Minor trauma and venous thromboembolism: the threshold for antithrombotic prophylaxis

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Abstract

Trauma is an established risk factor for venous thromboembolism (VTE). Whether minor trauma is linked to greater risk of VTE remains unclear given that many studies evaluating trauma and VTE risk have not differentiated risk by trauma severity. Furthermore, the underlying risk of VTE is not uniform across all injured patients. While it is generally accepted that severely and moderately injured patients requiring prolonged hospitalization benefit from early and consistent administration of thromboprophylaxis, the threshold for its initiation following minor injury or in patients managed in an ambulatory setting is less clear. This review will describe how trauma is classified, summarize the evidence of the risk of VTE in patients with minor trauma, and guide clinicians through an approach to individualize these treatment decisions based on contemporary evidence. Guidance will be provided for both injured patients requiring hospitalization (who may have severe, moderate or minor trauma), and those suitable to be managed in an ambulatory setting (minor trauma).

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is common following traumatic injury and is associated with increased morbidity and mortality.[1] A recent meta-analysis of nearly two million trauma patients demonstrated that the median (Q1 to Q3) incidence of post-traumatic VTE was 7% (6-9%) in studies with screening ultrasound and 3% (2-7%) in studies without screening ultrasound.[2] While greater VTE risk following significant trauma has been established, whether minor trauma predisposes to VTE is less clear.

For all trauma types, the predisposition to VTE is likely multifactorial including venous stasis from immobilization, hypercoagulability from tissue injury as well as impaired fibrinolysis.[3] As such, the early administration of pharmacological thromboprophylaxis (e.g., prophylactic dosing of low molecular weight heparin [LMWH]) for most trauma patients is a mainstay of evidence-based care and has been endorsed by several clinical practice guidelines.[4,5] However, the risk of VTE is not uniform across all injured patients. A prognostic meta-analysis of trauma patients demonstrated, with moderate or higher certainty of association, that older age, obesity, male sex, higher injury severity score, pelvic injury, lower extremity injury, spinal injury, delayed administration of thromboprophylaxis, need for surgery and use of tranexamic acid, were associated with a higher risk of VTE in this patient population.[2] While it is generally accepted that severely and moderately injured patients requiring prolonged hospitalization benefit from early and consistent administration of thromboprophylaxis, the threshold for its initiation following minor injury is less clear. This review will describe how trauma is classified, summarize the evidence that minor trauma is associated with elevated VTE risk, and guide clinicians through an approach to individualize these treatment decisions based on contemporary evidence. Guidance is provided for both injured patients requiring hospitalization (who may have severe, moderate or, less often, minor trauma), and those suitable to be managed in an ambulatory setting (typically minor trauma).

What is trauma?

Trauma care refers to the diagnosis and treatment of a wide array of conditions suffered as a consequence of physical injuries.[6] Injury accounts for over 16,000 deaths worldwide per day and 16% of the global burden of disease. Approximately 90% of all traumas are disproportionately concentrated in low- and middle-income countries. Trauma may range from isolated limb injuries in an ambulatory patient to severe life-threatening injuries requiring prolonged hospitalization and rehabilitation. Despite this important burden of disease, there is no global consensus with regards to the identification and care of trauma patients.[7] Even among high-income countries, less than half of the institutions have a well-defined and documented trauma system, and even fewer have a trauma registry.[7] For these reasons, the provision of trauma care is unfortunately limited in many instances by heterogeneity with regards to patient identification, definitions of conditions, and universally adopted standards of care.

Defining trauma severity

Trauma is inherently heterogeneous. Therefore, within organized trauma systems, the most common method for defining trauma severity involves the use of injury severity scoring systems, which typically provide an aggregation of a patient's anatomic or physiologic injury burden. These scores act to standardize injury burden across a variety of anatomic patterns to assist with risk adjustment and benchmarking across trauma registries.[8,9] The Injury Severity Score (ISS) is a commonly used anatomical scoring system that provides an overall score from 1 to 75 based on the highest Abbreviated Injury Scale (AIS) scores from the 3 most severely injured body regions.[10] Within the ISS scoring system, major trauma is most commonly defined as ISS ≥16, moderate trauma as ISS 9-15, and minor trauma is considered any combination of injuries with ISS <9.[11] To put this in context, the majority of lower extremity injuries only requiring immobilization or outpatient surgery would be classified minor (ISS<9), assuming there are no concomitant injuries. Most fractures are classified as minor, though severe fracture (e.g., femur) would be rated higher (ISS ≥9). A patient with multiple injuries that in isolation would be classified as minor may, however, have a total injury burden which leads to classification as moderate or severe trauma given the summative nature of the score.

Though an important tool, the ISS framework is characterized by important limitations. It is dependent on the accuracy of the contributing AIS codes, which are periodically updated to better reflect modern clinical practice though with meaningful implications for interpretation of patient outcomes across settings and time.[9] For example, the re-classification of injuries in the 2008 update resulted in a 20% decrease in patients meeting the "major trauma" threshold for ISS.[12] This change resulted in a perceived increase in mortality, length of stay, and need for intensive care unit admission among major trauma patients.[8,13] Similar derivatives of the ISS framework include the New Injury Severity Score (NISS),[14] the Trauma and Injury Severity Score (TRISS),[15] and the International Classification of Disease (ICD)-based Injury Severity Score (ICISS).[16] However, a systemic review evaluating the comparative predictive performance of these tools demonstrated that high-quality studies were limited, and that performance was highly variable due to important heterogeneity in eligibility criteria and computational methods employed by trauma registries.[17] In addition, the calculation of an injury severity score is typically performed retrospectively, allowing for delayed identification of injuries missed on initial assessment, of which up to 25% may be clinically significant.[18] Therefore, the utility of injury severity scoring frameworks for real-time clinical decision making is limited, especially as it pertains to VTE risk stratification among admitted trauma patients.

For the purposes of this review, trauma will be considered from two different perspectives: 1) the injured patient requiring hospitalization (who may have severe, moderate or, less often, minor trauma); and 2) the injured patient suitable for ambulatory care (typically minor trauma).

Venous thromboembolism risk following minor trauma

Trauma is an established VTE risk factor[1,2] (see above) and this is reflected in clinical practice guidelines which recommend pharmacological thromboprophylaxis for many hospitalized trauma patients.[4,5] Whether minor trauma is linked to greater VTE risk is less clear, since many studies evaluating trauma and VTE risk have not differentiated risk by trauma severity. The Multiple Environmental and Genetic Assessment of risk factors for venous thromboembolism (MEGA) case-control study is one of the few to explicitly evaluate the role of minor trauma in VTE risk.[19] For this analysis, minor injury was defined with a more conservative definition than ISS <9. The authors classified injuries such as minor sural muscle ruptures and ankle sprains as minor, while injuries requiring a plaster cast or extended bed rest were considered more severe. Minor injury was associated with a 3-fold greater risk of VTE. The association was present only for minor injuries located in the leg, and strongest for injuries that occurred within four weeks of the VTE event.[19]

The association between minor trauma and VTE risk is inherently challenging to study. MEGA was a well-designed case-control study. However, injuries were assessed via administration of questionnaires to cases and controls after the VTE event, therefore, it is possible that there was some recall bias. Cohort study designs also pose challenges for rigorously addressing this research question. Prospective cohorts typically only assess exposure status at infrequent intervals, and would, therefore, miss many acute injury occurrences that could provoke VTE events. Retrospective cohorts dependent on medical records would also miss minor injuries for which the individual did not seek medical care. Of course, confounding is also a potential threat to validity for all observational study designs.

In the absence of additional data on the relationship between minor trauma and VTE risk, it seems reasonable to hypothesize a dose-response effect, whereby VTE risk would be highest among those with severe trauma, intermediate among those with moderate trauma, and lowest among those with minor trauma. This attributable risk is likely multifactorial related to venous stasis from immobilization, hypercoagulability from prothrombotic changes following tissue injury, and impaired fibrinolysis.[3]

We will review VTE risk stratification and guidelines for thromboprophylaxis for injured patients requiring hospitalization, and those suitable for management in an ambulatory setting.

The injured patient requiring hospitalization

The recent clinical practice guidelines for thromboprophylaxis sponsored by the American Association for the Surgery of Trauma / American College of Surgeons Committee on Trauma (AAST / ACS-COT)[5] and those by the Western Trauma Association (WTA)[4] offer a more pragmatic approach. Both guidelines suggest that the majority of hospitalized trauma patients should receive pharmacological thromboprophylaxis with the exception of ambulatory patients with expected length of stay <24 hours. This is likely best achieved with LMWH (e.g., enoxaparin, tinzaparin, dalteparin, etc.), as it has been demonstrated, with moderate certainty, to reduce the risk of VTE as compared to subcutaneous administration of unfractionated heparin.[20] The WTA provides additional clarification that patients capable of ambulation but who are confined to bed due to intoxication, restraints or other reasons likely also warrant pharmacological thromboprophylaxis.[4] These recommendations are based on extrapolations from existing clinical decision rules (CDR) that predict the risk of VTE following traumatic injury.

Venous thromboembolism risk stratification

Several CDR have been developed and validated to stratify patients with traumatic injuries according to their underlying risk of VTE and help clinicians make a decision about initiation of pharmacological thromboprophylaxis.[5] The Trauma Embolic Scoring System (TESS) incorporates age, ISS, obesity, need for mechanical ventilation, and lower extremity fracture to create a score between 0 and 14, and was validated using the National Trauma Data Bank in the United States.[21] A TESS score of <6 identifies patients at low risk of VTE. The sensitivity and specificity of the TESS score cutoff of 6 to identify low-risk patients were 82% and 84%, respectively. However, external validation studies have demonstrated mixed results.[22,23] Similarly, the Risk Assessment Profile (RAP) score is a complex CDR that incorporates underlying conditions such as prior thrombotic history, iatrogenic factors (e.g., recent surgical procedures, etc.), injury-related factors (e.g., spinal or pelvic fractures, etc.), and age.[24] A RAP score of ≥5 selects patients at high-risk of VTE complications. Predictive performance at external validation was also highly variable across patient cohorts,[25-27] offering 82% sensitivity and 57% specificity in intermediate-risk patients, but only 15% sensitivity and 97% specificity in high-risk patients.[27] Furthermore, the reliance on highly dynamic prognostic variables (e.g., Glasgow Coma Scale, etc.) results in frequent fluctuations in the predicted risk, which may hinder the clinical utility of the CDR.[25] Additional observational studies have also demonstrated that a clinically significant number of patients with traumatic injury who develop VTE were classified as low-risk by both the TESS and RAP scores.[28] Furthermore, the absence of clinically meaningful prognostic variables and important limitations in both models' development methodology have limited their incorporation into routine clinical practice. While there is a clinical need for an evidence-based VTE risk stratification tool to guide decisions about thromboprophylaxis in patients with traumatic injury, it remains unclear whether the existing CDR are sufficiently validated for this purpose and ready to be incorporated into routine clinical practice.[28] Ultimately, clinicians should individualize treatment decisions based on the risks and benefits of thromboprophylaxis with an understanding that older age, obesity, male sex, higher injury severity score, pelvic injury, lower extremity injury, spinal injury, delayed thromboprophylaxis, need for surgery and tranexamic acid use are likely to increase the risk of VTE.[2]

The bottom line

Most injured patients requiring hospitalization will likely benefit from pharmacological thromboprophylaxis with LMWH, especially those with restricted mobility or additional risk factors (Table 1). A variety of CDR may assist in stratifying patients according to their underlying risk of VTE and help with individualized decision-making, but clinicians should be aware of their potential limitations.

The injured patient suitable for ambulatory care

Many injured patients do not require hospitalization and can be managed in the ambulatory care setting (e.g., isolated limb injuries). Injury patterns in this patient population may include extremity fractures, often requiring immobilization and/or ambulatory surgery. These patients would often be classified as having a minor injury by an ISS <9.

Extremity fractures

Clinical guidelines typically recommend pharmacological thromboprophylaxis to reduce the risk of death and VTE-related complications after traumatic orthopedic injuries.[29] The Prophylaxis in Non-major Orthopaedic Surgery (PRONOMOS) trial was an international, parallel-group, randomized, double-blind, non-inferiority trial enrolling 3,604 adult patients undergoing lower-limb non-major orthopedic surgery who were at risk for VTE.[30] Patients were randomized to receive rivaroxaban 10 mg daily or enoxaparin 40 mg subcutaneously daily. Rivaroxaban was more effective than enoxaparin for the prevention of VTE (0.2% and 1.1% in patients receiving rivaroxaban and enoxaparin, respectively; Risk Ratio [RR] 0.2, 95% Confidence Intervals (CI): 0.09-0.75) without any important difference in major bleeding (0.6% and 0.7% in patients receiving rivaroxaban and enoxaparin, respectively) during the period of immobilization after non-major orthopedic surgery of the lower extremities.[30] More recently, the Prevention of Clot in Orthopaedic Trauma (PREVENT CLOT) study was a pragmatic, multicenter, randomized, non-inferiority trial conducted to examine the effectiveness and safety of thromboprophylaxis with aspirin (81 mg twice daily) as compared to LMWH (enoxaparin 30 mg SC BID) in 12,211 patients with a fracture of an extremity (i.e., anywhere from hip to midfoot or shoulder to wrist) that had been treated operatively, or who had any pelvic or acetabular fracture.[31] Thromboprophylaxis with aspirin was non-inferior to LMWH in preventing all-cause death at 90 days (0.78% and 0.73% in patients receiving ASA and enoxaparin, respectively; difference 0.05 percentage points, 95% CI: -0.27 to 0.38). The incidence of pulmonary embolism (1.49% in each group), bleeding complications, and other serious adverse events were also similar in the 2 groups. However, DVT was lower in the enoxaparin group (1.71%) than the aspirin group (2.51%) (difference, 0.80 percentage points; 95% CI: 0.28-1.31).[31] It is important to highlight that patients enrolled in the PREVENT-CLOT trial might have been at a relatively lower risk of VTE (mean age 44.6 years, median ISS = 9 with interquartile range 4-10, and 27.4% of upper extremity injury) compared to other trials. The median ISS = 9 is worthy of note, since, as described above, an ISS of <9 is typically used to define minor injury. Therefore, this study included a mix of minor and more severe injuries.

Lower limb immobilization

In patients with temporary lower limb immobilization after trauma, the absolute risk of symptomatic VTE is relatively low and estimated to be approximately 2%.[32] However, this risk may be decreased to 1% with appropriate pharmacological thromboprophylaxis. Such a reduction is likely to be clinically important given the high prevalence of such injury patterns. A recent Cochrane meta-analysis including 8 randomized control trials (RCT) (N=3,680 patients) demonstrated, with moderate certainty evidence, that the use of LMWH in outpatients reduced DVT when immobilization of the lower limb was required (meta-analysis odds ratio: 0.45 [95% CI: 0.33-0.91]).[33] Similarly, a network meta-analysis including 14 RCT (N=8,198 patients) demonstrated that, compared to the control group, rivaroxaban, fondaparinux, and LMWH were associated with a significant risk reduction of major VTE (Tables 1 and 2).[34] In addition, no increase in the major bleeding risk was observed with either treatment. Overall only 6 major bleeding events were reported (rivaroxaban [N=0], ASA [N=0], LMWH [N=5], fondaparinux [N=1]) supporting a favorable risk benefit ratio for using thromboprophylaxis in this patient population. Rivaroxaban was noted to have the highest likelihood of being ranked top in terms of efficacy and net clinical benefit. Similarly, another systematic review and economic evaluation confirmed that thromboprophylaxis for lower-limb immobilization due to injury is clinically effective (reducing VTE) and cost effective, resulting in a net gain of quality-adjusted life years.[35]

Venous thromboembolism risk stratification

Although patients with lower limb injuries are at higher risk of VTE, applying a population-based approach and providing thromboprophylaxis to all these patients is unlikely to be effective.[36] Hence, CDR have been developed to stratify patients according to their underlying risk of VTE. These CDR enable clinicians to consider thromboprophylaxis in patients at high risk of VTE and avoid potential bleeding complications from anticoagulants in patients at low risk of thrombotic complications. The Leiden Thrombosis Risk Prediction for Patients with Cast Immobilization TRiP(cast) score was derived using data from a large population-based case-control study and included 19 items with associated scores ranging from 1 to 5. The Leiden-TRiP(cast) score was retrospectively validated in a database.[37,38] However, the Leiden-TRiP(cast) score did not account for the severity of trauma, and absolute risks for individual patients were computed according to the case-control setting, thus limiting its clinical utility.[39] Hence, a second CDR score, the Trauma, Immobilization and Patients Characteristics (TIP) score stratifying patients with lower extremity non-surgical trauma requiring immobilization, was developed.[40] The TIP score included 30 variables (patients [N=14], trauma [N=13], and immobilization [N=3] characteristics) and was developed through a Delphi process including an international panel of experts. Although the model performed well, its usability in clinical settings was questionable due to the large number of variables. Given that most variables from the Leiden-TRiP(cast) score were also incorporated in the TIP score, both CDR were combined to develop the Throm-

Table 1. Types of thromboprophylaxis evaluated following traumatic injury requiring lower extremity immobilization.

Thromboprophylaxis	Dosing
Nadroparin	2,850 IU SC
Certoparin	3,000 IU SC
Reviparin	1,750 IU SC
Tinzaparin	3,500 IU SC
Dalteparin	5,000 IU SC
Enoxaparin	40 mg SC
Fondaparinux	2.5 mg SC
Rivaroxaban	10 mg orally

IU: International Unit; SC: subcutaneous.

bosis Risk Prediction for Patients with Cast Immobilisation TRiP(cast) score (Table 3).[41] The TRiP(cast) score has a total of 14 variables (patients [N=12]; e.g., personal or family history of VTE), trauma severity [N=1], and immobilization [N=1]). Each variable can be calculated on a scale of 1 to 4 and the sum of these scores corresponds to the overall TRiP(cast) score. A TRiP(cast) score <7 identifies patients at low risk of VTE (mean absolute risk = 0.8%), whereas a score ≥7 is associated with a high-risk of VTE (mean absolute risk = 2.5%), for which pharmacological thromboprophylaxis may be potentially beneficial.[41]

More recently, the CASTING study was a stepped-wedge, multicenter, cluster-randomized trial enrolling 2,120 patients with lower limb trauma requiring immobilization without

Table 2. Characteristics of studies assessing the efficacy and safety of different thromboprophylaxis strategies in injured patients eligible for ambulatory care.[34]

N and type of RCT (N of patients)	Years of publication	Intervention (N of studies)	Type of injury (N of patients)	Management (N of patients)
14 RCT (8,198) 7 double-blind (3,257) 4 open with blinded adjudication (3,635)	1993-2021	LMWH (13) Fondaparinux (1) Rivaroxaban (1) ASA (1)	Fractures and/or Achilles tendon rupture (5,530)	Conservative (2,850) Surgical (2,817) Conservative and surgical (2,531) Lower limb trauma (2,668)

ASA: acetylsalicylic acid; LMWH: low molecular weight heparin; N: number; RCT: randomized controlled trial.

Table 3. TRiP(cast) score.

	Score
Trauma (choose 1 – most severe trauma)	
High-risk	
Fibula and/or tibia shaft fracture; tibial plateau fracture; Achilles tendon rupture	3
Intermediate-risk	
Bi or tri-malleolar ankle fracture; patellar fracture; ankle dislocation; Lisfranc injury; severe knee sprain (with edema/hemarthrosis); severe ankle sprain (grade 3)	2
Low-risk	
Single malleolar ankle fracture; patellar dislocation; (meta)tarsal bone(s) or forefoot fracture; non-severe knee sprain or ankle sprain (grade 1 or 2); significant muscle injury	1
Immobilization, cast	
Upper-leg	3
Lower-leg	2
Foot (ankle free) or any semi-rigid without plantar support	1
Other or bracing with plantar support	0
Patients' characteristics	
Age in years	
<35	0
≥35 and <55	1
≥55 and <75	2
≥75	3
Male sex	1
BMI	
≥25 and <35 kg/m^2	1
≥35 kg/m^2	2
Family history of VTE (first-degree relative)	2
Personal history of VTE or known major thrombophilia	4
Current use of oral contraceptives or estrogenic hormone therapy	4
Cancer diagnosis within the past 5 years	3
Pregnancy or puerperium	3
Other immobilization within the past 3 months	2
Hospital admission, bedridden or flight >6 hr; lower limb paralysis or surgery within the past 3 months	2
Comorbidity	
Heart failure, rheumatoid arthritis, chronic kidney disease, COPD, IBD	1
Chronic venous insufficiency (varicose veins)	1

BMI: body mass index; COPD: chronic obstructive pulmonary disease; hr: hours; IBD: inflammatory bowel disease; VTE: venous thromboembolism.

Table 4. Summary of suggestions for thromboprophylaxis use in patients with minor trauma.

Injured patient requiring hospitalization
Most injured patients requiring hospitalization are likely to benefit from pharmacological thromboprophylaxis with LMWH.
Injured patient suitable for ambulatory care
Most injured patients with fractures requiring orthopedic surgical procedures are likely to benefit from thromboprophylaxis (LMWH, rivaroxaban or ASA).
Injured patients requiring lower limb immobilization without surgery and a TRiP(cast) score <7 are unlikely to benefit from thromboprophylaxis.

ASA: acetylsalicylic acid; LMWH: low molecular weight heparin; TriP(cast): Leiden Thrombosis Risk Prediction for Patients with Cast Immobilization TRiP(cast) score.

surgery across 15 emergency departments in France and Belgium.[42] The TRiP(cast) score was utilized to identify patients at low risk of VTE for whom thromboprophylaxis can be safely withheld (i.e., TRiP(cast) score <7).[41] Approximately 77% of patients had a TRiP(cast) score <7 and did not receive anticoagulant treatment. The symptomatic venous thromboembolism rate was only 0.7%, allowing the authors to conclude that a large proportion of patients with lower limb trauma and immobilization could safely avoid thromboprophylaxis (Table 4).

The bottom line

Injured patients suitable for ambulatory care should be risk stratified based on factors including the presence of fractures, the need for surgery, and the need for lower limb immobilization. The majority of patients with fractures requiring orthopedic surgical procedures are likely to benefit from thromboprophylaxis (LMWH, rivaroxaban or ASA), although the evidence and recommendations for ideal choice of agent is mixed.[29] Among patients requiring lower limb immobilization without surgery, the TRiP(cast) may help identify patients at sufficiently low risk of VTE to safely avoid thromboprophylaxis.

Unique challenges in the use of venous thromboembolism prophylaxis for trauma patients

Trauma care clinicians face several challenges when making decisions regarding the appropriateness and timing of pharmacological thromboprophylaxis. Physicians' clinical appraisal of the perceived risk of VTE, balancing this with the competing risk of bleeding in order to initiate pharmacological thromboprophylaxis following a traumatic injury is heterogenous.[43-45] In addition, factors such as personal opinions, disagreement among clinicians, system-based barriers, and lack of awareness contribute to inconsistency in clinical care and deviations from practice guideline recommendations.[43,46] Furthermore, the persistence (e.g., nurse's non-administration) and compliance (e.g., patient refusal) to pharmacological thromboprophylaxis remains an important knowledge gap. It is unclear how consistently thromboprophylaxis is administered following its initiation.[46] Trauma patients are particularly vulnerable for challenging medication compliance due to a high predisposition for poor socioeconomic status, high-risk health behaviors, lower educational background, and racial disparity.[46,47]

Conclusions

Venous thromboembolism is a common and clinically important contributor to morbidity and mortality in patients following a traumatic injury, regardless of injury severity. Most injured patients requiring hospitalization will likely benefit from pharmacological thromboprophylaxis. Injured patients suitable for ambulatory care should be risk stratified based on additional risk factors (e.g., need for surgery, presence of fracture, etc.) (Table 4). Among patients requiring lower limb immobilization without surgery, the TRiP(cast) may help identify patients at sufficiently low risk of VTE to safely avoid pharmacological thromboprophylaxis.

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Contributions

AT was responsible for narrative review conception and wrote the manuscript. PLL and MC provided key revisions to the manuscript.

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