Venous Thromboembolism Prophylaxis in Trauma Patients

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Learning Objectives:

1. Identify risk factors for venous thromboembolism in trauma patients.
2. Describe the pathophysiology of coagulopathy in trauma patients.
3. Compare and contrast the pharmacokinetics of unfractionated heparin and low-molecular weight heparin.
4. Summarize landmark trials of venous thromboembolism prophylaxis in trauma patients.
5. Discuss recent guideline updates for venous thromboembolism prophylaxis in trauma patients.
6. Evaluate the results of relevant clinical studies looking at alternative venous thromboembolism prophylaxis dosing strategies in trauma patients.
7. List limitations of available studies investigating alternative venous thromboembolism prophylaxis dosing strategies in trauma patients.
8. Select an appropriate venous thromboembolism prophylactic agent and dose for a specific patient.

Background[1-7]

Venous thromboembolism (VTE) is estimated to occur in up to 58% of trauma patients not receiving prophylaxis and in up to 31% of trauma patients receiving prophylaxis. Trauma patients often have many risk factors in addition to pathophysiologic changes that make them susceptible to VTE. Type of injury, severity of injury, surgical procedures, and past medical history all contribute to the risk of VTE in trauma patients. Risk factors for VTE in trauma patients include: spinal cord injury (SCI), spinal cord fracture, older age (≥40 years), injury severity score (ISS) ≥10, blood transfusion, repair of venous injury, history of VTE, inherited clotting disorders, >3 ventilator days, fracture of long bones (femur, tibia), major operative procedure, >2-hour operation, Glasgow Coma Score (GCS) <8 for >4 hours, obesity, pelvic fracture, and traumatic brain injury (TBI). Trauma patients are also at risk of bleeding as a result of the pathophysiologic changes that occur in trauma, making the selection and dosing of VTE agents for prophylaxis more complex than in other patient populations. Trauma patients at high risk of bleeding include patients with SCI and TBI, specifically. VTE prophylaxis in trauma patients has historically been and remains an area of interest as VTE is associated with an increased mortality of up to 50%.

Pathophysiology[8-12]

Virchow's Triad describes 3 factors necessary for the development of VTE: venous stasis, hypercoagulability, and endothelial injury. Venous stasis and endothelial injury are often present in trauma patients as a result of the underlying injury, and hypercoagulability is also present in the form of trauma-induced coagulopathy (TIC). TIC is one component of the Lethal Triad described in trauma patients.

The Lethal Triad is often present in patients with severe trauma and is associated with increased mortality. Components of the Lethal Triad include TIC, acidosis, and hypothermia. TIC is a dynamic, patient-specific process that consists of both coagulation activation and hyperfibrinolysis. Coagulation

activation and hyperfibrinolysis do not occur in isolation, but instead co-exist. Coagulation activation occurs as a result of an increase in procoagulants (tissue factor) in the systemic circulation, impairment of endogenous anticoagulants (decreased antithrombin, protein C depletion), and increased thrombin generation. Hyperfibrinolysis occurs as a result of increased thrombomodulin and coagulation activation-induced fibrinolysis without increased activity of plasminogen activator inhibitor (PAI). Increased thrombomodulin binds to and decreases thrombin, which results in activation of protein C, decreased factor VIIIa and Va activity, and increased release of tissue plasminogen activator (tPA). Increased release of tPA results in conversion of plasmin to plasminogen. Together, coagulation activation and hyperfibrinolysis result in a consumption coagulopathy. Acidosis contributes to the lethal triad by interfering with the assembly of coagulation factor complexes and accelerating fibrinogen degradation. Hypothermia contributes by impairing platelet activity, impairing enzymatic reactions of the coagulation cascade, and inhibiting fibrinogen synthesis. While the lethal triad and TIC describe a dynamic process resulting in both increased risk of clotting and bleeding, patients are typically at risk of bleeding immediately following trauma, with the risk of clotting occurring later.

In addition to pathophysiologic changes resulting from trauma, there are pharmacokinetic changes that occur in trauma patients. Trauma patients have an increased volume of distribution, decreased protein binding, and augmented renal clearance. These changes occur as a result of resuscitation, increased cardiac output, and increased renal blood flow and may result in higher dosage requirements.

VTE prophylaxis in trauma patients requires a balance between risk of bleeding and risk of VTE, both of which trauma patients are at risk for as a result of TIC and pharmacokinetic changes.

Choice of Agent[1-2,13-19]

Unfractionated heparin (UFH) and low-molecular weight heparin (LMWH), or enoxaparin, are both options for VTE prophylaxis in trauma patients. Their mechanism of action is similar, with both potentiating the action of antithrombin, inactivating thrombin, factor IXa, factor Xa, factor XIa, factor XIIa, and plasmin, and preventing the conversion of fibrinogen to fibrin. LMWH, however, has a higher ratio of anti-factor Xa to antithrombin activity. UFH is dosed every 8 hours, while LMWH is dosed every 12 hours. UFH does not require renal dosage adjustments, while LMWH is contraindicated in trauma patients with a creatinine clearance <30 mL/min. LMWH has several pharmacokinetic properties that make it a more attractive agent compared to UFH. LMWH has greater bioavailability, a longer half-life (4.5-7 h vs. 0.5-2 h), less protein binding, and fewer platelet interactions compared to UFH. The longer half-life of LMWH also allows for less frequent dosing/fewer injections for the patient.

Studies comparing UFH and LMWH date back decades. A landmark randomized, double-blinded study by Geerts and colleagues published in 1996 compared UFH 5000 units every 12 hours (Q12H) to LMWH 30 mg Q12H in 256 trauma patients. The mean age of patients was ~38 years, and the mean ISS was ~23. The most common site of major injury included lower limb (~55%), followed by face, chest, or abdomen (~37%), spine (~15%), and head (~5%). Of note, patients with frank intracerebral hemorrhage (ICH) were excluded. Deep vein thrombosis (DVT) occurred in 44.1% of patients receiving UFH versus 31.0% of patients receiving LMWH (relative risk reduction 30%, 95% confidence interval 4-50%, P= 0.014). There were no fatal pulmonary emboli (PE) in either groups, though there was one suspected PE in the LMWH group. Major bleeding occurred in 0.6% of patients receiving UFH versus 2.9% of patients receiving

LMWH (P= 0.12). The authors concluded LMWH was more efficacious than UFH in preventing DVT in patients recovering from major trauma, and LMWH should be considered the method of choice for VTE prophylaxis in trauma patients provided they do not have frank ICH. Limitations of this study include the exclusion of patients with ICH, the UFH dosing regimen (5000 units Q12H instead of 5000 units Q8H), and a lack of information regarding the weight of patients.

Subsequent studies have been performed to address these limitations. Studies investigating VTE prophylaxis in patients with TBI have found similar results favoring LMWH. Studies comparing LMWH 30 mg Q12H to UFH 5000 units Q8H have also been performed. A prospective, randomized, two-arm, noninferiority trial suggested noninferiority of UFH 5000 units Q8H in terms of total new VTE in trauma patients. However, this study had methodological issues, including being underpowered. A subsequent retrospective cohort of 18,010 patients suggested LMWH was associated with lower odds of VTE, PE, DVT, and mortality compared to UFH 5000 units Q8H.

These studies have been the basis of many guideline recommendations, and LMWH is generally recommended over UFH. Notably, many studies do not provide information regarding the weight of patients included.

Historical Guidelines[4,20-24]

The Eastern Association for the Surgery of Trauma (EAST) published guidelines for the prevention of VTE in trauma patients in 2002. They state that there is little evidence to support the use of UFH, and LMWH should be used for VTE prophylaxis in all patients with an ISS >9 who can receive anticoagulants. Of note, the EAST guidelines do not address the dosing of agents.

Several other guidelines are available to help guide the choice of agent for VTE prophylaxis in specific injuries. The American College of Chest Physicians published guidelines for prevention of VTE in non-orthopedic surgical patients in 2012 in which they recommended UFH, LMWH, or mechanical prophylaxis. The Neurocritical Care Society published guidelines in 2016 recommending either LMWH or UFH for TBI and SCI patients. The Brain Trauma Foundation published guidelines for VTE prophylaxis in TBI in 2016 and recommended either LMWH or UFH for TBI patients. The Consortium for Spinal Cord Medicine published guidelines for VTE prophylaxis in patients with SCI in 2016 and recommended for the use of LMWH and against the use of UFH. Lastly, the Congress of Neurological Surgeons/American Association of Neurological Surgeons published guidelines for VTE prophylaxis in patients with thoracolumbar spine trauma in 2019 and concluded there was insufficient evidence to recommend a specific regimen of VTE prophylaxis. As with the EAST guidelines, many of these guidelines do not address the dosing of agents, nor do they address adjusting doses in certain patient populations, including in patients who are overweight or obese.

Recently Updated Guidelines[1,25-26]

In 2020, the Western Trauma Association published updated guidelines to reduce VTE in trauma patients. They addressed both choice of agent and dosing, stating that LMWH 40 mg Q12H should be considered the standard for most trauma patients, because 30 mg Q12H frequently results in inadequate pharmacologic prophylaxis. They also provide weight-based dosing recommendations for patients with normal renal function and recommend LMWH 0.5 or 0.6 mg/kg Q12H, or LMWH 30 mg

Q12H for patients weighing 50-60 kg, LMWH 40 mg Q12H for patients weighing 61-99 kg, and LMWH 50 mg Q12H for patients weighing >100 kg. They recommend monitoring anti-Xa levels for patients initiated on higher doses based on weight, with a goal anti-Xa peak level of 0.2-0.4 IU/mL and a goal anti-Xa trough level of 0.1-0.2 IU/mL. The guidelines also address specific patient populations in whom a higher dose of LMWH may not be appropriate. In patients >65 years of age, weighing <50 kg, or with a creatinine clearance (CrCl) 30-60 mL/min, the guidelines recommend LMWH 30 mg Q12H. In patients with ESRD or a CrCl <30 mL/min, the guidelines recommend UFH 5000 units Q8H. In patients with brain and spine trauma, the guidelines recommend LMWH 30 mg Q12H. Lastly, in pregnant patients, the guidelines recommend LMWH 30 mg Q12H if the patient weighs ≤90 kg or LMWH 40 mg Q12H if the patient weighs >90 kg.

Following suit, the American Association for the Surgery of Trauma Critical Care Committee published updated guidelines in 2021 and the American Association for the Surgery of Trauma and American College of Surgeons-Committee on Trauma published updated guidelines in 2022. The American Association for the Surgery of Trauma Critical Care Committee recommends a weight-based approach in patients with a body mass index (BMI) >30 kg/m^2, with LMWH 30 mg Q12H for patients weighing 50-60 kg, LMWH 40 mg Q12H for patients weighing 61-99 kg, and LMWH 50 mg Q12H for patients weighing >100 kg. They also recommend titrating to a goal anti-Xa peak level of 0.2-0.4 IU/mL. The American Association for the Surgery of Trauma and American College of Surgeons-Committee on Trauma recommends LMWH 40 mg Q12H, except for patients who are >65 years of age, weigh less than 50 kg, have a CrCl of 30-60 mL/min, have a TBI or SCI, or are pregnant. In these patients, LMWH 30 mg q12H is recommended. Adjusting the dose of LMWH to an anti-Xa peak level of 0.2-0.4 IU/mL or anti-Xa trough level of 0.1-0.2 IU/mL may be considered. Additionally, for patients with a BMI >30, initiating VTE prophylaxis with LMWH 0.5 mg/kg Q12H is appropriate. In patient with ESRD or a CrCl <30 mL/min, the guidelines recommend UFH 5000 units Q8H.

Recently published guidelines challenge the common practice of initiating VTE prophylaxis with LMWH 30 mg Q12H based upon historical data. They claim that new evidence shows LMWH 30 mg Q12H leads to inadequate prophylaxis. A review of the new evidence and dosing strategies is necessary prior to implementation of these new guideline recommendations.

Dosing Strategies[27-28]

LMWH dosing strategies include fixed-dosing (30 mg Q12H, 40 mg Q12H, or 50 mg Q12H), weight-based dosing (0.5 mg/kg Q12H or 0.6 mg/kg Q12H), and anti-Xa level-guided dosing. Anti-Xa level-guided dosing is founded on the theory that fixed-dosing may lead to subprophylactic anti-Xa levels, which in turn may lead to decreased efficacy and more VTE events. This theory is supported by a prospective study from Malinoski and colleagues published in 2010. The study included 54 SICU patients, with 85% of patients suffering from trauma. All patients received LMWH 30 mg Q12H for VTE prophylaxis. The primary outcome of proportion of low anti-Xa trough levels (defined as ≤0.1 IU/mL, drawn 1-hour before the fourth dose) occurred in 50% of patients. VTE occurred in 26% of patients. The authors found that patients with low anti-Xa trough levels had a higher incidence of VTE (41% vs. 11%, P= 0.013) and DVT (37% vs. 11%, P= 0.026). Patients with low anti-Xa trough levels had lower anti-Xa peak levels, but anti-Xa peak levels were not different in those with and without a DVT. This study from Malinoski and

colleagues suggests low anti-Xa trough levels are associated with higher rates of VTE, and a large proportion of patients receiving LMWH 30 mg Q12H may have low anti-Xa trough levels.

It is important to note that anti-Xa levels may be influenced by several factors. Impaired renal function, hypertriglyceridemia, sampling close to heparin administration site, and direct oral anticoagulants may lead to increased anti-Xa levels, while delay in sample analysis, hemolysis, antithrombin deficiency, increased heparin-binding proteins, obesity, and hyperbilirubinemia may lead to decreased anti-Xa levels. It has also been suggested that consumption coagulopathy may influence anti-Xa levels. Severe trauma patients often possess several factors known to influence anti-Xa levels as a result of TIC (antithrombin deficiency, consumption coagulopathy), and therefore anti-Xa levels should be interpreted cautiously.

Despite inherent limitations with anti-Xa level monitoring in trauma patients, anti-Xa level monitoring has been adopted and utilized in many studies investigating higher LMWH dosing regimens.

Literature Review[29-44]

At least 16 studies investigating different VTE prophylaxis dosing strategies in trauma patients have been published in recent years. Generally, studies have shown that both weight-based dosing (LMWH 0.5-0.6 mg/kg Q12H) and increased fixed-dosing (LMWH 40-50 mg Q12H) result in a greater proportion of patients achieving goal anti-Xa levels (peaks 0.2-0.6 IU/mL, troughs ≥0.1 IU/mL). However, only 3 studies have shown a lower incidence of VTE with these dosing strategies, and only 1 study has shown increased bleeding suggested by more patients requiring ≥4 blood transfusions. Some studies have also found patients with VTE to have anti-Xa levels at goal. It is important to note that most of these studies were not powered to detect a difference in VTE and bleeding, though it does raise the question of the clinical significance of increasing the dosage of LMWH to achieve goal anti-Xa levels. Recall, however, that Malinoski and colleagues found low anti-Xa trough levels to be associated with a higher incidence of VTE. Additionally, patient populations in these studies are limited to less critically ill trauma patients, with few studies including a substantial number of patients at increased risk of bleeding (TBI and SCI patients). Studies also do not account for doses held/missed due to surgeries or other reasons. Two of these 16 studies will be discussed in depth.

Association Between Enoxaparin Dosage Adjusted by Anti-Factor Xa Trough Level and Clinically Evident Venous Thromboembolism After Trauma (Ko et al.)

Ko and colleagues published a single institution, historic vs. prospective cohort comparison study in 2016 investigating whether targeting a prophylactic anti-Xa trough level by adjusting the LMWH dose would reduce the VTE rate in trauma patients. Patients were included if they received ≥3 doses of LMWH. The retrospective control group received LMWH 30 mg Q12H while the prospective, adjustment cohort was initiated on 30 mg Q12H with dosage adjustments occurring in 10-mg increments if the anti-Xa trough level (drawn 30-60 minutes before the 4th dose) was ≤0.1 IU/mL. Outcomes included hospital and ICU length of stay, transfusion requirements, hematocrit at discharge, and diagnosis of VTE (prompted by signs/symptoms and confirmed by duplex ultrasound or CT).

This study included 205 patients: 118 in the retrospective control group and 87 in the prospective, adjustment cohort. The median age of patients was 36 (27-52) years, and the median BMI was 24.4

(21.9-27.5) kg/m^2. 75.1% of patients were male and 49.3% of patients were white. The median ISS was 13 (9-22) and was statistically significantly higher in the prospective, adjustment cohort (17 vs. 10, P= 0.01). The median CrCl was 118.8 mL/min. The most common injury type was lower extremity fracture (38.5%), followed by spine fracture (22.0%), pelvic fracture (18.0%), upper extremity fracture (17.1%), TBI (12.2%), and SCI (6.8%). Significantly more patients in the prospective, adjustment cohort had spine fractures (28.7% vs. 16.9%, P= 0.04).

There was no difference between the prospective, adjustment cohort and retrospective control group in the percentage of patients receiving packed red blood cells (pRBCs) (6.9% vs. 12.7%, P= 0.18), median mL of pRBCs transfused (0 vs. 0, P= 0.20), median hematocrit at discharge (34.4% vs. 32.7%, P= 0.19), or median length of hospital stay (10 days vs. 8 days, P= 0.09). However, the prospective, adjustment cohort had a lower incidence of VTE (1.1% vs. 7.6%, P= 0.046) and a shorter median ICU length of stay (2 days vs. 1.5 days, P= 0.009). The 1 VTE event in the prospective, adjustment cohort was associated with an anti-Xa trough level of 0.1 IU/mL, which by study definition was consider sub-prophylactic (goal anti-Xa trough level >0.1 IU/mL). Sub-prophylactic anti-Xa trough levels occurred in 83.9% of patients and 65.5% of those patients required a dosage adjustment to 40 mg Q12H. The authors also compared patients with sub-prophylactic anti-Xa trough levels to patients with prophylactic anti-Xa trough levels in the prospective, adjustment cohort and found that a higher median CrCl was the only baseline characteristic associated with sub-prophylactic anti-Xa trough levels (117.1 mL/min vs. 92.8 mL/min, P= 0.046). The authors concluded that when LMWH is dosed to achieve a target anti-Xa trough level in trauma patients, there is a decreased rate of VTE without an increased risk of bleeding.

Strengths of this study include the large sample size (n= 205), variety of injuries included, inclusion of critically ill patients (67.8% of patients in the prospective, adjustment cohort received ICU care), and inclusion of patients at risk for VTE (median ISS 13, 38.5% of patients with lower extremity fracture, 22.0% of patients with spinal cord fracture, and 18.0% of patients with pelvic fracture). Additionally, by only checking for VTE in patients with signs/symptoms, the authors minimized the risk of information bias. A limitation of this study includes the lack of a power calculation/risk of a type II error. Considering the authors found a difference in the incidence of VTE, a type II error seems unlikely. The authors also did not report a median weight for the retrospective control group, which raises the question of a difference in weight-based dosing being responsible for the difference in the incidence of VTE. However, considering there was no statistically significant difference in BMI between groups, this seems less likely. The young median age (36 years), high percentage of males (75.1%), high percentage of white patients (49.3%), low median BMI (24.4 kg/m^2), and relatively low median ISS (13) also limit the external validity/generalizability. Additionally, the study did not include many patients at risk of bleeding (12.2% of patients with TBI, 6.8% of patients with SCI).

In summary, this was the first study to demonstrate that when LMWH is dosed to achieve a target anti-Xa trough level in trauma patients, there is a decreased rate of VTE without an increased risk of bleeding. Most patients requiring dosage adjustment were adjusted to 40 mg Q12H, or 0.52 mg/kg Q12H based on the median weight of 76 kg in the prospective, adjustment cohort. It is difficult to generalize the results of this study to all trauma patients, especially those at risk of bleeding (TBI, SCI patients). Remaining questions include whether LMWH 30 mg Q12H should remain the starting dose and whether anti-Xa levels need to be routinely monitored.

Weight-Based Enoxaparin Achieves Adequate Anti-Xa Levels More Often in Trauma Patients: A Prospective Study (Stutsrim et al.)

Stutsrim and colleagues published a single institution, historic vs. prospective cohort comparison study in 2021 evaluating the adequacy of factor Xa inhibition with an emphasis on adequate trough levels in noncritically ill trauma patients using weight-based LMWH 0.6 mg/kg Q12H. Patients were included if they received 3 consecutive doses of LMWH, and patients were excluded if they were at high risk of bleeding (patients with TBI, spine fracture, and/or epidural catheters). The pre- group received LMWH 30 mg Q12H and the post- group received LMWH 0.6 mg/kg Q12H. Outcomes included the percentage of patients with adequate anti-Xa levels (defined as a peak ≥0.2 IU/mL checked 4 hours after the fourth dose and a trough ≥0.1 IU/mL checked 30-60 minutes prior to the fourth dose), VTE incidence (prompted by signs/symptoms), and major bleeding (defined as bleeding requiring transfusion or return to the operating room).

This study included 200 patients: 100 in the pre- group and 100 in the post- group. The median age was 48 years and 63-65% of patients were male. 76-85% of patients suffered from blunt injury. The median CrCl was 114.4-128.6 mL/min. The median ISS was 17 in the pre- group vs. 13 in the post- group (P= 0.003), the median BMI was 25.8 kg/m^2 in the pre- group vs. 28.2 kg/m^2 in the post- group (P= 0.045), and the median number of consecutive LMWH doses received prior to anti-Xa level was 7 in the pre- group vs. 5 in the post- group (P= 0.038).

The median anti-Xa peak level (0.22 vs. 0.47, P <0.001), median anti-Xa trough level (0.07 vs. 0.2, P <0.001), percentage of patients with an adequate peak (61% vs. 97%, P <0.001), percentage of patients with an adequate trough (34% vs. 82%, P <0.001), percentage of patients with an adequate peak and trough (31% vs. 79%, P <0.001), percentage of patients with an appropriate range peak (0.2-0.6 IU/mL) (51% vs. 74%, P= 0.001), and percentage of patients with a supratherapeutic peak (>0.6 IU/mL) (3% vs. 21%, P <0.001) were all statistically significantly different in the pre- group vs. the post- group, with the post- group having higher values and percentages for all outcomes. There was no difference in bleeding or VTE incidence. No patients in the pre- group experienced VTE, while 1 patient in the post- group experienced VTE. The one patient in the post- group who experienced VTE had adequate anti-Xa levels. On univariate analysis, median BMI, median creatinine, and weight-based dosing were found to be associated with anti-Xa levels. On multivariable analysis, weight-based dosing was associated with higher odds of adequate anti-Xa levels (odds ratio 8.238, P <0.001). Further evaluation of peaks and troughs showed that adequate peaks did not predict adequate troughs, but adequate troughs predicted adequate peaks. 116/200 patients had adequate troughs, and of those 116 patients, 110 (95%) had adequate peaks.

The authors concluded that weight-based dosing achieves adequate VTE prophylaxis, as indicated by prophylactic anti-Xa trough levels, for the large majority of noncritically injured trauma patients. They also concluded that there is no need for dose adjustment when using weight-based dosing, and the adequacy of VTE prophylaxis should be defined by anti-Xa trough levels rather than anti-Xa peak levels.

Strengths of this study included the large sample size (n= 200), evaluation of both anti-Xa trough and peak levels, and inclusion of patients at risk for VTE (median age 48 years, median ISS 13-17). By only

checking for VTE in patients with signs/symptoms, the authors minimized the risk of information bias. A limitation of this study is the lack of a power calculation/risk of a type II error. Considering the authors found a difference in the percentage of patients with adequate anti-Xa levels, a type II error seems unlikely. However, a type II error could have occurred with the outcomes of VTE and bleeding. The authors also did not report median weights for either group, which raises the question of whether the weight-based dose in the post- group was different from the dose in the pre- group (30 mg Q12H). However, considering the post- group had a statistically significantly higher median BMI compared to the pre- group, this seems unlikely. The lack of weight reporting also makes it impossible to determine the median dose and difficult to implement the results. The young median age (48 years), high percentage of males (63-65%), low median BMI (25.8-28.2), and exclusion of critically ill patients also limit the external validity/generalizability. Additionally, the study excluded patients at risk for bleeding (patients with TBI, spinal cord fractures). The clinical significance of the outcome of adequate anti-Xa levels is unknown, as there was no difference in bleeding or VTE events between groups. However, the 1 VTE event that occurred was in a patient with adequate anti-Xa levels.

In summary, this study showed weight-based dosing (0.6 mg/kg Q12H) was associated with a greater proportion of patients achieving adequate anti-Xa levels compared to 30 mg Q12H. Adequate troughs predicted adequate peaks, but adequate peaks did not predict adequate troughs, suggesting anti-Xa trough levels should be used to monitor the adequacy of VTE prophylaxis. The one patient in the post- group who experienced VTE had adequate anti-Xa levels, questioning the relationship between anti-Xa levels and risk of VTE. Additionally, since a high proportion of patients achieved anti-Xa trough levels on 0.6 mg/kg Q12H (82%), routine anti-Xa monitoring is likely unnecessary. It is difficult to generalize the results of this study to all trauma patients, especially those at risk of bleeding (TBI, SCI patients). Overall, this study suggests initiating VTE prophylaxis with LMWH 0.6 mg/kg Q12H in patients not at risk of bleeding is an option and would not require routine anti-Xa level monitoring.

Factors Associated with Lower/Higher Dosage Requirements[30,35-36,40,43,45-46]

Several studies have performed analyses to identify predictors of lower/higher LMWH dosage requirements. Lower CrCl (81.5 mL/min vs. 93.7 mL/min, 93.3 mL/min vs. 138.8 mL/min) and older age (48 vs. 32 years) have been associated with lower dosage requirements (LMWH 30 mg Q12H), while higher CrCl (125.9 mL/min vs. 93.7 mL/min, 131 vs. 89 mL/min, 117.1 mL/min vs. 92.8 mL/min), greater weight (87.5 kg vs. 70.5 kg, 69-100 kg vs. ≤69 kg, >100 kg vs. ≤69 kg), higher body surface area (BSA) (2.05 m^2 vs. 1.90 m^2), and lower weight-based doses (0.38 mg/kg vs. 0.45 mg/kg) have been associated with higher dosage requirements. Monitoring anti-Xa levels may be appropriate in patients with a low creatinine clearance, older age, and/or greater weight.

Key Takeaways

Recent guideline updates have brought into question the practice of initiating all trauma patients on LMWH 30 mg Q12H for VTE prophylaxis. This practice is based upon decades-old literature which found LMWH 30 mg Q12H resulted in a lower incidence of VTE compared to UFH. However, most historic literature did not report patient weights. More recently, studies have suggested that anti-Xa level monitoring can be used to monitor the adequacy of VTE prophylaxis. An association between inadequate anti-Xa trough levels (≤0.1 IU/mL) and increased incidence of VTE has been described by a few studies, though not all studies consistently show this association and some studies have even

described patients with VTE as having adequate levels. Several studies have also reported a lower percentage of patients achieving adequate anti-Xa levels with LMWH 30 mg Q12H vs. increased fixed-dosing (LMWH 40-50 mg Q12H) and weight-based dosing (LMWH 0.5-0.6 mg/kg Q12H). Only 1 study has suggested an increased risk of bleeding (defined as a greater proportion of patients requiring ≥4 blood transfusions) when LMWH was adjusted based on anti-Xa levels. Major limitations of available studies include lack of power calculations to detect statistically significant differences in the clinical outcomes of VTE and bleeding, as well as underrepresentation of patients at increased risk of bleeding (TBI, SCI patients).

Initiating VTE prophylaxis with either LMWH at increased fixed-doses (40-50 mg Q12H) or with weight-based dosing of LMWH (0.5-0.6 mg/kg) appears to be appropriate, as these regimens have been shown to increase the proportion of patients with adequate anti-Xa levels and may decrease the incidence of VTE without increasing the risk of bleeding. Maximum weight-based doses are rarely mentioned, but a maximum dose of 50 mg Q12H seems reasonable based on studies with fixed-doses and median patient weights reported in available studies. While routine anti-Xa level monitoring is likely unnecessary, monitoring anti-Xa levels may be appropriate in certain patient populations (older age, lower CrCl, greater weight). When anti-Xa level monitoring is desired, anti-Xa trough levels should be monitored. LMWH 30 mg Q12H remains appropriate for patients at increased risk of bleeding, including patients with TBI, SCI, >65 years of age, weighing <50 kg, or with a CrCl 30-60 mL/min, until these patient populations are better represented in the literature. UFH 5000 units Q8H remains appropriate for patients with ESRD or a CrCl <30 mL/min. Additional studies investigating the incidence of VTE and bleeding events with these dosage strategies are needed, as well as studies including more critically ill, severely injured trauma patients and patients at increased risk of bleeding. Studies better identifying patient populations who may benefit from anti-Xa level monitoring would also be beneficial. Ultimately, decisions regarding the dosing of VTE prophylaxis in trauma patients should take into account patient-specific factors, including risk of bleeding.

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