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Approaches for Optimizing Venous Thromboembolism (VTE) Prevention in Injured Patients: Findings from the Consensus Conference to Implement Optimal VTE Prophylaxis in Trauma

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Abstract

Venous thromboembolism (VTE) is a major issue in trauma patients. Without prophylaxis, the rate of deep venous thrombosis approaches 60%, and even with chemoprophylaxis may be nearly 30%. Advances in VTE reduction are imperative to reduce the burden of this issue in the trauma population. Novel approaches in VTE prevention may include new medications, dosing regimens, and extending prophylaxis to the post-discharge phase of care. Standard dosing regimens of low molecular weight heparin (LMWH) are insufficient in trauma, shifting our focus towards alternative dosing strategies to improve prophylaxis. Mixed data suggest that anti-Xa guided dosage, weight-based dosing, and thromboelastography are among these potential strategies. The concern for VTE in trauma does not end upon discharge, however. The risk for venous thromboembolism in this population extends well beyond hospitalization. Variable extended thromboprophylaxis regimens utilizing aspirin, LMWH, and direct oral anticoagulants have been suggested to mitigate this prolonged VTE risk, but the ideal approach for outpatient VTE prevention is still unclear. As part of The 2022 Consensus Conference to Implement Optimal Venous Thromboembolism Prophylaxis in Trauma, a multidisciplinary array of participants, including physicians from multiple specialties, pharmacists, nurses, advanced practice providers, and patients met to attack these issues. This paper aims to review the current literature on novel approaches for optimizing VTE prevention in injured patients and identify research gaps which should be investigated to improve VTE rates in trauma.

Keywords

Venous thromboembolism; thromboprophylaxis; low molecular weight heparin; unfractionated heparin; trauma

Introduction

Venous thromboembolism (VTE) is a highly pervasive issue in trauma patients. Without chemoprophylaxis, rates of deep venous thrombosis (DVT) are as high as 58%.(1) Despite advances in prophylaxis, VTE continues to be a significant cause of morbidity and mortality in trauma. Low molecular weight heparin (LMWH) has demonstrated significant efficacy over unfractionated heparin (UH) in this population, with DVT rates reported up to 31% with LMWH versus 44% with UH.(2) Although we have made some advances in VTE reduction, there remain significant opportunities for improvement. Approaching this issue with novel, new strategies may allow us to optimize VTE prevention and ultimately reduce the burden of this issue in the trauma population. These novel approaches may include new medications (i.e., aspirin, direct oral anticoagulants), dosing regimens (i.e., based on weight or lab values), and extending prophylaxis to the post-discharge phase of care.

As part of The 2022 Consensus Conference to Implement Optimal Venous Thromboembolism Prophylaxis in Trauma, a multidisciplinary array of participants,

including physicians from multiple specialties, pharmacists, nurses, advanced practice providers, and patients met to attack this issue.(3)

This paper aims to review the current literature on novel approaches for optimizing VTE prevention in injured patients and identify research gaps that could be investigated to improve VTE rates in trauma. (Table 1)

Current Management Strategies for the Prevention of VTE in Trauma

Alternative Dosing Strategies for Low Molecular Weight Heparin

Low molecular weight heparin (LMWH) has consistently demonstrated superiority over unfractionated heparin (UH) for the prevention of DVT and pulmonary embolism (PE).(2, 4) The ideal dosing regimen of LMWH, however, continues to be under investigation. (Table 2)

Using Anti-Xa Levels to Dose Adjust Low Molecular Weight Heparin—Standard 30-milligram (mg) twice-daily administration in trauma patients often results in sub-prophylactic anti-Xa levels and may be inadequate chemoprophylaxis for VTE.(5–8) Costantini et al found that only 29.5% of patients had prophylactic anti-Xa levels when this standard dosing was given.(9) Similarly, Ko et al. found that initial dosing was suboptimal in 83.9% of patients when anti-Xa levels were used to guide dose adjustments, with the majority requiring dose adjustments to 40 mg twice daily.(6) Monitoring anti-Xa has been suggested for optimization of LMWH dosing because serum levels are prone to fluctuations based on renal function, weight, bioavailability, and coagulation profile, all factors subject to variability in trauma and critical illness. Appropriate target dosing for LMWH include peak levels of 0.2–0.4 international units (IU)/milliliter (mL) or trough levels of 0.1–0.2 IU/mL.(10)

Evidence has been inconsistent, however, regarding the correlation between sub-prophylactic anti-Xa levels and rates of VTE.(6, 11–14) The literature outside of trauma surgery suggests that dose adjustment leads to lower VTE rates. Anti-Xa guided dosing in surgical oncology patients has been associated with fewer VTE without increasing bleeding.(15) In trauma patients, some studies report significantly lower venous thromboembolism rates when doses were altered accordingly.(6, 11, 16–18) For example, Ko et al. found that dose adjustment by anti-Xa level reduced VTE from 7.6% to 1.1%.(6) Similarly, Singer et al. observed that anti-Xa guided LMWH dosing reduced VTE from as high as 20% to 7%.(11) A recently published systematic review and meta-analysis found that anti-Xa based dosing of LMWH may reduce DVT (adjusted odds ratio (aOR) 0.52, 95% CI 0.40 to 0.69), PE (aOR 0.48, 95% CI 0.30 to 0.78) or any VTE (aOR 0.54, 95% CI 0.42 to 0.69).(18) In contrast, other trauma studies have not demonstrated a difference in rates of venous thromboembolism despite prophylactic dosing.(13, 17, 19)

Additionally, data suggest a correlation between antithrombin-III (ATIII) deficiency and sub-prophylactic anti-Xa levels in trauma patients.(13, 20) Heparin enhances anticoagulant activity of ATIII, therefore UH and LMWH have poor efficacy in the setting of ATIII deficiency. Connelly et al. found ATIII deficiency in 18.9% of trauma patients and 33% of patients with VTE.(21) Similarly, in a recent prospective cohort, Vincent et al. demonstrated

that antithrombin activity decreased universally immediately after injury but rebounded in most patients. Those with VTE, however, did not have this rebound. In fact, for every 10% reduction in ATIII activity, there was a 1.5-fold increase in VTE incidence.(22) The implications and frequency of ATIII deficiency in the trauma population are still under investigation but may be useful in understanding strategies for prophylactic anticoagulation.

Weight-Based Dosing of Low Molecular Weight Heparin—Practices of dose adjusting LMWH vary across centers. Current recommendations from 2021 by the American Association for the Surgery of Trauma state that dose adjustment may be considered in trauma if there is a low bleeding risk and weight-based dosing should be utilized for those with body mass index (BMI) over 30-kilograms(kg)/meter(m)^2.(23) In addition, the Western Trauma Association recommends consideration of initiating LMWH dosing at 40-mg twice daily in adults under 65, weighing more than 50 kg, and creatinine clearance greater than 60-mg/deciliter(dl); reserving the “usual” 30-mg twice daily for those older than 65, weighing less than 50-kg, or having reduced creatinine clearance.(24)

Weight-based dosing has been advocated for in trauma patients with normal creatinine clearance, with anti-Xa levels used to monitor the dose.(10) Multiple studies have shown that weight-based dosing results in more consistent prophylactic anti-Xa levels in patients with normal creatinine clearance.(25–29) In a single-center prospective cohort study, Strutsrim et al. found that both peak and trough anti-Xa levels were improved with weight-based LMWH dosing. They found that in those without weight-adjusted regimens, 34% of trough and 62% of peak anti-Xa levels were adequate, but with weight adjustment, 82% of trough and 97% of peak levels were prophylactic.(28) Weight-based dosing in populations where bleeding risk is of elevated concern, such as traumatic brain injury (TBI), is not currently recommended. However, to date, some early retrospective data suggest that weight-based dosing in TBI is safe. (2, 17)

Thromboelastography to Guide Chemoprophylaxis—The use of thromboelastography (TEG) has demonstrated efficacy in guiding hemorrhagic trauma resuscitation.(30) TEG has not been validated for monitoring pharmacologic VTE prophylaxis at this time, however. Several small studies have mixed/inconclusive data in this regard. Hypercoagulable TEG results may have some correlation with the incidence of VTE.(31–34) Cotton et al. found maximum amplitude (MA) to independently predict PE with an odds ratio (OR) of 5.8 if MA>72.(33) In a single center prospective cohort study, Brill et al. correlated increased MA (>75) and reduced Reaction (R) Time (<5 minutes) with increased rates of DVT in trauma patients (15.6 vs. 8%). On multivariate analysis, they demonstrated a significant association between hypercoagulable TEG and DVT (OR 2.41).(35) Additional studies have replicated similar findings.(31, 32, 34)

In contrast, a multicenter randomized clinical trial found no difference in rates of VTE or bleeding when TEG was used to guide LMWH dosing. They also found similar hypercoagulable TEG parameters and ATIII deficiency rates in the control group and the TEG-guided dose adjustment group.(21) An earlier single center randomized trial found that while TEG-adjusted LMWH dosing (using R time) led to a significant increase in anti-Xa activity, it did not correlate with reduction in VTE.(13)

Although TEG-guided LMWH dosing has not been validated, in trying to better understand clotting pathophysiology in trauma, TEG-based analyses have uncovered an interesting connection between platelets and injury-associated hypercoagulability. Several studies have implicated the role of platelets and increased clot strength in trauma-related hypercoagulability.(36, 37) For example, Kornblith et al. demonstrated that platelets had a greater contribution to clot strength than fibrinogen in injured patients.(36) Similarly, a phase II randomized controlled trial found strong correlation between platelet count and clot strength. There was also a relative increase in platelet contribution to clot strength with LMWH early in the study. They hypothesized that this might be due to heparin-induced platelet activation.(37) These findings suggest TEG's role with platelet mapping may be in better understanding and monitoring platelet activity in trauma.

Mechanical Prophylaxis and Mobilization

Mechanical prophylaxis has historically shown promise for reduction of VTE in trauma, however, pharmacologic prophylaxis has consistently been found to be more effective than sequential compression devices (SCDs)/mobilization.(4) In the rare event that chemoprophylaxis is not possible, intermittent pneumatic compression is recommended to reduce the risk of DVT.(10) Additionally, while mobilization is safe and reduces trauma patient deconditioning, it is likely insufficient on its own to prevent VTE. Lau et al. performed a systematic review looking at 18 studies and concluded that mobility alone did not result in reduced rates of VTE.(38) The misconception that mobile patients are at lower risk for DVT or PE may result in inappropriate prophylaxis following injury and preventable VTE. Ambulation therefore is encouraged but should not be considered a mode of VTE prophylaxis.

Prophylactic Inferior Vena Cava Filters

The placement of prophylactic inferior vena cava filters (IVCF) for VTE risk reduction in trauma is highly controversial. Despite abundant data supporting chemoprophylaxis for VTE prevention in trauma, a subset of patients remains at high risk for bleeding. Historically, prophylactic IVCF has been advocated in this population to reduce VTE risk. This practice has become increasingly debated, with limited data supporting its efficacy.(39) A multicenter randomized control trial demonstrated no difference in rates of symptomatic PE with prophylactic IVC filter in patients not on chemoprophylaxis within 72 hours of admission.(40) Although there may be a benefit in preventing fatal PE, an overall mortality benefit has not been demonstrated.(41–43) Therefore, current recommendations suggest considering prophylactic IVCF in only the most high-risk patients with contraindications to chemoprophylaxis due to ongoing, life-threatening bleeding. These patients should receive retrievable IVCFs that are removed as soon as they are no longer needed.(23)

Extended/Outpatient Thromboprophylaxis

The risk for VTE in hospitalized patients has been well documented and the utility of prophylaxis repeatedly validated.(1, 2) This risk does not end on hospital discharge, however.(44, 45) There are significant data that thrombosis may occur 30-days after discharge and has been documented up to 90 days in high-risk patients.(44, 46–52) The

utility of extended thromboprophylaxis to mitigate this risk is dependent on patient and disease related factors. (Table 3)

A large study using the California Office of Statewide Health Planning and Development Discharge (OSHPD) database found a 3.97% incidence of VTE in trauma, 45.5% of which were diagnosed after initial admission. Rates were highest 3 months after injury (10.28%), in patients with spinal cord injury (9.1%), pelvic fractures (4.2%), and vertebral fractures (3.6%). This risk dropped to 0.54% by 6 months and 0.25% by 12 months (nearly the baseline population risk).(44) Outside of the orthopedics literature, patients with TBI in the OSHPD database had a 1.31% incidence of VTE during index admission, rising to 2.83% by one-year post-injury. Additional risk factors at one year were discharge to extended care facilities, age over 64, index admission operation, and hospital length of stay >7 days.(45) Extended VTE risk has also been documented in a variety of general surgical and surgical oncological conditions, including patients undergoing surgery for inflammatory bowel disease(53, 54), ventral hernia(55), abdominal/pelvic cancer(56), and in mixed surgical populations(52).

Numerous agents have been studied for extended duration VTE prophylaxis, primarily in the orthopedic literature – including LMWH, warfarin, direct oral anticoagulants (DOACs), and aspirin. Both initial studies and subsequent meta-analyses suggest a significant reduction in VTE without concomitant increased risk of major bleeding in the first 14–35 days post-operatively (the highest VTE risk period).(46, 50, 57–59) LMWH is supported by orthopedic clinical guidelines for extended prophylaxis and is the first-line agent in the The American College of Chest Physicians (CHEST) guidelines for orthopedic surgery prophylaxis.(49, 60–62) Several other studies have evaluated oral agents compared to LMWH, both aspirin and DOACs, with mixed results in orthopedic patients.(24, 63, 64)

One study of two different doses of dabigatran daily vs. enoxaparin daily for total hip arthroplasty (THA) showed no difference in VTE, death, or major bleeding.(65) Conversely, a paper comparing apixaban twice daily vs. enoxaparin daily after THA found fewer VTE with apixaban.(66) Rivaroxaban similarly reduced total VTE in two studies comparing daily dosing vs. daily LMWH after total knee arthroplasty (TKA) or THA, though reductions in symptomatic VTE were varied.(64, 67) The level of bleeding risk posed by DOACs is also still unclear – a recent study of elderly hip fracture patients showed that those treated with DOACs (as opposed to LMWH) for extended prophylaxis had a significantly higher risk of bleeding (OR 2.8 [1.5–5.0]).(68) Most of the above DOAC studies have little if any evidence on hematomas and wound infection rates, a concern frequently raised by orthopedic surgeons.

Like the orthopedic literature, extended duration prophylaxis after abdominopelvic cancer surgery has been shown to reduce clinical VTE without increasing bleeding events. (48) Intermediate/high-risk cancer patients have reduced rates of VTE with outpatient prophylaxis. Current recommendations include administering prophylactic LMWH or DOACs in ambulatory cancer patients on systemic therapy, at elevated risk for VTE.(69–72)

Regarding duration of thromboprophylaxis, four weeks of pharmacologic prophylaxis from the time of injury is recommended in most high-risk patients.(61) Patients with spinal cord injury (SCI) and resultant motor dysfunction are considered to be at particularly high risk for VTE for up to 6 months following trauma, and consensus guidelines recommend ongoing VTE prophylaxis for at least 3 months post-injury.(73, 74)

Research Gaps and Remaining Questions Regarding Optimal VTE Prevention in Trauma

Following an in-depth discussion of the current evidence as noted above, conference attendees discussed gaps in the literature and their implications for clinical care. Our objective was to synthesize research questions and strategize ways to fill these gaps to identify new approaches for optimal VTE prevention. Below is a summary of our findings.

Low-Molecular Weight Heparin Dosing

Conflicting data regarding the correlation between anti-Xa levels and VTE rates may be related to difficulty in consistently obtaining appropriately timed anti-Xa levels. With timing of levels being so critical to dose adjustment, if anti-Xa values correlate with VTE risk, streamlining a way to ensure lab accuracy is critical. The ATIII/anti-Xa connection may address this issue. Studies investigating ATIII levels are ongoing, looking for a more consistent way to monitor LMWH activity.

Safety of dose adjusting and weight-based dosing of LMWH in trauma subpopulations such as TBI, spinal injury or solid organ injury has been suggested but not demonstrated in a prospective fashion. More data are needed to examine how to administer chemoprophylaxis safely and effectively in this patient population. Specifically, questions surrounding the risk for increased bleeding with elevated anti-Xa levels are largely unanswered and require additional investigation.

TEG has not demonstrated consistent reliability in correlating with rates of VTE when used to dose adjust LMWH. There may, however, be utility in utilizing TEG with platelet mapping to better clarify and monitor the role of platelets in trauma hypercoagulability. If such a role is confirmed, what, if any, would be the utility of antiplatelet agents for VTE prophylaxis in trauma patients?

Mechanical Prophylaxis and Mobilization

Pneumatic compression and mobilization strategies for VTE prevention have demonstrated limited impact on rates of VTE in the trauma population, especially in the setting of pharmacologic prophylaxis. With ongoing improvements in strategies for chemoprevention, the major question that remains is whether there is true utility in these modalities at all, and if they should be discontinued as approaches for prophylaxis. Early mobilization programs and/or SCDs alone may lead to a false impression of sufficient prophylaxis, potentially delaying/reducing adequate pharmacologic prevention. In addition, while compression stockings have been suggested for VTE prophylaxis, their use is associated with device-related pressure injury and may cause more harm than provide benefit.(75)

Prophylactic IVC Filters

The trend in the literature and practice is moving away from the use of prophylactic IVCF. Although there is a small trauma population that achieves benefit from IVCF placement, additional prospective evidence narrowing down these “high risk” patients is needed. Additionally, IVCF has fallen out of favor because they are often not removed, leading to increased rates of DVT and the potential for vascular complications.(76) Developing strategies to improve retrieval rates may optimize complication-free removal success.

Extended/Outpatient Thromboprophylaxis

There is a paucity of data evaluating post-discharge VTE risk in trauma patients, partially due to difficult patient follow-up in this population. With data suggesting a benefit in high-risk surgical and orthopedic patients, how these risks translate to trauma patients is unclear and requires more study. If in-hospital prophylaxis is suboptimal for adequate VTE prevention, there remain a number of unanswered questions to address this issue: What is the ideal agent for extended VTE prophylaxis? What is the optimal time frame to continue thromboprophylaxis after discharge? Should all trauma patients be considered “at-risk” or is there a “high-risk” subset that should receive extended chemoprevention? To that regard, should patients be risk stratified based on their injuries and other clinical factors in order to determine the appropriate agent and duration of prolonged thromboprophylaxis? Additionally, what is the risk for bleeding in these patients, and is it outweighed by the potential VTE reduction?

Conclusion

VTE is a major contributor to morbidity and mortality in trauma patients. Despite advances in chemoprophylaxis, rates of DVT and PE remain high. Evidence suggests that standard LMWH dosing regimens are insufficient in many trauma patients. The focus has shifted towards dose adjustment to improve prophylaxis. Similarly, extended outpatient regimens may play a role in optimizing chemoprevention. By utilizing current data and approaching this issue with novel, new strategies, we may achieve enhanced VTE risk reduction, and ultimately improve outcomes associated with this significant trauma burden.

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Table 1:

Summary of Strategies to Prevent Venous Thromboembolism in Trauma

VTE Prevention Strategy	Previously Accepted Practice Patterns	Evolving VTE Prophylaxis Evidence	Future Directions and Unanswered Questions
Alternative Low Molecular Weight Heparin (LMWH) Dosing Strategies	Fixed dosing of LMWH at 30-mg twice daily in trauma patients.	• Anti-Xa guided LMWH dosing. • Weight-based LMWH dosing. • Thromboelastography (TEG) guided LMWH dosing. • Creatinine clearance based dosing	• Development of standardized strategy for prophylactic LMWH dosing • Implications of antithrombin III activity in VTE formation • Assessment of safety of weight based LMWH dosing in trauma subpopulations at elevated bleeding risk • Role of TEG with platelet mapping in characterizing trauma hypercoagulability
Mechanical Prophylaxis and Mobilization	Sequential compression device (SCD) use and early mobilization of trauma patients as part of VTE prevention regimen.	• Chemoprevention is superior to SCDs and mobilization for VTE prevention. • Mobilization alone may not reduce VTE rates.	May have limited utility in patients already receiving chemoprophylaxis.
Prophylactic Inferior Vena Cava Filters (IVCF)	Prophylactic IVCF placement in trauma patients at particularly high risk for bleeding.	• May not prevent symptomatic PE. • Mortality benefit has not been shown.	Fallen out of favor due to limited added benefit in those on chemoprophylaxis. low rate of retrieval, and risk for vascular complications. Consideration is reserved for those at highest risk for bleeding.
Extended/Outpatient Thromboprophylaxis	No standard accepted guidelines for chemoprophylaxis in trauma patients following discharge, however a benefit is suggested based on orthopedic literature.	• LMWH, direct oral anticoagulants (DOACs), and aspirin promising for extended VTE prevention. • Minimum 4-weeks extended chemoprophylaxis in high-risk patients.	• Optimal agent for outpatient extended VTE prophylaxis • Determination of duration of extended chemoprophylaxis • Outpatient regimen may be determined by VTE risk stratification

Table 2:

Alternative LMWH Dosing Strategies - Summary of evidence and considerations for practice

Alternative Dosing Strategy	Study	Study Design	Summary of Evidence	Considerations for Practice
Using Anti-Xa Levels to Dose Adjust Low Molecular Weight Heparin	*Studies suggesting reduction in VTE using anti-Xa levels to guide LMWH dosing:*			• There is likely utility in using anti-Xa levels to guide dosing of LMWH. • Conflicting data regarding anti-Xa levels and VTE rates may be due to difficulty in consistently obtaining appropriately timed anti-Xa levels. • Antithrombin III may play a role in explaining the inconsistencies between anti-Xa levels and VTE rates. This role is still under investigation.
	Malinoski 2010	Single center, prospective cohort	50% of the study sample had low anti-Xa levels and were found to have significantly more DVT than those with prophylactic levels (37% vs. 11%, p=0.026)	
	Lin 2011	Single center, retrospective	In burn patients, initial anti-Xa level was sub-prophylactic in 76.2% and never achieved prophylactic levels in 17.8% of the sample. Median LMWH dosing required to achieve prophylaxis was 40-mg every 12-hours.	
	Singer 2016	Single center, retrospective	Anti-Xa level guided LMWH dosing reduced VTE incidence over 1 year to 7.1% from 20.5% in the historical cohort (p=0.031).	
	Ko 2016	Single center, prospective cohort	Incidence of VTE in trauma was lower in the dose adjustment group than in the historical cohort (1.1% vs. 7.6%, p=0.046).	
	Dhillon 2021	Single center, retrospective	LMWH dosing protocol changed from 30-mg twice daily (PRE) to 40-mg twice daily with dose adjustment by anti-Xa (POST). POST had fewer VTE (3.6% vs 6.9 %, p<0.01) and was independently protective for VTE (aOR 0.54, p=0.01).	
	Gates 2022*	Single center, retrospective	Anti-Xa LMWH titration protocol resulted in significant reduction in overall VTE (p=0.01) and DVT (p=0.01).	
	Tran 2022	Systematic review, meta-analysis	Anti-Xa based dosing of LMWH associated with reduced DVT (aOR 0.52, 95% CI 0.40 to 0.69), PE (aOR 0.48, 95% CI 0.30 to 0.78) and any VTE (aOR 0.54, 95% CI 0.42 to 0.69).	
	Studies which did not demonstrate a reduction in VTE despite achieving prophylactic anti-Xa levels:			
	Louis 2014	Prospective, randomized control	Participants randomized to standard LMWH 30-mg twice daily or TEG to adjust LMWH dosing to achieve a ΔR of 1–2 minutes. TEG adjusted LMWH led to significant increases in anti-Xa activity but no correlation with rate of DVT.	
	Karcutski 2018	Single center, retrospective	There was no difference in rates of VTE in those who received anti-Xa dose adjustment versus those on standard LMWH dosing in the overall sample (6% vs 6.8%, p=0.68) or after propensity matching (2.3% vs. 3.6%, p=0.57).	

Alternative Dosing Strategy	Study	Study Design	Summary of Evidence	Considerations for Practice
	Gates 2022 *	Single center, retrospective	Despite significant reduction in overall VTE, significant reduction in PE was not observed (p=0.21)	
Weight-Based Dosing of Low Molecular Weight Heparin	Bickford 2013	Single center, prospective cohort	Implementation of a weight based LMWH dosing regimen in trauma patients resulted in 86% of the sample achieving target anti-Xa levels.	• Weight-based LMWH dosing should be used in obese trauma patients at low risk for bleeding. • More data are needed to support weight-based regimens in those who are older, underweight, or have reduced renal function
	Nunez 2015	Single center, prospective cohort	Weight-based dosing of 0.6mg/kg twice daily implemented in a trauma intensive care unit was associated with more prophylactic anti-Xa levels (61% vs 8%, p<0.01).	
	Rodier 2021	Single center, prospective cohort	LMWH weight-based dosing of 0.5mh/kg every 12 hours was associated with increased prophylactic anti-Xa levels (25% vs. 5%, p=0.03).	
	Stutsrim 2021	Single center, prospective cohort	In those without weight adjusted LMWH regimens, 34% of trough and 62% of peak anti-Xa levels were adequate, but with weight adjustment, 82% of trough and 97% of peak levels were prophylactic.	
Using Thromboelastography to Guide Chemoprophylaxis	*TEG and VTE in trauma:*			• Hypercoagulable TEG results correlate with rates of VTE • TEG guided LMWH dosing demonstrate similar inconsistencies as anti-Xa levels • TEG with platelet mapping may help to uncover the role of platelets in trauma hypercoagulability
	Van 2009	Single center, prospective cohort	TEG used to assess trauma and non-trauma surgical intensive care unit (SICU) patients. There was a 28% rate of DVT overall. R time was 1.5 times shorter in those with DVT (p<0.001).	
	Cotton 2012	Single center, prospective cohort	TEG obtained in 2,070 consecutive trauma patients. Found MA to independently predict PE with an OR of 5.8 if MA>72.	
	Gary 2016	Single center, retrospective	Compared TEG in orthopedic trauma to non-orthopedic trauma. Those with orthopedic injuries were more hypercoagulable, corresponding to higher rates of VTE (6.5% vs 2.7%, p<0.01). They also found that admission MA was an independent predictor of VTE in severe extremity trauma (OR 3.6 if ≥65 and OR 6.7 if ≥72).	
	Connelly 2016	Prospective, randomized control	TEG was used to guide LMWH dosing in surgical and trauma patients, they found no difference in rates of VTE or bleeding. There were also similar hypercoagulable TEG parameters and AT-III deficiency rates in both study groups.	
	Brill 2017	Single center, prospective cohort	Found that increased MA (>75) and reduced Reaction (R) Time (<5 minutes) correlated with increased rates of DVT in trauma patients (15.6 vs. 8%, p=0.039). On multivariate analysis,	

Alternative Dosing Strategy	Study	Study Design	Summary of Evidence	Considerations for Practice
			there was a significant association between hypercoagulable TEG and DVT (OR 2.41).	
	TEG to assess the role of platelets in trauma induced hypercoagulability:			
	Harr 2013	Single center, randomized control	Found a positive correlation between platelet count and clot strength. Early in the study, LMWH was associated with increased contribution of platelets to clot strength, possibly due to heparin induced platelet activation.	
	Kornblith 2014	Single center, prospective cohort	Demonstrated that platelets had a greater contribution to clot strength than fibrinogen in injured patients, suggesting that anti-platelet therapy may be of under-recognized importance to thromboprophylaxis in trauma.	

* Study with evidence that does and does not support VTE reduction with anti-Xa level dose adjustment

Table 3:

Extended Outpatient VTE Chemoprophylaxis – Summary of evidence and considerations for practice

Study	Study Design	Summary of Evidence	Considerations for Practice
Incidence of VTE following discharge			• Following total hip or knee replacement, extended duration chemoprophylaxis is supported by the literature. • Data extrapolating these results to the trauma population are lacking, but there is strong evidence that the risk for VTE in trauma extends beyond hospital discharge. • LMWH, aspirin, and direct oral anticoagulants have shown promise for extended duration chemoprophylaxis of VTE, however the ideal agent to reduce VTE without increasing bleeding has yet to be determined. • Duration of VTE chemoprophylaxis following hospital discharge should likely be at least 4 weeks, but in some high-risk patients may extended as long as 3 months (or longer).
Olufajo 2016	Large retrospective database analysis	TBI patients in the California Office of Statewide Health Planning and Development Discharge (OSHPD) database had a 1.31% incidence of VTE during index admission, rising to 2.83% by one-year post-injury.	
Godat 2015	Large retrospective database analysis	Trauma patients in the OSHPD database had a 3.97% incidence of VTE, 45.5% of which were diagnosed after initial admission.	
Evidence supporting extended duration chemoprophylaxis			
Bergqvist 1996	Prospective, randomized control	Patients undergoing total hip replacement received LMWH during their hospital stay and were randomly assigned to LMWH or placebo following discharge. There were significantly fewer VTE in the LMWH group vs control (24% vs 7%, p<0.001).	
Shaikh 2020	Systematic review, meta-analysis	Reduced VTE incidence in surgical patients receiving extending chemoprophylaxis as compared to those who did not (4.36% vs/ 12.23%, p=0.006).	
Knoll 2021	Systematic review, meta-analysis	Extended duration prophylaxis after abdominopelvic cancer surgery may reduce clinical VTE (1% vs 2.1%, relative risk (RR) 0.48, 95% CI 0.31–0.74) without increasing bleeding events.	
Assessment of agents used for extended prophylaxis			
Eriksson 2007	Prospective randomized control	Assessed two difference doses of dabigatran daily vs. enoxaparin daily for total hip arthroplasty. No difference in overall VTE or death between the three groups, and no difference in major bleeding.	
Eriksson 2008	Prospective, randomized control	Daily rivaroxaban was found to reduce total VTE more effectively than daily LMWH after total hip replacement (0.2% vs 2%, p<0.001).	

Study	Study Design	Summary of Evidence	Considerations for Practice
Lassen 2008	Prospective, randomized control	Daily rivaroxaban was found to reduce total VTE more effectively than daily LMWH after total knee replacement (1% vs 2.6%, p=0.005).	
Raskob 2012	Pooled data meta-analysis	Twice daily extended duration apixaban demonstrated reduced VTE incidence following total knee or hip replacement compared to daily LMWH (0.7% vs 1.5%, p=0.001).	
Anderson 2013	Prospective, randomized control	Following total hip replacement, patients were given LMWH or aspirin for 28 days following discharge without a significant difference in rates of either VTE or major bleeding.	
Haac 2020	Prospective, randomized control	Patients with pelvic or extremity fractures were given either LWMH twice daily or aspirin twice daily upon discharge. No difference in efficacy was observed.	
Matharu 2020	Systematic review, meta-analysis	Assessed aspirin in comparison to other anticoagulants for extended prophylaxis after total hip and knee replacement. Aspirin found to be non-inferior to other anticoagulants in the prevention of VTE.	
Beauchamp-Chalifour 2022	Two center, retrospective cohort	Looked at elderly hip fracture patients and found that those treated with DOACs (as opposed to LMWH) for extended prophylaxis had a significantly higher risk of bleeding (OR 2.8 [1.5–5.0]).	
Duration of post-discharge VTE prophylaxis			
Godat 2015	Large retrospective database analysis	In OSHPD database, VTE rates were highest 3 months after injury (10.28%), dropped to 0.54% by 6 months, and 0.25% by 12 months (nearly the baseline population risk).	
Ploumis 2009	Consensus Survey	Survey of 25 orthopedic and neurosurgical spine surgeons was conducted. Three months was the group consensus regarding duration of pharmacologic VTE prophylaxis after spinal cord injury.	