

# Venous thromboembolism prophylaxis in the trauma intensive care unit: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document

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## ABSTRACT

Venous thromboembolism (VTE) is a potential sequela of injury, surgery, and critical illness. Patients in the Trauma Intensive Care Unit are at risk for this condition, prompting daily discussions during patient care rounds and routine use of mechanical and/or pharmacologic prophylaxis measures. While VTE rightfully garners much attention in clinical patient care and in the medical literature, optimal strategies for VTE prevention are still evolving. Furthermore, trauma and surgical patients often have real or perceived contraindications to prophylaxis that affect the timing of preventive measures and the consistency with which they can be applied. In this Clinical Consensus Document, the American Association for the Surgery of Trauma Critical Care Committee addresses several practical clinical questions pertaining to specific or unique aspects of VTE prophylaxis in critically ill and injured patients.

## INTRODUCTION

The American Association for the Surgery of Trauma (AAST) Critical Care Committee develops Clinical Consensus Document for critical care-related aspects of patient care. The goal of these documents is to provide practical answers to common clinical questions based on the best evidence available. They address focused topics for which the levels of evidence guiding care may not be strong and/or practice is controversial, and are based on expert consensus and review of the literature. Venous thromboembolism (VTE) prophylaxis, emphasizing the intensive care unit (ICU) environment, was chosen by the Committee as an area of practice warranting review and consensus.

Although enoxaparin has been the agent of choice for VTE prophylaxis in trauma patients since the seminal study by Geerts *et al* in 1996,<sup>1,2</sup> two and a half decades later VTE remains a common complication for critically ill trauma and surgical patients.<sup>3–5</sup> Increased and uninterrupted enoxaparin doses, guided by anti-Xa levels and/or weight, are considered safe and associated with lower VTE rates.<sup>6–10</sup> Individual patient variables dictate when, how or if VTE prophylaxis is provided across the spectrum of traumatic injuries. Overall, the quality of published research on this topic is mixed with many studies

suffering from small numbers, heterogeneous populations, retrospective design, and potential bias.

This Clinical Consensus Document was created during the COVID-19 pandemic, a disease with its own unique risk of VTE, and for which elucidation of the pathophysiology and optimal management is still evolving as of this writing. Therefore, the Committee has opted to exclude discussion of COVID-related VTE from this work.

## METHODS

The topic for this document was chosen through discussion by the AAST Critical Care Committee. A subgroup was formed comprising the document's authors. The subgroup formulated the clinical questions to be addressed and assigned research and writing tasks. The authors were tasked with researching their clinical questions through literature review and writing their section. Recommendations and content were then reviewed by the subgroup and revised based on feedback to achieve consensus. The subsequent draft was distributed to the Committee for review and comment prior to final editing by the first and last authors.

## TRAUMATIC BRAIN INJURY

### When should chemical VTE prophylaxis be initiated after TBI?

#### Recommendation

Thromboprophylaxis should be initiated as soon as possible following traumatic brain injury (TBI), balancing the risks of hemorrhagic expansion and VTE. The available literature supports initiation of prophylaxis 24–72 hours following admission, pending stability of intracranial/extracranial hemorrhage and in conjunction with neurosurgical consultation.

#### Discussion

The incidence of VTE in trauma patients is highest during the first few days following hospitalization, and TBI confers its own elevated risk,<sup>11</sup> particularly when bleeding risk deters early administration of chemical prophylaxis. Among the TBI population, up to 54% may develop VTE in the absence of any form of prophylaxis and in 20%–30% of patients despite mechanical prophylaxis.<sup>12,13</sup> Although recommendations for the optimal timing

of prophylaxis initiation have evolved over the past 10 years, the data remain heterogeneous with a paucity of randomized controlled trials due to the complex nature of the problem. Retrospective reviews conducted in 2011 demonstrated that, on average, prophylaxis was initiated following TBI on hospital days 3–4 after injury stability on repeat head CT. These studies included multiple forms of TBI and a range of Abbreviated Injury Scale (AIS) scores, but did not demonstrate any association between progression of intracranial hemorrhage (ICH) and timing of prophylaxis initiation. Although initiation within this time range did not significantly affect VTE incidence, correlations with VTE were observed in severe chest injury, lack of ambulation by discharge and interruptions in prophylaxis.<sup>12–15</sup> In 2015, the American College of Surgeons Trauma Quality Improvement Project (TQIP) released guidelines on TBI management supporting consideration of VTE prophylaxis within the first 72 hours of hospitalization and following stable head CT.<sup>13</sup> These guidelines incorporate the modified Berne-Norwood criteria in the strategic timing of prophylaxis initiation based on risk of ICH progression.<sup>16</sup> In 2016, evaluation of the TQIP database used propensity score matching to optimize comparison of early (<72 hours) versus late (>72 hours) prophylaxis in severe TBI, showing lower rates of pulmonary embolus (PE) and deep vein thrombosis (DVT) in the early group without subsequent increases in neurosurgical intervention or mortality.<sup>2</sup> Most recently, Störmann *et al* presented findings from a single-center retrospective study in which patients with severe TBI were categorized into four groups by timing of prophylaxis initiation: <24 hours, 24–48 hours, >48 hours and no therapy. They showed that early (<24 hours) administration was not associated with ICH progression. While their overall incidence of ICH progression following prophylaxis (14.1%) is high versus historic comparison, it is less than that reported by Frisoli *et al* in a similar cohort (18%).<sup>17–18</sup> The most recent guidelines from the Brain Trauma Foundation (BTF) concluded that there is insufficient evidence to support recommended timing of VTE prophylaxis initiation following TBI, underscoring the need for further high-quality investigation.<sup>19</sup> More recently, a systematic review from 2020 evaluated 17 studies, and concluded that early chemoprophylaxis 24–72 hours after injury is associated with reduced VTE incidence without increasing ICH in patients with TBI with a stable repeat head CT.<sup>20</sup>

### Should severity of TBI influence timing and dosage of chemoprophylaxis?

#### Recommendation

Timing of prophylaxis initiation in TBI should be individualized and based on multiple factors, including injury severity.

#### Discussion

Severity of TBI is an incompletely understood factor in the timing of VTE prophylaxis, given the heterogeneity of head injury types. In surrogate, the Brain Injury Guidelines (BIG) and modified Berne-Norwood criteria provide guidance on classification of TBI and risk of ICH progression.<sup>16–21</sup> Categorized as BIG 1–3, only patients meeting BIG 3 criteria (>8 mm ICH) required neurosurgical intervention. Furthermore, the Berne-Norwood criteria suggest that, in the absence of multiple contusions, for isolated subarachnoid/intraventricular hemorrhage and subdural/epidural ≤8 mm prophylaxis may safely be initiated at 24 hours postinjury pending stability of head CT. Additional stratification of TBI into moderate-risk and high-risk groups follows with a 72-hour delay in VTE prophylaxis initiation and consideration

of an inferior vena cava (IVC) filter, respectively. While unfractionated heparin (UFH) and the low molecular weight heparin (LMWH) enoxaparin are most commonly dosed at 5000 units every 8 hours and 30 mg every 12 hours, respectively, in TBI evaluation with the antifactor Xa assay allows for assessment of LMWH within a targeted range without increased risk of ICH progression.<sup>22</sup>

### Is there a preferred chemoprophylaxis agent for patients with TBI?

#### Recommendation

Either UFH or LMWH may be used for VTE prophylaxis in TBI, although LMWH may be superior.

#### Discussion

Optimal timing and type of prophylactic agent are critically important. Byrne *et al* recently evaluated the TQIP database for comparison of UFH versus LMWH in prevention of PE in major trauma.<sup>23</sup> Following propensity matching, LMWH was correlated with a significantly lower rate of PE versus UFH (1.4% vs 2.4%). This relationship was maintained in subgroup analysis of isolated severe TBI (AIS ≥3, Glasgow Coma Scale ≤8). Further review of TQIP by Benjamin *et al* reveals UFH to be independently predictive of mortality and VTE in severe TBI. Moreover, prophylaxis with LMWH did not increase the risk of unplanned emergency operation.<sup>24</sup> Although the use of UFH has decreased over time, its employment in TBI may be favored by some due to a theoretic benefit of shorter half-life. Additionally, database studies leave gaps in understanding regarding the types of head injuries being studied among other factors that may bias usage of one agent over the other. Current recommendations from the BTF support either UFH or LMWH for VTE prophylaxis and cannot conclusively endorse superiority of either, leaving room for future prospective studies.<sup>19</sup> The use of LMWH offers some practical benefits over UFH, in that the lower number of injections may increase patient comfort and acceptance, decrease refusals and limit nurse-patient interactions (eg, for patients in isolation rooms). Emerging pharmacological VTE prophylaxis alternatives include the direct oral anticoagulants and aspirin, the latter of which is currently under investigation in a large randomized trial. Both options warrant further research but currently have insufficient evidence on which to formulate recommendations.

### SOLID ORGAN INJURY

#### What timing and agent is appropriate for VTE prophylaxis after blunt solid organ injury?

#### Recommendation

In patients with blunt solid organ injury (SOI) undergoing non-operative management, VTE prophylaxis with LMWH should be initiated within 48 hours from time of injury in the absence of ongoing bleeding or other contraindications.

#### Discussion

Patients with blunt SOI, including liver, kidney and splenic injuries, are increasingly being managed non-operatively leading to questions as to when it is safe to initiate VTE prophylaxis in this population. For patients who have definitive hemostasis, prophylaxis should be initiated as soon as possible afterwards. However, in patients undergoing non-operative management, the concern for bleeding must be weighed against the risk of VTE. One retrospective study evaluating the thromboelastography (TEG) parameters of patients with blunt SOI demonstrated

conversion to a hypercoagulable state at 48 hours, suggesting that VTE prophylaxis is important by this time point.<sup>25</sup>

While there has been no randomized trial comparing early and late initiation of VTE prophylaxis in SOI, there have been several observational studies comparing early (typically <48 hours after injury) with late (>48 hours after injury) initiation.<sup>26–32</sup> Uniformly in these studies, there has been no increase in post-prophylaxis transfusion requirements or failure of non-operative management requiring intervention. Therefore, it appears that institution of VTE prophylaxis in patients with blunt SOI is safe and may be performed within 48 hours from the time of injury in the absence of ongoing bleeding. Of note, however, there is a paucity of data about outcomes in patients with grade IV–V injuries, likely because these injuries are more commonly managed operatively. Clinical judgment must be used in these higher grade injuries.

There are no high-quality data or consensus in the literature about the superiority of UFH or LMWH with regard to SOI specifically. However, LMWH is recommended in this population based on the cumulative evidence in favor of LMWH for multitrauma patients.

## EPIDURAL ANALGESIA

### Should trauma patients with epidural catheters receive pharmacological prophylaxis and, if so, which agent and at what dose?

#### Recommendation

Trauma patients with epidural catheters should receive enoxaparin at similar doses to those patients without catheters. In the presence of renal failure, UFH three times daily should be provided.

#### Discussion

Enoxaparin dosing is often interrupted after epidural catheter placement,<sup>7</sup> leading to an increased VTE rate.<sup>33</sup> Regional anesthesia guidelines recommend a 12-hour interval between enoxaparin administration and placement or removal of an epidural catheter (24 hours if higher than standard dosing is used), and delaying resumption of the drug by 4–12 hours.<sup>34 35</sup> Efforts to minimize the time without pharmacological protection should be undertaken by meticulously coordinating epidural procedures with drug doses, such that no more than two doses of enoxaparin will be missed. For UFH, the interval between epidural placement or removal and drug administration may be reduced to 4–6 hours, with only a 1-hour gap before resumption. As a result no UFH doses need be held.<sup>6 34 35</sup>

## IMAGING SURVEILLANCE FOR DVT

### When is routine surveillance with venous duplex indicated after trauma?

#### Recommendation

Routine surveillance by venous duplex is not recommended for most trauma patients. Weekly surveillance may be performed in patients at high risk of VTE in whom chemical prophylaxis cannot be provided.

#### Discussion

Routine surveillance with venous duplex is not indicated or feasible for almost all trauma patients as it does not decrease the risk of VTE or fatal PE. In addition, false positive results

lead to unnecessary therapeutic anticoagulation.<sup>36</sup> Some centers advocate that routine surveillance in low-risk trauma patients will identify both acute and chronic DVT, which may help diagnose, treat or prevent the related complications such as venous insufficiency, venous stasis ulcers or pain with ambulation.<sup>37</sup> Alternatively, it is well known that increased imaging correlates with increased VTE rates,<sup>38</sup> with difficulty distinguishing clinically significant DVTs from incidental DVTs that would have remained clinically silent had they not been sought. Based on current evidence, routine surveillance duplex should be considered for trauma patients at high VTE risk who cannot be started or maintained on pharmacological prophylaxis, as this is associated with a reduced PE rate.<sup>37</sup>

### What is the appropriate strategy for diagnosis and prevention of VTE during and following venovenous extracorporeal membrane oxygenation?

#### Recommendation

Despite the use of systemic anticoagulation, venovenous (VV) extracorporeal membrane oxygenation (ECMO) is associated with a high rate of VTE that must be carefully evaluated and treated. Surveillance in patients who have undergone ECMO should use CT imaging to visualize deep veins and the IVC.

#### Discussion

While on VV ECMO, thrombotic events are provoked through interaction of the ECMO circuit and the patient's blood. To mitigate this risk, routine systemic anticoagulation and heparin-bonded circuits are used. However, anticoagulation may be held if significant bleeding occurs with the potential for exacerbating the inherent risk of VTE during VV ECMO. Although previous data during the H1N1 pandemic suggested the rate of VTE to be under 10%, recent data suggest this rate may be as high as 18%.<sup>39</sup> Thrombosis appears to occur more frequently with dual-lumen jugular cannulations compared with single lumen combined femoral cannulations. The sites of thrombosis are therefore more common in the internal jugular vein and IVC. Although the risk of VTE during VV ECMO may be related to both the duration of subtherapeutic anticoagulation and of the ECMO run,<sup>40–42</sup> this has been disputed.<sup>43</sup>

Following decannulation, DVT rates as high as 60% have been demonstrated and thus the routine use of venous duplex has been suggested at cannulation sites. Because of the inability to evaluate the iliac veins and vena cava through duplex, surveillance CT scan has been suggested as an adjunct. One study demonstrated the rate of overall cannula-associated thrombosis was 71% with 47% isolated to the vena cava.<sup>44</sup> This suggests that traditional duplex would miss a significant number of thromboses. In addition to DVT, 16% of patients were diagnosed with concurrent PE. The major modifiable factor associated with decannulation thrombosis was increased time of subtherapeutic anticoagulation. Although diagnosis is imperative, appropriate treatment should be initiated in patients with evidence of VTE. In patients without evidence of VTE, standard chemoprophylaxis should be initiated following decannulation.<sup>43–45</sup>

## PROPHYLACTIC INFERIOR VENA CAVA FILTERS

### When should prophylactic inferior vena cava filters be used?

#### Recommendation

The use of prophylactic (in the absence of known VTE) inferior vena cava filters (IVCF) in trauma patients is controversial, but should be considered in very high-risk patients who cannot

receive chemical VTE prophylaxis for long periods because of increased bleeding risk.

### Discussion

IVCF currently have indications in patients with known acute proximal (popliteal, femoral or iliac) DVT or PE who have an absolute contraindication to therapeutic anticoagulation; have suffered complications of anticoagulation or who have recurrent VTE while on adequate anticoagulation. The introduction of the retrievable IVCF in 2003 markedly increased insertion rates.<sup>46 47</sup> Despite earlier evidence of a significant reduction in the incidence of PE following prophylactic IVCF in trauma patients,<sup>48</sup> more recent studies failed to show improvement in mortality<sup>49</sup> and report higher risk of DVT following insertion.<sup>50</sup> In the absence of level I evidence, conflicting professional guidelines regarding the use of IVCF in trauma patients have emerged.<sup>51–53</sup> We suggest consideration of prophylactic IVCF only in the highest risk patients with contraindications to chemoprophylaxis due to an ongoing risk of life-threatening bleeding. Examples of such high-risk conditions include severe head injury plus long bone fractures, head injury plus spinal cord injury, multiple long bone fractures, severe pelvic fracture plus long bone fractures and/or medical conditions that predispose to bleeding.<sup>51 54</sup>

### How long should an IVCF remain in place?

#### Recommendation

It is essential that IVCFs be removed as soon as protection is no longer needed or when the patient can safely have chemoprophylaxis or therapeutic anticoagulation, to avoid long-term complications related to their presence. If a patient with an IVCF is later able to start anticoagulation, it should be initiated while the filter is still in place and the filter removed as soon as feasible. Multidisciplinary and systematic follow-up protocols should be established to optimize filter retrieval rates.

### Discussion

Prolonged IVCF dwell times are associated with DVT, chronic pain, caval thrombosis, IVC perforation, filter migration and fracture.<sup>55 56</sup> Retrieval success also decreases with duration of placement, with strut epithelialization and penetration through the caval wall making removal technically difficult.<sup>55 56</sup> If the risk of PE has passed, prophylactic IVCF should be removed 1–2 months after implantation.<sup>56</sup> The American College of Chest Physicians recommends filters be removed 6 months following PE, regardless of the ability to anticoagulate the patient.<sup>57</sup> Despite the known complications of longer dwell times, most studies show retrieval rates remain lower than 50%.<sup>58–60</sup> In response, the Food and Drug Administration issued an updated safety alert in 2014 recommending that implanting physicians accept responsibility for removal of filters as soon as clinically appropriate. A comprehensive follow-up program that tracks patients, assigns an individual dedicated to monitoring the program and educates physicians and patients is effective in minimizing loss to follow-up and improving retrieval rates.<sup>61</sup>

## ANTIFACTOR XA MONITORING AND ASSOCIATED DOSE ADJUSTMENTS

### What is the utility of antifactor Xa monitoring for VTE chemoprophylaxis?

#### Recommendation

A regimen for VTE prophylaxis using enoxaparin with dose adjustment based on anti-Xa levels may be considered for trauma and surgical ICU patients thought to have a low bleeding risk.

Such a regimen results in more patients having anti-Xa levels in the target range than with a fixed dosing regimen. However, evidence is insufficient to determine if this practice results in lower VTE rates. This strategy may not be appropriate for some patients (eg, those with TBI) and individual patient characteristics should be considered when choosing a dosing regimen.

### Discussion

The study by Geerts *et al* in 1996<sup>1</sup> showed benefit of enoxaparin 30 mg twice a day in reducing venogram-diagnosed DVT rates, and minimal reduction with UFH (5000 units twice a day) in trauma. More recent evidence, mostly from underpowered retrospective studies, has suggested that the typical fixed dosing regimen of enoxaparin 30 mg two times per day does not inhibit factor Xa in a uniform and predictable manner in all patients.<sup>62–64</sup> This makes intuitive sense, given the variable degree of VTE risk, hypercoagulability and sometimes unpredictable pharmacokinetics in critically ill and injured patients.

Anti-Xa activity is assessed via a functional assay that measures the degree of inhibition of factor Xa by UFH or LMWH. Blood for anti-Xa testing is typically drawn 4 hours after the third dose of enoxaparin. Levels are measured in International Units per milliliter, with target prophylactic levels falling in the range of 0.2–0.4 IU/mL (the target for therapeutic full anticoagulation is >0.5 IU/mL). If levels are below target, the dose may be increased by 10 mg and levels rechecked again 4 hours after the third new dose. Data on the maximum safe dose are insufficient, but several authors have recommended not exceeding 60 mg two times per day dosing. While true therapeutic dosing often exceeds 60 mg two times per day, the conditions under which clinicians may provide prophylactic enoxaparin may differ from those for therapeutic, especially when considering bleeding risk. Also, if anti-Xa levels have not reached prophylactic targets at higher doses, one should consider heparin resistance or anti-thrombin-III deficiency, occult VTE with high clot burden or other undetected factors that may prompt further investigation.

Studies supporting dose adjustments based on anti-Xa levels have suggested either that fixed dosing is insufficient to reach target anti-Xa levels,<sup>62–65</sup> or that using a dose-adjustment regimen results in lower VTE rates.<sup>8 9</sup> One larger retrospective study reported no decrease in VTE rates with an anti-Xa-based regimen<sup>66</sup>; however, over half of study patients never achieved target levels during their hospital stay. Perhaps most relevant in this discussion is that the studies consistently report no increase in bleeding complications with anti-Xa-based dosing, which is a key concern in surgical ICU patients. Another possible use of anti-Xa monitoring is in patients with altered renal function. Since enoxaparin is cleared by the kidneys, renal dysfunction requires dose adjustment or discontinuation to avoid overanticoagulation due to drug retention. This is an area needing further study.

Given the low quality of the collective evidence, a broadly applicable recommendation cannot be made. A reasonable body of evidence supports the idea that standard enoxaparin dosing (30 mg two times per day) fails to raise anti-Xa levels to target, and that dose adjustment helps increase levels. However, many patients do not attain target anti-Xa levels despite incremental dose increases, and the relationship between drug dose and anti-Xa is not consistent between patients.

Anti-Xa-based regimens have not been well studied in patients with TBI, in whom bleeding complications can be catastrophic. Also, many studies on VTE prophylaxis are limited by missed doses of enoxaparin, which may alter drug efficacy and raise VTE risk.<sup>67</sup> The method of VTE diagnosis in studies is also

variable (routine screening vs symptom-prompted radiography), which is relevant since the clinical significance of small occult VTE is unknown.

## VISCOELASTIC MONITORING AND DOSE ADJUSTMENT

### What is the role of viscoelastic monitoring of VTE chemoprophylaxis?

#### Recommendation

Current evidence is inadequate to draw conclusions about the utility of TEG-guided enoxaparin dosing. Results from small studies in trauma and non-trauma patients have been mixed and inconclusive.

#### Discussion

TEG and rotational thromboelastometry are used frequently to provide a comprehensive assessment of coagulation status in trauma and surgical ICU patients. Many trauma patients become hypercoagulable after injury, as measured by TEG, which has been associated with higher VTE rates.<sup>68,69</sup> Despite receiving presumably adequate pharmacological prophylaxis (enoxaparin 30 mg two times per day), VTE is still a major complication of severe injury. Dose adjustment of enoxaparin has been practiced based on weight and antifactor Xa levels but TEG has also been entertained as a monitoring method due to its ease of use and more complete assessment of coagulation. Although enoxaparin mainly inhibits factor Xa, it has minor effect on other elements of the clotting system and this makes TEG an attractive option for monitoring.<sup>70</sup>

Few studies have examined TEG for VTE prophylaxis monitoring in trauma. A study of 61 trauma and general surgery patients with a 28% DVT rate showed that TEG distinguished those with and without DVT, while anti-Xa measurements did not.<sup>71</sup> Patients with DVT had a shorter R-time (the TEG component measuring time to clot initiation). The same group examined TEG-guided versus standard enoxaparin dosing in a randomized trial of 87 patients,<sup>72</sup> in which the dose was adjusted to achieve an R-time of 1–2 min. The median adjusted dose was 50 mg two times per day, with no difference in the change in R time between groups. Although the TEG-guided treatment led to increases in anti-Xa levels, this did not correlate with DVT rates. Interestingly, they also uncovered many patients with antithrombin-III deficiency, which the authors theorized may have accounted for the lack of change in R-time. In their follow-up study, the authors analyzed 89 patients and found that those with TEG-guided enoxaparin did not have a rise in anti-Xa levels until day 6, and that only about 12% of all patients achieved an increase in R-time over 1 min.<sup>73</sup>

A study of 50 coronary care unit (CCU) patients receiving therapeutic dose enoxaparin<sup>70</sup> showed a positive association of TEG R-time and maximum rate of thrombin generation with enoxaparin dose, but no correlation of dosing with anti-factor Xa levels. Furthermore, TEG did not predict anti-Xa levels. Another study of 24 patients undergoing elective orthopedic surgery receiving prophylactic enoxaparin showed correlation of peak and trough anti-Xa activity with TEG R-time.<sup>74</sup>

TEG remains worthy of investigation to determine its role in guiding pharmacological VTE prophylaxis. Currently, evidence is lacking to support its routine use in clinical patient care for this purpose.

## WEIGHT-BASED DOSING OF ENOXAPARIN IN OBESITY

### Should enoxaparin dosing be adjusted in patients with obesity?

#### Recommendation

Weight-based enoxaparin dosing for VTE prophylaxis is an acceptable strategy for trauma patients with body mass index (BMI)

>30 kg/m<sup>2</sup>, based on earlier attainment of target anti-Xa levels and the significant prevalence of VTE in trauma patients receiving standard prophylaxis. Careful patient selection including assessment of both VTE and bleeding risk is warranted. Weight-based dosing is currently not recommended in patients with traumatic ICH.

#### Discussion

Obesity (defined as BMI >30 kg/m<sup>2</sup>) and traumatic injury are each associated with hypercoagulability and are well-known risk factors for VTE.<sup>75,76</sup> VTE remains a common preventable complication in critically injured patients despite being a clinical focus of multiple national agencies<sup>77</sup> and the existence of best practice guidelines for prophylaxis.<sup>51</sup> Patients with obesity have been under-represented in clinical trials of VTE prophylaxis, and recommendations for pharmacological prophylaxis in this population were not included in the American College of Chest Physicians 2012 guidelines.<sup>78</sup> Therefore, it is unclear if conventional prophylaxis measures are as effective in patients with obesity versus patients without obesity. Weight-based enoxaparin dosing has been used to attempt to improve efficacy of prophylaxis and reduce VTE rates in trauma patients with obesity. Although evidence for this strategy is still emerging, it is a common practice. In one multicenter study of trauma ICUs, 81.6% of 49 trauma centers reported using a weight-based dosing regimen.<sup>79</sup>

Weight-based enoxaparin prophylaxis is commonly initiated at a dose of 0.5 mg/kg, 0.6 mg/kg or 30 mg for patients weighing 50–60 kg, 40 mg for patients weighing 61–99 kg and 50 mg for patients weighing >100 kg,<sup>10</sup> in conjunction with measurement of anti-factor Xa levels toward a target range of 0.2–0.4 IU/mL. Small studies in trauma patients with obesity and non-trauma patients with obesity<sup>80–84</sup> have demonstrated an advantage of the weight-based strategy in achieving target anti-Xa levels without an increased risk of bleeding. The predictable dosing relationship of enoxaparin among the LMWHs (1 mg enoxaparin inhibits 100 anti-Xa units) makes weight-based dosing based on anti-Xa measurements logical and convenient. A large retrospective study of hospital inpatients also reported a significant reduction in VTE rates in patients with morbid obesity (BMI >40 kg/m<sup>2</sup>) receiving higher dosing of enoxaparin and UFH compared with standard dosing.<sup>85</sup> Studies in bariatric surgery patients and other non-trauma populations have found no difference in bleeding complications with higher dosing.<sup>85</sup>

Currently, weight-based enoxaparin dosing for VTE prophylaxis has a sound physiological rationale and support from low-quality studies in non-trauma patients. More investigation is needed in trauma patients with obesity, especially since these patients often have an elevated risk of VTE. While bleeding complications appear to be a rare event in non-trauma patients with a weight-based regimen, the nature of traumatic injury calls for careful patient selection when considering this practice in trauma ICU patients. Enoxaparin is renally cleared and therefore dose adjustment or use of UFH is necessary with acute or chronic kidney injury. It should be noted that there is a lack of evidence on the use of weight-based prophylaxis dosing in patients with traumatic ICH, unlike that which exists for standard dosing. Due to the unknown effect on progression of ICH with higher doses, at this time weight-based dosing is not recommended in this patient population.

## OTHER HIGH-RISK SCENARIOS AND WHEN TO HOLD VTE PROPHYLAXIS

### How should VTE prophylaxis be managed with active bleeding or coagulopathy?

#### Recommendation

Pharmacological prophylaxis should be delayed in patients with active bleeding or coagulopathy, until these conditions have

been controlled or reversed. Mechanical prophylaxis should be employed in these patients.

### Discussion

It is appropriate to withhold chemical prophylaxis in patients with active bleeding or coagulopathy, or hemodynamic instability resulting from those conditions.<sup>6</sup> Delaying initiation of enoxaparin should be minimized to the shortest acceptable time period, since the early trauma-induced coagulopathy soon gives way to a hypercoagulable state.<sup>25,86</sup> In the setting of trauma coagulopathy, enoxaparin may be considered after completing the initial resuscitation, even though laboratory parameters of coagulation have not yet normalized.<sup>87,88</sup> As holding pharmacological prophylaxis is associated with an increased VTE rate, enoxaparin initiation is encouraged if there are no signs of bleeding and the hypocoagulable state is expected to resolve.<sup>87</sup> Intermittent pneumatic compression as a means of mechanical prophylaxis is an important adjunct in conditions that prohibit chemical prophylaxis, especially in patients with moderate-to-high VTE risk.<sup>6</sup>

### Should pharmacological VTE prophylaxis dosing be adjusted during pregnancy?

#### Recommendation

Dosing of pharmacological VTE prophylaxis should be adjusted in pregnant trauma patients.

### Discussion

Pregnant trauma patients are at increased risk of VTE. Increases in weight and creatinine clearance make dosing adjustments for enoxaparin necessary, namely higher and more frequent dosing regimens. At admission, a pregnant trauma patient should receive enoxaparin 30 mg two times per day, and if the patient weighs >90 kg then 40 mg two times per day should be initiated. The dosing should then be titrated by antifactor Xa levels to target a range of 0.2–0.4 IU/mL.<sup>89,90</sup>

### When is it appropriate to hold doses of VTE chemoprophylaxis?

#### Recommendation

Once pharmacological prophylaxis is initiated, it should only be held or stopped for significant or potentially significant bleeding events and development of heparin-induced thrombocytopenia.

### Discussion

The use of chemoprophylaxis is associated with a significant reduction in the risk of VTE. Initiation early during hospitalization in patients at high risk for the development of VTE is considered standard of care. However, initiation must be balanced with risk of bleeding, and as a result should be started when the risk of bleeding is acceptable. Once initiated, continuous therapy is essential. Interruption of VTE prophylaxis for a period of 24 hours and even missing a single dose is associated with an increased risk of VTE.<sup>7</sup> As a result, chemoprophylaxis once initiated should be only held under unique circumstances. Despite this, interruption is common and up to 40% of patients have chemoprophylaxis held at some point or another. Interruptions due to surgery and procedures are an even more common reason for inconsistent chemoprophylaxis administration. Debate surrounds which operations and procedures are safe to continue chemoprophylaxis without interruption. Absolute indications for holding chemoprophylaxis include active hemorrhage and recent spine or intracranial surgery. However, the optimal timing of restarting chemoprophylaxis in

this patient population remains uncertain and ranges between 24 and 72 hours without clear data to guide decision making. Upcoming surgery or invasive procedures are considered relative indications for holding chemoprophylaxis. Outside of spine and intracranial surgery, little to no data exist demonstrating that continuing chemoprophylaxis without interruption leads to increased bleeding complications. In patients with a low risk of bleeding complications but high risk of VTE, chemoprophylaxis should be continued uninterrupted.<sup>77,91,92</sup> If interruption in chemoprophylaxis is indicated, mechanical prophylaxis should be instituted prior to interruption and preferably continued in combination with re-initiation of pharmacological prophylaxis.

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