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Prevention of Deep Vein Thrombosis in Obese Trauma Patients

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Background:

Deep vein thrombosis (DVT) is a frequent occurrence in trauma patients secondary to traumatic injury due to immobilization, reparative surgeries, and procedures, if no/minimal prophylaxis is utilized. Traumatic injury increases risk for DVT by 50%, with the highest risk categories of injuries including spinal injuries (62%), pelvic fractures (61%), and leg fractures (80%)[1]. Undiagnosed or untreated, a thrombus from DVT can cause pulmonary embolism (PE) and sudden death for 25% of patients with PE[2]. Unfortunately, DVT screening protocols using duplex ultrasound imaging or D-dimer measurement[1] varies widely among trauma centers in the United States[3], even though the majority of DVT occurrences are asymptomatic[2]. According to Costantini et al, trauma centers employing "more aggressive screening protocols [are] associated with higher DVT rates," suggesting that asymptomatic DVTs may exist in far greater quantities than the current data suggest.

The current data may not discriminate between patient characteristics, such as weight and BMI, that affect the development of venous thromboembolisms (VTE) and appropriate dosing strategy of chemoprophylaxis. Most clinical studies examining VTE chemoprophylaxis efficacy only include patients with a BMI <30 kg/m^2. In the studies that include obese patients, this population is a small subset of the study subjects, and therefore the sample size of patients with a BMI ≥30 kg/m^2 is relatively small[2]. CDC obesity statistics[5] estimate that more than 42% of the American population falls within the overweight or obese category, defined as a BMI ≥30 kg/m^2, and severe obesity defined as ≥40 kg/m^2. It is critical to study these patients in relation to traumatic injury and VTE prevention for several reasons: 1) a large percentage of the population is defined as obese; 2) obesity rates and VTE occurrence have been correlated[4,6]; and 3) the pharmacokinetic behavior of chemoprophylaxis such as low molecular weight heparin (LMWH) medications, specifically enoxaparin, is different in the obese patient due to elevated levels of adipose tissue and decreased vasculature within that tissue relative to their non-obese counterparts[4]. In a review article by Sakers et al[14] describing adipose tissue function and regulation in both obese and non-obese individuals, adipose-tissue metabolic dysfunction can be induced by hypoxia. Hypoxemic conditions within tissues arise when "hypertrophic adipocytes (reaching 200+ μm in diameter) ...exceed the diffusion limit of O_2 (typically 100-200 μm in tissues)"[14]. Obesity causes the body's genetic response to hypoxia, the creation of new blood vessels, to malfunction and promote inflammation and fibrosis instead[14].

While there are unhealthy non-obese individuals who have adipose-tissue metabolic dysfunction and there are healthy obese individuals who do not have this type of metabolic dysfunction, obesity has been shown to be a culprit in inhibiting angiogenesis[14], which is the formation of new blood vessels. Reduced or avascular abdominal adipose tissue could prevent enoxaparin from reaching the bloodstream and reaching its full prophylactic efficacy.

As enoxaparin is a subcutaneous injection into the abdomen, it generally distributes from the injection site into the blood and vascular tissue[6]. In obese patients, the amount of adipose tissue retained at the injection site is of concern due to the high molecular weight of adipose tissue, low lipid solubility, and high plasma protein binding[4,8]. These dynamics may prevent therapeutic levels of enoxaparin from reaching the bloodstream, reducing efficacy of VTE

chemoprophylaxis. For these reasons, obesity increases the risk of VTE by 2 to 3 times[11], and according to Wang, et al. "morbid obesity increases the risk of fatal PE twelve-fold."

Monitoring of patients prescribed LMWH is done using an Anti-factor Xa (AFXa) laboratory assay, which is considered the gold standard measurement. Consensus is AFXa levels should reach 0.2 – 0.5 IU/mL for prophylactic dosing[18], although this study does not specify if these are peak or trough levels. However, much like DVT screening, not all trauma centers routinely monitor AFXa levels in patients once LMWH has been initiated.

There is currently an ongoing debate over what standard dosing regimens of enoxaparin should be utilized in achieving therapeutic levels of AFXa in the prevention of DVT and PE in trauma patients: 30 mg BID or 40 mg QD[7]. This debate includes when to initiate enoxaparin, when to hold for surgeries and/or epidural placement, and when to resume[9]. Other weight-based dosing regimens have been suggested as well: 40 or 50 mg BID[2,4], with the rationale that obese patients have higher risk of VTE -- even when following a standard dosing regimen[6] -- and consequently the standard dosing protocols may be insufficient[2,6,8,11].

In a study performed by Riha, et. al.[7], the surgical population was studied in correlation with the two standard dosing strategies of enoxaparin with the objective of comparing DVT rates and corresponding anti-Xa levels. 63 patients were included in the study; 39 males and 24 females comprised the subject population. The mean BMI was 34.5 ± 14.3 kg/m^2, placing the mean sample within range of obese values. Anti-factor Xa levels were monitored, and it was found that in the first 2 days, the median anti-Xa levels were lower in the group that developed DVTs compared to the group that did not. In the 30 mg BID group, 25% of the patients developed a DVT; only 2.9% of the 40 mg once daily group developed a DVT[7]. Although this study's sample size was small and the population was not a trauma inpatient population, the trends found may be extrapolated to the trauma population due to the similarity of procedures and time spent immobilized.

In a retrospective cohort study performed by Wang, et al.[11], the data from over 3900 morbidly obese patients with a BMI ≥40 kg/m^2 were analyzed. It was found that increasing thromboprophylaxis for patients with a weight >100 kg and BMI ≥ 40 kg/m^2 from 40 mg QD (low dose) to 40 mg BID (high dose), reduced in-hospital VTE by 50% (1.48% vs 0.77%). The high dose group did not have higher incidence of increased bleeding, concluding that high dose thromboprophylaxis can be utilized without increasing bleeding complications.

The current literature also does not reach a consensus as to what the guiding weight-based parameter should be in prescribing prophylactic enoxaparin dosing: body mass, body surface area (BSA), or BMI. In the study performed by Constantini, et al., BMI was not found to have a relationship with plasma AFXa levels; rather, an inverse relationship was found correlating body mass and BSA[3,12]. In a European study performed by Rodier, et al., it was body surface area (BSA) followed by weight that most closely corresponded with plasma AFXa levels[12]. Rodier et al. also found that "using a weight-based dosing regimen of 0.5 mg/kg q12h with 10 mg dose adjustments based on plasma AFXa assays resulted in improved chemoprophylaxis"[12]. This dose adjustment protocol varies from the weight-based dose adjustment protocol evaluated by Rondina, et al., who found that 0.5 mg/kg once daily resulted in "peak AFXa levels within or near recommended range for thromboprophylaxis"[13]. However, Rondina, et al.'s study only evaluated 28 morbidly obese patients and the average daily dose was 67 mg (±12), a much higher dose than many other studies or trauma institutions utilize. The study also did not find a correlation between peak AFXa levels and weight or BMI[13], a contrary finding compared to other studies.

In contrast, in a study performed by Veatch et al, it was found that creatinine clearance (CrCl), and not BMI, was an important predictor and factor in the determination of appropriate enoxaparin dosing[2]. A multivariate regression analysis of age, weight, Injury Severity Score (ISS), and CrCl was performed to analyze the association between factors determining enoxaparin dosing and AFXa levels. They concluded that for trauma patients with a low creatinine clearance (<50), the lower standard dose of enoxaparin 30 mg BID was sufficient to reach therapeutic levels of AFXa. While some obese patients were included in each sample, this study did not categorically study obesity related to enoxaparin dosing. The study did suggest that starting selected patients on 40 mg BID may be appropriate, as approximately 64.9% of the patients in their sample required an increase after starting at 30 mg BID due to sub-therapeutic trough AFXa levels of <.1 IU/mL.

In a study performed in 2012 by Nunez et al[17], the efficacy of weight-based dosing of enoxaparin at 0.6 mg/kg BID compared to 30 mg BID in critically ill trauma patients was evaluated using AFXa levels. 37 patients were included in this study; 31 patients (84%) achieved target trough AFXa levels between 0.1-0.2 IU/mL at the weight-based dosing strategy of 0.6 mg/kg BID. Only one bleeding complication occurred but was related to a rapid decrease in weight with diuresis. While this study utilized AFXa levels to monitor the therapeutic benefits of their higher weight-based dosing strategy, they concluded that evaluating AFXa levels may not be necessary.

In 2020, the Western Trauma Association (WTA) updated the algorithm for VTE prophylaxis posttraumatic injury[9] in patients 18 years and older with an Injury Severity Score (ISS) of 10 or more (Figure 1). Because ISS cannot be calculated upon initial examination at the hospital emergency department (ED), the WTA recommends that either the Greenfield Risk Assessment Profile (RAP) or the Trauma Embolic Scoring System be utilized to calculate VTE risk. As obesity is the second risk factor assessed (age is the first factor) on the Greenfield RAP[10], the presence of obesity is included in step B as a consideration for VTE risk on the new algorithm.

The implications of this updated trauma algorithm are the increased recognition of the growing body of literature concluding that previous chemoprophylactic guidelines were unclear and insufficient to address the widespread incidence of VTE, especially in the obese trauma patient population. Therefore, we intend to evaluate trauma patients admitted to Oregon Health & Science University (OHSU) with an ISS ≥9 who received prophylactic enoxaparin for the prevention of VTEs between 2017 and 2020, with the goal of providing support of a dosing strategy specific to the obese trauma patient population. Our hypothesis is that higher body weight and BMI will correlate with larger enoxaparin doses, and therefore a non-standard dosing strategy will lower DVT rates in this population.

Methods:

Institutional Review Board approval was obtained for this retrospective chart review. The population included trauma patients identified through OHSU's Trauma Registry who were >17 years of age and had an ISS ≥9 from January 2017 through December 2020. Additional data was obtained from OHSU's OCTRI Data Warehouse regarding medications, surgical procedures, and clinical outcomes. Patients with a BMI ≥30 kg/m^2 were identified and categorized into four groups based on prophylactic enoxaparin dosing: 1) 30 mg BID, 2) 40 mg QD, 3) 60 mg in any dosing schedule, and 4) other non-standard doses, including 80, 90, 100, 105, 120, or 135 mg in any dosing schedule. These groups were chosen because standard practice is to prescribe either

30 mg BID or 40 mg QD to the trauma population, while some providers will choose to prescribe a higher dose based on body weight or body surface area (BSA). However, there is no consensus on what the higher dose should be across providers.

The initial sample size was 838 patients. Patients were excluded if they had a past medical history of developing DVTs or PEs, were never prescribed enoxaparin for VTE chemoprophylaxis, received other anticoagulant medication, or was prescribed a non-standard dose indicative of renal dysfunction. 24 patients were excluded based on these criteria, lowering the sample size to 814 subjects.

DVT diagnoses (positive or negative) were confirmed through provider notes of duplex ultrasound imaging results. Duplex ultrasound imaging is performed on day three after admission and repeated every seven days, per OHSU institutional protocol.

The variables analyzed were divided into four different categories: Baseline Patient Characteristics, Physiological Variables, Admission Data, and Overall Data. Baseline Patient Characteristics included sex (male/female), Age in years, and Injury Statistics (Injury Type—Blunt/Penetrating—and ISS). Physiological Variables included BMI, body surface area (BSA), and Weight in kilograms. Admission Data included Hospital Length of Stay (LOS), Days on a Ventilator, Intensive Care Unit LOS (ICU LOS), and number of surgeries. Overall Data included number of DVTs, number of PEs, Time to Positive DVT Diagnosis in Days, and Time to VTE prophylaxis (VTEp) in days.

IBM SPSS Statistics version 27.0 was used to perform data analytics: a Fisher's exact test was used to analyze categorical variables and a Pearson's Chi-square test was used to analyze numerical variables and relationships.

Results:

None of the variables in tables 1, 2, 3, or 4 were normally distributed and are therefore reported as a median and interquartile range (IQR). Table 5 variables are normally distributed.

Of the 814 subjects evaluated in this study, two-thirds of the subjects identified as male. There was no difference in sex, (p=0.52), age (p=0.34), or ISS (p=0.74) (Table 1). 757 of the subjects (93.0%) had suffered a blunt rather than penetrating trauma (Table 1). Among the total positive DVT diagnosis group, 100 (91.7%) had suffered blunt trauma. Although the number of penetrating injuries is considerably smaller, indicating less frequent occurrence, no significant difference was found between the blunt versus penetrating injury types (p=0.75).

Table 1 Baseline Patient Characteristics	30 mg BID n= 166	40 mg QD n= 609	60 mg n= 24	Other Dosing Schedules n= 15	P value
Sex					
Male (66.3 % of patients)	102 (61.4%)	412 (67.7%)	16 (66.7%)	10 (66.7%)	0.52
Female (33.7 % of patients)	64 (38.6%)	197 (32.3%)	8 (33.3%)	5 (33.3%)	
Age (years)	56.00 (39.50, 69.25)	57.00 (42.00, 70.00)	46.50 (40.25, 61.50)	51.00 (40.00, 60.00)	0.34
Injury Statistics					
Injury Type (% Within Enoxaparin Dose)					
Blunt	157 (94.6 %)	563 (92.4 %)	23 (95.8 %)	14 (93.3 %)	0.75
Penetrating	9 (5.4 %)	46 (7.6 %)	1 (4.2 %)	1 (6.7 %)	
ISS	14.00 (10.00, 21.00)	14.00 (10.00, 21.00)	14.00 (9.25, 22.00)	19.00 (10.00, 26.00)	0.74

A significant difference was found in BMI (Table 2) in the 60 mg BID group with BMI being significantly higher than all other groups ($p<0.01$). Significant differences were also found among BSA and weight ($p<0.01$).

Table 2 Physiological Variable	30 mg BID n= 166	40 mg QD n= 609	60 mg n= 24	Other Dosing Schedules n= 15	P value
BMI (kg/m2)	33.81 (31.83, 37.69)	34.06 (31.74, 38.75)	53.10 (36.88, 61.88)	32.45 (30.90, 37.14)	<0.01
BSA (m2)	3.02 (2.77, 3.24)	3.08 (2.85, 3.31)	3.37 (3.25, 3.37)	2.96 (2.83, 3.09)	<0.01
Weight (kg)	101.25 (89.98, 113.55)	104.30 (93.05,118.80)	130.30 (117.83, 180.28)	99.00 (92.50, 107.50)	<0.01

A significant difference was found between the dosing groups and the Hospital LOS ($p<0.01$) with the 60 mg BID and Other Dosing Schedules groups admitted twice as long as the other groups (Table 3). ICU LOS ($p=0.02$) and number of surgeries ($p=0.01$) were also significantly different. Days on a Ventilator was not found to be significantly different among the dosing groups ($p=0.28$). A significant difference was also found in number of surgeries ($p=0.01$), as the median number of surgeries in the Other Dosing Schedules group is three times higher than all other groups (Table 3).

Table 3 Admission Data	30 mg BID n= 166	40 mg QD n= 609	60 mg n= 24	Other Dosing Schedules n= 15	P value
Hospital LOS	7.00 (4.00, 12.00)	7.00 (4.00, 12.00)	11.50 (6.00, 14.75)	12.00 (9.00, 27.00)	<0.01
Days on a Ventilator	3.00 (2.00, 7.00)	3.00 (2.00, 9.00)	2.00 (1.50, 14.50)	9.00 (4.00, 19.50)	0.28
ICU LOS	2.00 (1.00, 4.00)	3.00 (1.25, 5.00)	3.50 (2.00, 9.00)	7.00 (3.00, 13.75)	0.02
# of surgeries	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	3.00 (2.00, 6.00)	0.01

Of the 814 subjects included in the study, 109 (13.4%) developed a DVT (Table 4). A significant difference in comparisons in positive DVT diagnoses was found between the 60 mg group and the 30 mg BID and 40 mg QD dosing groups ($p < 0.01$), as well as between the Other Dosing Schedules group and the 30 mg BID, 40 mg QD, and 60 mg groups ($p<0.01$).

Table 4 Overall Data	30 mg BID n= 166	40 mg QD n= 609	60 mg n= 24	Other Dosing Schedules n= 15	P value
# of DVTs (% of DVTs per group)	17 (10.2%)	77 (12.6%)	9 (37.5%)	6 (40.0%)	<0.001
# of PEs (% of PEs per group)	3 (0.02%)	10 (0.02%)	2 (0.08%)	2 (0.13%)	
% within total # PEs	17.60%	58.80%	11.80%	11.80%	0.002
Time to + DVT diagnosis in days	3.00 (3.00, 5.00)	3.00 (3.00, 4.00)	3.00 (3.00, 4.50)	3.00 (2.75, 12.25)	0.514
Time to VTEp in days	2.00 (1.00, 3.00)	1.91 (1.00, 2.00)	2.00 (1.00, 5.00)	8.00 (3.00, 13.00)	0.001

The enoxaparin dosage guideline is 0.5 mg/kg of body weight. The mean dosage prescribed for all subjects is 0.38 mg/kg (Table 5), which is below the guideline by 24%; therefore, the dosing guideline is not being met. While there is no significant difference in this sample between those who were diagnosed with a DVT and those who were not (p = 0.78), the enoxaparin chemoprophylaxis protocol most likely needs to be evaluated at an institutional level.

Table 5 Enoxaparin Mean Dose DVT No/Yes mg/kg	All Subjects	DVT-No	DVT-Yes	p-value
N	813	705	108	0.78
Mean ± Std. Dev.	0.38 ± 0.11	0.38 ± 0.10	0.39 ± 0.15	

Table 6 Enoxaparin Mean Dose By Group mg/kg	30 mg BID	40 mg QD	60 mg BID	Other Dosing Schedules
Mean	0.30	0.39	0.50	0.95

Discussion:

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The 60 mg and Other Dosing Schedules groups had higher positive DVT rate than the 30 mg BID and 40 mg QD groups. More risk factors were present in these two groups so the likelihood of higher DVT rates is expected.

The significantly higher BMI, BSA, and weight (Table 2) in the 60 mg BID group may be a contributing factor to the higher DVT rate compared to the 30 mg BID and 40 mg QD groups (37.5% vs 10.2% and 12.6% respectively). While there is no difference in length of time before VTE prophylaxis was initiated (Time to VTEp in days, Table 4) and the number of days before positive DVT diagnosis occurred (Time to +DVT diagnosis in days, Table 4) between the 60 mg group and the 30 mg BID and 40 mg QD groups, the proportion of positive DVT diagnoses and BMI, BSA, and weight of the 60 mg group is significantly higher than all other groups in this study. The average enoxaparin kg/mg dose prescribed for the 60 mg group was 0.5 mg/kg (Table 6) , the exact enoxaparin dosing guideline. The higher proportion of positive DVT diagnoses in this group support the indication for a higher weight-based dose.

While the median Days on a Ventilator, ICU LOS, and number of surgeries (Table 3) is consistent with the 30 mg BID and 40 mg QD groups, the Hospital LOS is equivalent to the higher acuity Other Dosing Schedules group. This finding implies that obesity increases recovery time equivalent with more injured patients.

The median Time to VTEp in Days (Table 4) is four times longer in the Other Dosing Schedules group than 30 mg BID, 40 mg QD, and 60 mg BID. The median number of surgeries is three times higher, and the median ISS is five points higher in this group. The time required to

achieve patient stabilization and reduced chance of bleeding risk increases with injury severity demonstrated by higher ISS scores in this group. DVT prophylaxis cannot initiated until there is little to no risk of bleeding complications. The length of time patients are immobilized is longer, which is a risk factor for the development of DVTs. Higher acuity patients often require more reparative surgeries, especially in cases of multisystem trauma. DVT prophylaxis is withheld for surgery and epidural placement per protocol due to the risk of excessive bleeding.

There is a significant difference between the dosing schedules for PE diagnosis ($p < 0.01$) (Table 4). This is significant because there is an increased frequency of both positive DVT and PE diagnosis in the higher dosing groups. While the positive PE diagnosis rate is higher within the 60 mg and Other Dosing Schedules groups when compared against the number of subjects within each dosing group, the proportion of PEs is higher in the 40 mg QD group (58.80%) when compared to total number of PEs. Of the 17 PE diagnoses, 10 (58.8%) had not developed a DVT prior to development of a PE.

While the Western Trauma Association (WTA) algorithm recommends 40 mg BID of enoxaparin for the majority of trauma patients[9], standard-of-care at OHSU has historically used the FDA-approved enoxaparin dosing protocols of 30 mg BID and 40 mg QD. The WTA does acknowledge that weight-based dosage may be necessary for some patients in their article published in the *Journal of Trauma, Acute Care, and Surgery* (2020)[ref]. Other weight-based recommendations from the WTA include 0.5 mg/kg BID, 0.6 mg/kg BID, 40 mg (61-99 kg), or 50 mg (>100 kg) dosing. They do recommend monitoring AFXa levels for patients on higher doses due to metabolic changes in CrCl that occur post-traumatic injury[9]. However, no protocol is provided with a rationale or metric besides weight to guide providers' decision in dosing protocol for an obese patient. Further, the WTA algorithm (Figure 1) does not contain a protocol within it that providers can quickly reference when determining the appropriate dosing regimen for patients of this population.

While weight and BSA provide a concrete physical measurement of an individual patient, BMI is a height and weight calculation performed electronically that is incapable of evaluating a patient's body composition. A "fit" patient may have a height/weight ratio that places them in the "obese" category, but not have the elevated amount of adipose tissue dispersed throughout their body. A patient who presents as "thin" may have more visceral fat in the abdomen than a patient who presents as "overweight." Therefore, the BMI metric is inaccurate at best and deceiving at worst. Overall body composition, and not BMI, should be the guiding metric for the determination of obesity status as higher proportions of lean muscle mass cannot be accounted for in the BMI metric. Ideally biotechnology measuring body composition should be created for the hospital setting. Rudimentary technology providing this measurement already exists on the consumer market; by improving the technology and designing or modifying an existing medical instrument, more data can be generated about a patient's overall body composition to inform more appropriate medication dosages across all fields of medicine.

Limitations to this study include the small sample sizes in the 60 mg and Other Dosing Schedules groups as the small sample sizes provide limited data to inform dosing protocols that improve patient outcomes. Lack of AFXa peak and trough data are also limitations as testing of peak and trough AFXa levels indicate therapeutic efficacy of enoxaparin. This test is not currently part of OHSU's standard of care for trauma patients, so no AFXa data was available for evaluation and therefore this analysis was not performed in our retrospective chart review.

As we are not including CrCl as a variable, we are assuming normal CrCl for all, as no patient included was prescribed a renal dosing protocol.

Even though AFXa testing is not the standard of care at this institution and CrCl was not a variable included in this study, it is important to note what therapeutic practices produce the best outcomes, which may lay the groundwork for consensus and nationwide protocols. It is also important to iterate that the variation in conclusions drawn by numerous studies do not support a consensus to guide providers as to how to effectively prevent VTE development by prescribing appropriate doses of enoxaparin in the obese trauma patient population.

Conclusion

This retrospective chart review analyzed the VTE outcomes of obese trauma patients prescribed 30 mg BID, 40 mg QD, 60 mg, or Other Dosing Schedules of the low molecular weight anticoagulant, enoxaparin. Despite small sample sizes in the latter two groups, we believe that re-evaluation of the standard dosing guideline of 0.5 mg/kg is not sufficient in obese (≥30 kg/m^2) and morbidly obese trauma patients (≥40 kg/m^2). It is also our recommendation that new technology be created for the hospital inpatient setting in order that body composition be utilized in guiding medication protocols due to the physiological functions of lean muscle mass. Future studies in comparative metric analysis between BMI and body composition may help lead the way in improving medication dosing protocols throughout the field of medicine.

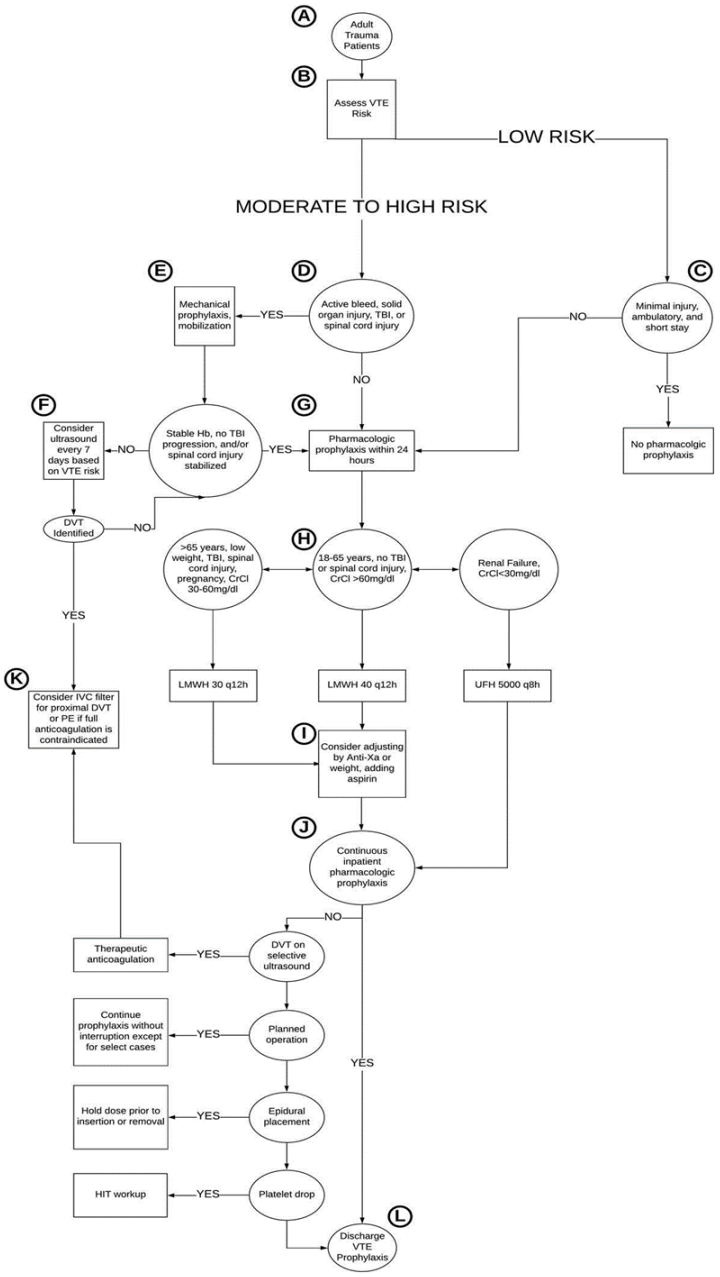

Figure 1. The WTA algorithm for VTE prophylaxis after trauma. Circled letters correspond to sections in the associated article. Algorithm circle-bubbles represent patient criteria; algorithm square-bubbles represent expert recommendations. CrCl, creatinine clearance; Hb, hemoglobin; LMWH, enoxaparin; q8h, every 8 hours; q12h, every 12 hours; UFH, unfractionated heparin.

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