19% (35/188) *PE 1% (2/221)*	< 0.5% (1/221)			
Şamama, 2013	RCT, OL	Mean 46 ± 16 yo; 47% male *≥18 yo, at least 1 major risk factor for VTE + unilateral, nonsurgical below-knee injury requiring SLC/Brace for 21–45 d within 72 h of injury*	Lateral malleolus fracture (463), Metatarsal fx (283), Unspecified below-knee fx (357), Achilles tendon rupture (25), Other below-knee injury (141) 87% fractures *SLC (1042), brace (771, other immobilization (124), mean 34 ± 9 d PWB permitted 100% nonoperative*	Fondaparinux, 2.5 mg/d, 33.5 d (n = 621), NR	DVT by bilateral compression sonography ≤ 2 d after cast removal scintigraphy, helical CT, or pulmonary angiography for suspected PE (by telephone 5 ± 1 wks after cast/brace removal)	DVT 2.4% (13/583) *PE 0.3% (2/621)* Any VTE OR 0.27 [0.14,0.50] Fx-specific OR 0.3 ($p < 0.001$) Symptomatic VTE not stat sig	0.1% (1/621)	Fondaparinux may be a valuable therapeutic alternative to nadroparin for preventing VTE after below-knee injury requiring prolonged immobilization in patients with additional risk factors; Only blinded to adjudication committee	84	69
				Nadroparin, 2850 IU/d, 33.9 d (n = 622), NR		DVT 8.2% (48/586) *PE 0*	None			
Selby, 2015	RCT, DB	Mean 49 ± 16 yo, Range 18–87 yo; 52% male *≥16 yo, unilateral/ bilateral, closed/open fracture of tibia/fibula/ ankle surgically treated w/in 72 h injury*	Tibial plateau fracture (37), Tibial shaft fx (74), Fibular shaft/distal fibula fx (92), Ankle fx (156) *SLC or splint, mean 43 ± 29 d 100% operative*	Dalteparin, 5000 IU/d, 14 ± 2 d (n = 130), 90%	Symptomatic VTE w/in 3 mo after surgery (confirmed) or asymptomatic proximal DVT by bilateral Doppler sonography at end of tx Spiral CT pulmonary angiography, high probability scintigraphy, or leg imaging for suspected PE (3 mo post-op)	DVT 1.5% (2/130), *PE 0* Not stat sig	None	Using more clinically relevant outcome criteria demonstrates no difference between dalteparin and placebo. Routine prophylaxis for isolated, distal lower extremity fractures is not recommended; Recruitment stopped after first interim analysis due to low overall incidence	86	65
				Placebo, 14 ± 2 d (n = 128), 92%		DVT 2.3% (3/128) *PE 0.1% (1/128)*	None			
van Adrichem, 2017	RCT, OL	Mean 46 ± 16 yo; 50% male *≥18 yo, lower leg cast for ≥ 1 wk with or without surgery before/ after casting*	Ankle fracture (497), Metatarsal fx (532), Calcaneus fx (56), Pilon fx (3), Tibia/fibula shaft fx (3), Talus fx (50), Tarsal fx (98), Phalanx fx (23), Lisfranc fx (6), Unspecified fx (11), Achilles rupture (94), Other injury without fx (62) 90% fractures *SLC, mean 4.9 ± 2.5 wks 12% operative*	Nadroparin, 2850 IU/d or Dalteparin 2500 IU/d or double dose for > 100 kg, 4.9 wks (n = 719), 87%	Symptomatic DVT or PE w/ in 3 mo of casting, as reported by patient, general practitioner, or records review. (by telephone for 3 mo)	DVT 0.8% (6/719) PE 0.4% (3/719) DVT + PE 0.1% (1/719) Not stat sig	None	Routine thromboprophylaxis with standard dosing of LMWH during the full period of immobilization due to casting is not effective for prevention of symptomatic VTE. Increased dose or duration might be effective if restricted to high-risk groups; Designed pragmatically to maximize generalizability	97	72
				No tx, 4.9 wks (n = 716)		DVT 1.1% (8/716) *PE 0.6% (4/716) DVT+PE 0.1% (1/716)*	None			

(*continued*)

Table 1
(continued).

Study	Design	Population (Mean, SD) *Inclusion criteria*	Injury (n) *Orthopaedic treatment*	Intervention, dose, and average duration (number of patients analyzed), % Adherence	VTE outcome measurement (length of follow-up)	VTE incidence, OR/RR [95% CI] DVT, *PE*	Bleeding* incidence	Author recommendation; Notes	CONSORT 2010 (%)	Modified Coleman (%)
Zheng, 2016	RCT, DB	Mean 46 ± 16 yo; 62% male *> 18 yo, unilateral/ bilateral, closed/open fracture of ankle/foot requiring operative tx*	Ankle fracture (342), Calcaneus fx (171), Metatarsal fx (130), Phalange fx (90), Talus/ Tarsus fx (81) *No immobilization to facilitate ultrasound screening, not FWB for 6 wks 100% operative*	Unspecified LMWH once daily for 14 d (n = 411), NR	DVT by bilateral Doppler sonography at 1 wk and 1 mo post-op (3 mo total)	DVT 0.98% (4/411) *PE 0* Not stat sig	None	Routine chemical prophylaxis for patients with no known risk factors is not necessary for foot and ankle fractures; Under-powered study	65	55
				Placebo once daily for 14 d (n = 403)		DVT 2.01% (8/403) *PE 0*	None			

CI = confidence interval, CT = computed tomography, d = days, DB = double-blinded, DVT = deep venous thrombosis, FWB = fully weight-bearing, fx = fracture, h = hours, LMWH = low molecular weight heparin, mo = months, NR = not reported, OL = open-label, OR = odds ratio, PE = pulmonary embolism, post-op = post-operatively, PWB = partial weight-bearing, RCT = randomized, prospective controlled trial, RR = relative risk, SB = single-blinded, SD = standard deviation, SLC = short leg cast, stat sig = statistically significant, tx = treatment, VTE = venous thromboembolism, w/in = within, wks = weeks, yo = years old,.

* Bleeding incidence is defined as clinically apparent, requiring transfusion, retroperitoneal/intracranial, or resulting in termination of treatment; minor bleeding events such as hematomas are not included.

quality, (2) clinically important VTE was not consistently assessed, (3) LMWH is not consistently superior for preventing VTE, and (4) there were no prospective, randomized studies assessing aspirin as chemoprophylaxis meeting the inclusion criteria.

Surgeons seeking recommendations for VTE chemoprophylaxis following traumatic injury distal to the knee continue to find limited guidance despite numerous systematic reviews and meta-analyses on the topic.[17–19] Secondary studies repeatedly mention quality of evidence as the main factor hindering consensus, and many provide a brief assessment of methodological quality or risk of bias.[18–21] However, this study investigated the strength of evidence via qualitative assessment of the primary literature.

One barrier to consensus on optimal prophylaxis is disagreement over the pathophysiology of venous thromboembolism.[22] Classically it has been assumed that hypercoagulability, tissue damage, and stasis inherent to lower extremity trauma predisposes a patient to DVT of the leg. Due to mortality risk, the feared complication of DVT is progression to PE, as thrombi extend proximally and risk of embolism increases. The advent of noninvasive detection with Doppler ultrasound facilitates screening asymptomatic patients for DVT and mitigating PE risk. However, an evolving understanding of the pathophysiology of VTE questions the link between asymptomatic lower extremity thrombi and progression to clinically relevant VTE. Selby et al used "clinically important" venous thromboembolism as the primary outcome measure and found 2% incidence,[11] contrasted with reported incidences of venographically-detected VTE from 27% to 78%.[21] Two prospective studies of foot and ankle injuries without chemoprophylaxis found that no calf thrombi detected with duplex ultrasound progressed proximally; a combined total of 8 patients with distal DVT had no progression despite no treatment with anticoagulation, 4 patients treated with anticoagulation also experienced no progression, and none of the twelve patients experienced symptoms.[23,24] Two systematic reviews challenge the link between DVT and PE and question appropriate prophylaxis and screening methods for preventing PE.[25,26]

Significant disparity among recommendations made by systematic reviews and meta-analyses persists with inclusion of the same 9 RCTs we qualitatively analyzed (Table 4). Four of the most frequently included RCTs were excluded from our study for lacking modern management practices regarding immobilization of fractures distal to the knee. Gehling et al, the only RCT with an aspirin arm, had only 37% fractures, and lacked clarity regarding inclusion of above knee immobilization.[27] Kock et al included only 21% fractures and used cylinder casts for 14% of the patients.[28] Kujath et al included only 31% fractures with unclear extent of lower limb immobilization.[29] Spannagel et al appears to be a duplicate publication with identical data and statistics to Kujath et al.[30] Some secondary studies based on these common RCTs conclude that chemoprophylaxis with LMWH should be utilized regardless of patient risk factors, while others conclude LMWH is indicated only in patients stratified as high-risk. Expert opinion expressed in various guidelines ranges from recommending for and against chemoprophylaxis based on risk stratification, though evidence regarding risk factors is variable (Table 5). The American College of Foot and Ankle Surgeons consensus discusses the factors conveying highest risk, especially personal history of VTE and > 4 weeks of immobilization, though it provides no concrete guidance on evaluating bleeding versus VTE risk.[31] Sub group analysis of 1 trial[15]

Table 2

CONSORT 2010 criteria with average scores by line item.

CONSORT criteria			Average score
Title and abstract	1a	Identification as a randomized trial in the title	44%
	1b	Structured summary of trial design, methods, results, and conclusions	100%
Introduction background and objectives	2a	Scientific background and explanation of rationale	89%
	2b	Specific objectives or hypotheses	100%
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	67%
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	100%
Participants	4a	Eligibility criteria for participants	100%
	4b	Settings and locations where the data were collected	67%
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	89%
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	100%
	6b	Any changes to trial outcomes after the trial commenced, with reasons	100%
Sample size	7a	How sample size was determined	100%
	7b	When applicable, explanation of any interim analyses and stopping guidelines	100%
Randomization: sequence generation	8a	Method used to generate the random allocation sequence	67%
	8b	Type of randomization; details of any restriction (such as blocking and block size)	56%
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	67%
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	44%
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	88%
	11b	If relevant, description of the similarity of interventions	100%
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	100%
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	86%
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	100%
	13b	For each group, losses and exclusions after randomization, together with reasons	100%
Recruitment	14a	Dates defining the periods of recruitment and follow-up	89%
	14b	Why the trial ended or was stopped	100%
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	100%
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	100%
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	89%
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	22%
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	50%
Harms	19	All important harms or unintended effects in each group	89%
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	67%
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	56%
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	100%
Other information			
Registration	23	Registration number and name of trial registry	38%
Protocol	24	Where the full trial protocol can be accessed, if available	22%
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	67%

identified body mass index (BMI), family history of VTE, and surgical treatment as most associated with VTE, though LMWH was not effective for reducing symptomatic VTE in any subgroup.[32] A recent systematic review including several of our primary studies identified age and injury type as the only risk factors supported by evidence.[33] No published risk assessment models have been externally validated, and recent analysis suggests major components of the models have no association with VTE.[34]

Clinical practice guidelines and expert opinion consistently incorporate stratification via risk factors into their recommendations, including the Orthopaedic Trauma Association (OTA) Expert Panel,[3] the OTA Expert Survey on Ankle Fractures,[35] the American College of Foot and Ankle Surgeons,[31] and the National Institute for Health and Care Excellence[36] in the United Kingdom. A weakness of the OTA Expert Panel is no specific recommendation for lower extremity trauma requiring non-weight bearing status. The American College of Chest Physicians

Table 3

Modified Coleman scale with average score by line item.

Modified Coleman criteria	Points	Average score (% possible)
Inclusion criteria		
Not described	0	3.7 (41%)
Described without %'s given	3	
Enrollment rate < 80%	6	
Enrollment rate > 80%	9	
Power		
Not reported	0	5.0 (83%)
> 80%, methods not described	3	
> 80%, methods described	6	
Alpha error		
Not reported	0	3.0 (50%)
<0.05	3	
<0.01	6	
Sample size		
Not stated or < 20	0	9.0 (100%)
20–40	3	
41–60	6	
> 60	9	
Randomization		
Not randomized	0	7.6 (94%)
Modified/partial - Not blinded	2	
Modified/partial - Blinded	4	
Complete - Not blinded	6	
Complete - Blinded	8	
Follow-up		
Short-term (<6 months) - Patient retention < 80%	0	2.7 (33%)
Short-term (<6 months) - Patient retention 80%–90%	2	
Short-term (<6 months) - Patient retention > 90%	4	
Medium-term (6–24 months) - Patient retention < 80%	2	
Medium-term (6–24 months) - Patient retention 80%–90%	4	
Medium-term (6–24 months) - Patient retention > 90%	6	
Long term (>24 months) - Patient retention < 80%	4	
Long term (>24 months) - Patient retention 80%–90%	6	
Long term (>24 months) - Patient retention > 90%	8	
Patient analysis		
Incomplete	0	5.0 (83%)
Complete	3	
Complete and intention-to-treat based	6	
Blinding		
None	0	2.9 (48%)
Single	2	
Double	4	
Triple	6	
Similarity in treatment		
No	0	2.7 (44%)
Similar co-interventions	3	
No co-interventions	6	
Treatment description		
None	0	5.7 (94%)
Fair	3	
Adequate	6	
Group comparability		
Not comparable	0	5.7 (94%)
Partially comparable	3	
Comparable	6	
Outcome assessment		
Written assessment by patient with assistance	0	4.2 (70%)
Written assessment by patient without assistance	2	
Independent investigator	4	
Recruited patients	6	
Description of rehabilitation protocol		
Not reported	0	0.2 (6%)
Not adequately described	2	
Well described	4	
Clinical effect measurement		
Effect size - Not reported	0	2.4 (41%)
Effect size < 50%	2	
Effect size 50%–75%	4	
Effect size > 75%	6	
or Relative risk reduction - Not reported	0	
Relative risk reduction < 25%	3	
Relative risk reduction > 25%	6	
or Absolute risk reduction - Not reported	0	
Absolute risk reduction < 10%	3	
Absolute risk reduction > 10%	6	
Number of patients to treat		
Not reported	0	0.4 (11%)
Reported	4	

(*continued*)

Table 3

(continued).

makes no mention of risk factors and is the only recommendation uniformly against chemoprophylaxis.[37] The American Academy of Orthopaedic Surgeons does not have a recommendation specific to lower extremity fracture, but recommend uniform chemoprophylaxis for hip and knee arthroplasty, which is not consistently comparable to lower extremity fracture due to differences in early mobilization, extent of dissection, and degree of soft tissue disruption. These variable recommendations are associated with variable practice patterns among surgeons treating patients with lower extremity trauma. The OTA Expert Panel acknowledged that practice patterns are unsupported by evidence, with 47% of surgeons screening asymptomatic patients, and 35% of surgeons prescribing chemoprophylaxis to avoid litigation.[3] The OTA Expert Survey on Ankle Fractures similarly identified that the majority of surgeons routinely prescribe chemoprophylaxis against their recommendation.[35]

Our literature review revealed a significant gap in evidence regarding aspirin as VTE prophylaxis. We found only 1 RCT comparing aspirin to LMWH,[27] likely resulting from ethical concerns after LMWH was established as the standard of care in the 1980 s and the relatively low cost of aspirin in a costly clinical trial.[38] We ultimately excluded this study for consisting of > 50% soft tissue injuries. However, the Pulmonary Embolism Prevention trial demonstrated aspirin as effective for PE prophylaxis following hip fracture,[39] and increased adherence among young males required to self-administer oral aspirin versus subcutaneous injection LMWH, suggesting a potential role for aspirin following trauma for indicated patients.[40] Aspirin prescriptions following arthroplasty increased after the most recent American College of Chest Physicians guideline changed to support aspirin monotherapy versus no prophylaxis, indicating a preference by surgeons previously dissuaded by medicolegal concerns.[41] The Warfarin and Aspirin and Aspirin to Prevent Recurrent Venous Thromboembolism RCTs demonstrated the superiority of aspirin versus no treatment for prevention of recurrent VTE.[38] A retrospective study showed aspirin does not impair union rates in ankle fractures, though this same study secondarily found no statistically significant

Table 4

Summary of secondary study findings.

Study	Design	Population (inclusion)	VTE prophylaxis Intervention	Outcome measurement	Risk factors	Prophylaxis recommendations	Major bleeding	Overall effect on VTE (including asymptomatic)	Clinically significant VTE
Bikdeli, 2019	SR	Isolated Foot and Ankle Surgery	LMWH only	Sonography or venography	No analysis	Young patients without identified risk factors may not need prophylaxis	No significant difference	Significantly decreased risk	No difference in proximal DVTs, PEs, or all-cause mortality; no fatal PEs; high event rate due to distal DVTs and screening asymptomatic patients
Hickey, 2018	SR/MA	Immobilized foot or ankle trauma	LMWH, Fondaparinux, No ASA	Sonography or venography	No analysis	LMWH reduces incidence of symptomatic VTE	10 symptomatic DVT prevented for every major bleed	Not discussed	Significantly decreases risk of symptomatic DVT, NNT 86; no significant difference in symptomatic PE
Horner, 2020	SR/MA	Lower extremity immobilization	LMWH, Fondaparinux, ASA	Sonography, venography, or clinically detected	No association with patient characteristics, type of injury, treatment, or duration	Fondaparinux or LMWH effective for reducing odds of both asymptomatic and clinically detected VTE	Very uncommon thus effect uncertain	Fondaparinux is likely more effective than LMWH, and both significantly decrease risk	Fondaparinux is likely more effective than LMWH, and both significantly decrease risk (note: only 1 of the included studies focused on CIVTE); event rates for symptomatic DVT and PE low
Patterson, 2017	SR/MA	Operatively managed fractures of the tibia and distal bones	LMWH only	Sonography or venography	No analysis	Routine prophylaxis not necessary in patients without risk factors for VTE	None occurred	LMWH significantly reduced risk of VTE, NNT = 31	LMWH did not significantly reduce the risk of CIVTE, NNT= 584
Testroote, 2014	SR/MA	Lower extremity immobilization, outpatient	LMWH only	Sonography or venography	No analysis	Administer LMWH during the entire period of immobilization	Very rare, does not outweigh benefit	LMWH significantly decreases VTE	No analysis
Zee, 2017	SR/MA	Lower extremity immobilization, outpatient	LMWH, Fondaparinux, No ASA	Sonography, venography, or clinically detected	No analysis	LMWH reduced the incidence of VTE in immobilization	Very rare	LMWH significantly decreases VTE	No analysis

ASA = acetylsalicylic acid or aspirin, CIVTE = clinically important venous thromboembolism, DVT = deep venous thrombosis, LMWH = low molecular weight heparin, MA = meta-analysis, NNT = number needed to treat, PE = pulmonary embolism, SR = systematic review, VTE = venous thromboembolism.

Major bleeding incidence is defined as clinically apparent, requiring transfusion, retroperitoneal/intracranial, or resulting in termination of treatment; minor bleeding events such as hematomas are not included.

Table 5

Summary of clinical practice guidelines.

Organization	Year	Chemoprophylaxis recommended?	Strength	ASA recommendations	Notes
American College of Chest Physicians (CHEST)	2012	Not for isolated lower extremity fracture requiring immobilization	Grade 2C (weak confidence, low quality of evidence)	Not discussed	None
American Academy of Orthopaedic Surgeons (AAOS)	2011	Yes (agent unspecified)	Moderate	Discontinue antiplatelet therapy 2 weeks prior to arthroplasty for bleeding risk	Based on THA/TKA only, not LE fracture
National Institute for Health and Care Excellence (NICE)	2018	Consider LMWH or fondaparinux for immobilization if risk of VTE > bleeding (risk factors unspecified), or if anesthesia >90 minutes	"Close balance between benefits and harms"	Not discussed	Immobilization "up to 42 days"
Orthopaedic Trauma Association (OTA) Expert Panel	2015	Not for isolated lower extremity fracture without risk factors (unspecified) if able to independently mobilize	Moderate	Aspirin recommended if LMWH not feasible	Does not address patients unable to mobilize
American College of Foot and Ankle Surgeons (ACFAS)	2015	Not routinely	Consensus	ASA not supported by evidence	Best discussion of risk factors, though consensus-based
		Yes for high-risk patients, use multi-modal prophylaxis	Consensus		
Orthopaedic Trauma Association (OTA), Ankle Fractures	2019	Not routinely	Strong	Not discussed	None
		Consider in patients with risk factors (unspecified)	Moderate		

ASA = acetylsalicylic acid or aspirin, LE = lower extremity, LMWH = low molecular weight heparin, THA = total hip arthroplasty, TKA = total knee arthroplasty, VTE = venous thromboembolism.

difference in symptomatic VTE rates between aspirin and no treatment.[42] Stronger evidence regarding aspirin is likely forthcoming in 2 ongoing trials: PREVENTion of Clot in Orthopaedic Trauma (NCT02984384), and A Different Approach to Preventing Thrombosis (NCT02774265).

4.1. Limitations

There are limitations to the design of our study. The CONSORT 2010 elaboration document states that the guidelines are not designed to be qualitative.[43] However, Cowan et al successfully implemented the older CONSORT guidelines as a qualitative tool. Although 4 of 9 studies were published before CONSORT 2010, we feel it still provides a reasonable qualitative assessment, and supplementing with a second qualitative tool complements its faults. Our analysis, like all analysis on the topic, is encumbered by the heterogeneity of the available studies, particularly proportion of fractures and operative management. We partially mitigated this weakness by using fracture-specific comparisons when provided. We also included tibia shaft fractures due to the limited number of studies matching our inclusion criteria. These fractures may have been treated with intramedullary fixation and immediate weight bearing, similar to management of arthroplasty or femur fractures, and could be a source of excessive heterogeneity.[44] We chose to do so because the applicable studies lacked specificity regarding fixation methods and to capture the remaining fractures most relevant to our purpose.

5. Conclusions

The evidence informing recommendations for VTE chemoprophylaxis following traumatic injuries distal to the knee is limited by qualitative concerns and the low incidence of clinically important venous thromboembolism. Recommendations continue to rely on poorly defined risk stratification. Creation of a practical, externally validated risk assessment tool will require high-quality studies of relevant risk factors. Future studies should utilize symptomatic events as the outcome measure given evolving understanding of VTE pathophysiology. There is a paucity of high-quality studies investigating aspirin, but recommendations in arthroplasty and hip fracture literature suggest a possible role that merits further investigation.

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