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### SUMMARY

Obesity is associated with an increased rate of venous thromboembolism (VTE) among trauma and surgical patients. The optimal dosing of enoxaparin for VTE prophylaxis in this population is not clearly defined as the relationship between monitoring of therapy and outcomes is lacking, obese patients may not follow a predictable dose response, and they often have multiple other risk factors for VTE. Non-standard enoxaparin dosing should therefore be considered in these patients to reduce their risk of VTE.

### RECOMMENDATIONS

- **Level 1**
  - **None**
- **Level 2**
  - **In trauma and surgical patients with a BMI >35 kg/m<sup>2</sup>, standard enoxaparin dosing (30 mg SQ twice daily) is inadequate; such patients should receive 40 mg SQ twice daily.**
- **Level 3**
  - **Standard heparin and enoxaparin dosing should be used in traumatic brain injury patients until the safety of weight-based therapy has been documented.**
  - **Non-standard high-dose enoxaparin dosing and weight-based dosing does not increase the risk of bleeding.**
  - **In patients with BMI > 30 kg/m<sup>2</sup>, consider monitoring anti-Xa levels to ensure appropriate prophylaxis (target anti-Xa level: 0.2-0.5 IU/mL) if using the low non-standard enoxaparin dose, but not needed if doing weight-based dose.**

### INTRODUCTION

VTE is a serious complication in hospitalized patients, contributing to increased hospital length of stay, cost, morbidity, and mortality. Among the many risk factors for VTE are surgery, trauma, history of malignancy, and immobility. Obesity, which is increasing in incidence by 0.4-0.5 kg/m<sup>2</sup> a year worldwide, is also a well-established risk factor for VTE (1). For every 5 kg/m<sup>2</sup> increase in BMI, there is an 85% increase risk of VTE complication among bariatric surgery patients (2). There are proinflammatory and procoagulant consequences of having excess adipose tissue resulting in up to a 2.5-fold increase risk of venous and arterial thromboembolism likely attributed to mediators of coagulation (3). Trauma, a well-established risk factor for VTE, is associated with prolonged immobility as well as the potential of serious bleeding risk. Chemical thromboprophylaxis against VTE in trauma patients is commonly achieved with subcutaneous enoxaparin. Enoxaparin is a low molecular weight heparin routinely given at a standard 30 mg twice-daily dosage--or in a single 40 mg dose daily—and favored for the ease of administration and its

### LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based on the medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

predictable pharmacokinetics. It inactivates Factor Xa to a greater extent than unfractionated heparin, and due to its predictable efficacy, anti-Xa levels are not routinely monitored (4). Current research suggests that target anti-Xa levels may not be achieved in many patients with “standard” enoxaparin dosing regimens. Thus, when standard enoxaparin dosages are administered to obese trauma patients, they may not be achieving the desired therapeutic effect (5-7). An evidence-based approach to the dosing of low molecular weight heparin is needed to provide appropriate thromboprophylaxis in high-risk obese trauma patients.

## LITERATURE REVIEW

There are no published multi-center, randomized controlled trials of high quality evaluating the dose of enoxaparin for VTE prophylaxis in obese trauma patients.

### Anti-Xa Level

Variation exists in the methods used to assess anti-Xa levels. Early recommendations were based on “trough” levels, however more recent studies use “peak” levels. Other studies have measured anti-Xa levels at variable time points making comparison of effect among studies difficult (8-12). The American College of Chest Physician in guidelines recommend measuring peak anti-Xa levels 4 hours after dosing (3). The generally accepted target peak anti-Xa level for prophylactic VTE anticoagulation is 0.2-0.4 IU/ml (13).

Multiple studies demonstrate an inverse relationship between BMI and anti-Xa level following administration of enoxaparin (5-7,9-11). A prospective study with 61 patients found most patients actually had a sub target anti-Xa level and that lower anti-Xa levels were more likely to be seen in obese patients (6). Celik et al. observed a linear relationship between achieved anti-Xa level and patient weight when three groups (150 kg) were all given the same “high-dose” prophylactic enoxaparin regimen (40 mg BID) (8). Patients with the greatest weight had the lowest anti-Xa levels.

There is also concern that standard dose regimens may not achieve target levels in all critically ill trauma and surgical patients. In a prospective study by Malinoski D et al., 54 critically ill trauma and surgery patients were given a standard dose regimen of enoxaparin 30 mg BID and their anti-Xa levels were monitored. They found that standard doses led to low anti-Xa levels in half of the patients and this was associated with higher rates of VTE (5). A prospective study by Lin H et al. reviewed 84 burn patients found a low incidence of VTE (2.4%) and no increase in bleeding events when an escalating dosage regimen guided by anti-Xa level monitoring was utilized (14). In a prospective observational study of trauma patients, Constantini et al. found that 70% of patients receiving standard enoxaparin dosing failed to achieve target anti-Xa levels and were more likely to be both male and obese (6).

There is increasing evidence that adjusting enoxaparin dosing for a patient’s weight or BMI increases the likelihood a patient will achieve target anti-Xa levels. Freeman et al. prospectively studied 31 medical patients with BMI >40 kg/m<sup>2</sup> (10). Patients were given one of three different weight-based regimens of enoxaparin: 40 mg daily, weight-based low-dose (0.4 mg/kg), or weight-based high-dose (0.5 mg/kg). The weight-based high-dose enoxaparin regimen resulted in a target anti-Xa level of 0.2-0.5 IU/ml in 85% of patients. This is in comparison to 82% of patients in the standard dose group and 36% in the weight-based low-dose group. Bickford et al. evaluated a weight-based enoxaparin regimen and found a dose of 0.5 mg/kg resulted in 86% of patients achieving therapeutic anti-Xa levels (7). They did not observe any bleeding complications and had no patients develop symptomatic pulmonary embolism. Rowan et al. showed that increasing the dose of enoxaparin from 30 mg BID to 40 mg BID improved the number of patients that reached target anti-Xa levels from 9% to 42% after the third dose of enoxaparin; however, despite the higher dose, more than half of bariatric surgery patients failed to achieve target anti-Xa levels (11). Kopelman et al. also showed high-dose enoxaparin improved the number of obese trauma patients that reached target anti-Xa levels (15). Borkgren-Okonek et al. examined anti-Xa levels in 223 obese patients, stratifying patients by BMI and adjusting their dose accordingly: patients with BMI > 50 kg/m<sup>2</sup> received 60 mg BID. They found anti-Xa levels to be within target range after the third dose in 69% of patients respectively. The study had 7.6% of patients undergo a workup for VTE and had only one VTE event - that patient eventually was found to have hyperhomocysteinemia (12). A retrospective study published in 2021 by Taylor et al of a single institution site reviewed 300 trauma patients given enoxaparin 0.5 mg/kg twice daily and these patients were able to meet anti-Xa goal 91% of the time. This study categorized obese and non-obese groups, and the obese group met anti-Xa goals 95.6%. The conclusion of this study was to stop checking anti-Xa levels and offer weight based dosing for enoxaparin (16).

### Anti-Xa level and VTE incidence

Despite the evidence that weight-based enoxaparin dosing improves the likelihood that patients will achieve a target anti-Xa level, it is unclear what anti-Xa level correlates with decreased VTE risk. This is explicitly acknowledged by the College of American Chest Physicians VTE prophylaxis guidelines (4). This is partly based upon the recognition that it remains unclear whether trough or peak anti-Xa levels are better measures of risk of bleeding and thrombosis. In one of the earliest studies by Levine et al., trough anti-Xa levels correlated with VTE and hemorrhage, however the study's results have not been fully replicated in subsequent trials (14,17,18). A number of studies examining dosing regimens either examined anti-Xa levels, or VTE incidence, but often are not powered to assess both. Further appropriately powered studies will be needed to clarify the relationship between anti-Xa levels and VTE incidence.

### Non-Standard Dose Enoxaparin in Obese Patients and VTE Incidence

Despite the lack of literature directly examining the relationship between non-target anti-Xa levels and VTE occurrence, there is support for non-standard enoxaparin dosing in improving VTE incidence in obese surgical and trauma patients. In a small study by Kopelman et al. of obese trauma patients that was not adequately powered to show a difference, high-dose enoxaparin trended towards but did not significantly decrease VTE rate (15). The PROBE study retrospectively surveyed the enoxaparin dosing regimens at five different bariatric surgery centers. They determined that the center that used a high dose enoxaparin (40 mg BID) regimen had the lowest rates of VTE compared to the other centers with increased risk of adverse events (19). In a study of 481 morbidly obese bariatric surgery patients with a mean BMI of 50 kg/m<sup>2</sup>, who were given two different dosing regimens (30 mg BID vs. 40 mg BID) with the primary outcome of thrombosis, it was found that the rate of VTE in the standard dose regimen was 5.4%, and the rate of VTE in the high-dose regimen was 0.6% (20).

In a retrospective cohort study evaluating greater than 9000 trauma patients with weight >100 kg, assigned to either standard (40 mg daily) or high-dose (40 mg BID) enoxaparin, Wang et al. found that high-dose thromboprophylaxis nearly halves the rate of VTE in patients with a BMI greater than 40 kg/m<sup>2</sup> (1.48% vs 0.77%, OR 0.52, p=0.05, 95% confidence interval [CI] 0.27-1.00). In patients with BMI <40 kg/m<sup>2</sup>, there was no demonstrated benefit to high dose thromboprophylaxis, even though those patients had weights greater than 100 kg. They also conducted an analysis of bleeding complications, which found that there was no statistically significant increase in bleeding complications with high dose thromboprophylaxis for BMI both less than and greater than 40 kg/m<sup>2</sup> (21).

## **DISCUSSION**

The literature examining anti-Xa levels uses three different dosing approaches: 1) weight-adjusted; 2) nonstandard high-dose enoxaparin (40 mg BID); and 3) anti-Xa level-adjusted enoxaparin dosing. The literature demonstrating a decrease in VTE outcomes among obese patients primarily uses non-standard high-dose enoxaparin as its intervention (15,19-21). A literature review by Shelkrot et al. in 2014 looking at eight studies in patients with BMI >40 kg/m<sup>2</sup> concluded that the strongest evidence for thromboprophylaxis in obese patients is enoxaparin 40 mg BID (22). These studies demonstrated increased success in achieving target anti-Xa levels and variably demonstrated a trend towards lower VTE rates. However, a more recent literature review from 2021 by Rappold JF et al. reported 81.6% of 49 trauma centers use weight base dosing regimens in their trauma ICU's, with 0.5-0.6 mg/kg twice daily as the regimen with anti-Xa level target of 0.2-0.4 IU/mL and shown decrease VTE and no increase in bleeding complications (13).

There are advantages and disadvantages to each dosing approach mentioned above. The advantages to using high dose enoxaparin, in contrast to a weight-adjusted or anti-Xa level-adjusted enoxaparin strategy, are ease of dosing, decreased chance of medication error, and ease of dispensing. For weight adjusted dosing, this could change during a hospitalization; in particular, critically ill patients receiving fluids can retain weight, thus receiving a higher dose of enoxaparin than needed. This remains an area where additional research is needed on a proper dosing regimen, as the studies evaluating a weight-based regimen have not been adequately powered or directly compared to a high-dose regimen. An internal review of our experience with pulmonary embolism and obesity identified a seven-fold higher risk of pulmonary embolism among patients with a BMI > 35. For this reason, we recommend high dose enoxaparin 40 mg BID for trauma and surgical patients with a BMI >35 kg/m<sup>2</sup> (Class II recommendation). However, given the ease of reversal, consideration should be given to using unfractionated heparin in patients with a high bleeding risk or with kidney injury as low molecular weight heparin is cleared through the renal system.

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