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**Journal article:** *A retrospective analysis of the effectiveness of low molecular weight heparin for venous thromboembolism prophylaxis in trauma patients*

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# A retrospective analysis of the effectiveness of low molecular weight heparin for venous thromboembolism prophylaxis in trauma patients

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**KEYWORDS:**
Low molecular weight heparin;
Deep vein thrombosis;
Pulmonary embolism;
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Trauma

**Abstract**

**BACKGROUND:** In trauma patients, Enoxaparin (a low molecular weight heparin, LMWH) prophylaxis for venous thromboembolism (VTE) risk reduction is unproven.

**METHODS:** Cohort analysis conducted consisting of all trauma patients age >13 admitted to Level-I trauma center and hospitalized >48 hours. VTE risk determined by the Risk Assessment Profile. High risk patients received LMWH unless contraindicated, while low and moderate risk patients received LMWH at attending surgeon's discretion. Odds ratio for VTE by logistic regression. VTE incidence, relative risk (RR), and number needed to treat (NNT) to prevent deep vein thrombosis (DVT) or pulmonary embolism determined by risk category.

**RESULTS:** Cohort consisted of 2,281 patients (1,211 low, 979 moderate, 91 high risks). VTE occured in 254 patients (11.1%). High-risk patients had significantly higher VTE incidence, odds ratio = 31.8 ($P < .001$). VTE was significantly reduced in high-risk patients receiving LMWH versus those who did not (.26 vs .53, $P = .02$). Among moderate and high risk, prophylactic LMWH reduced the incidence of pulmonary embolism (RR = .19, NNT = 40.4, $P = .01$), and trended toward reduced DVT incidence (RR = .81, NNT = 27.3, $P = .15$). LMWH lowered DVT incidence (RR = .52, NNT = 4.1, $P = .03$) in high risk patients.

**CONCLUSION:** Prophylactic LMWH is associated with reduction of VTE in trauma patients.


Deep vein thrombosis (DVT) and pulmonary embolism (PE), known collectively as venous thromboembolism (VTE), are common life-threatening conditions in acute trauma patients. A study by Geerts et al[1] found DVT incidence to be as high as 58% among patients without prophylaxis. PE is the 3rd most common cause of death in patients who survive the 1st 24 hours.[1,2] Multiple approaches have been recommended for VTE prophylaxis, including the use of sequential compression device (SCD),[3] low-dose unfractionated heparin (LDUH),[4] inferior vena cava filter,[5] and low molecular weight heparin (LMWH).[2,6–8] Conflicting data exist as to whether LMWH is more effective than LDUH for the prevention of VTE. Initial findings by Geerts et al[6] suggested that LMWH was more effective than LDUH in preventing VTE; however, a more recent study published by Arnold et al[4] concluded that there was no difference in efficacy

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**Table 1** Demographics

| | LMWH | No LMWH | *P* value |
|---|---|---|---|
| Mean age | 45.4 | 45.2 | .82 |
| Total male | 332 | 1,259 | .98 |
| Total female | 143 | 541 | .98 |
| Mean ISS | 18.1 | 14.9 | <.001 |

Comparison of various demographic factors of patients who received LMWH to those who did not.

ISS = injury severity score; LMWH = low molecular weight heparin.

**Table 2** Logistic regression of VTE by RAP risk

| RAP risk | Odds ratio | Low 95% CI | High 95% CI | *P* value |
|---|---|---|---|---|
| Low | .0369 | .0262 | .0502 | <.001 |
| Moderate | 6.0797 | 4.2004 | 8.9909 | <.001 |
| High | 31.82 | 16.80 | 61.15 | <.001 |

Logistic regression of odds ratio of developing VTE by RAP risk group. Associated *P* values in right-hand column.

CI = confidence interval; RAP = Risk Assessment Profile; VTE = venous thromboembolism.

and that the use of LDUH resulted in significantly lower pharmacy costs to the hospital and patient. Mechanical prophylaxis with SCD has been shown to be a useful tool in preventing DVT, but because of its nature it cannot be implemented on patients with multiple extremity injuries which constitute a large proportion of trauma patients.[2,9,10] As reported by McMurtry et al,[11] the use of inferior vena cava filters has not been shown to decrease the overall incidence of PE, and because of this they should only be implemented in high-risk patients who have contraindications to anticoagulation.[2] The data for the effectiveness of LMWH are lacking; only one study by Knudson et al[8] in 1996 that consisted of 372 subjects has found that the use of LMWH was associated with decreased incidence of DVT in trauma patients. In 2008, Adams et al[12] published a large series consisting of nearly 3,000 subjects over the course of 4 years and found that aggressive ultrasound (US) screening with prophylactic treatment with LMWH resulted in a significant decrease in VTE incidence. The study failed to quantify the effectiveness of LMWH in decreasing the prevalence of VTE but rather advocated for an aggressive screening and prophylaxis protocol. Aggressive US screening and the use of LMWH prophylaxis as a recommendation require a significant demand on hospital resources; however, there has been no cost analysis performed to our knowledge with respect to the effectiveness of such a protocol. The purpose of this article is to evaluate the efficacy of Enoxaparin, an LMWH, for the prevention of VTE in trauma patients.

## Methods

We performed a retrospective cohort analysis of all trauma patients 13 years of age and older admitted to an American College of Surgeons-verified Level-I trauma center and hospitalized for more than 48 hours during the years 2003 and 2006. VTE risk assessment was based on the Risk Assessment Profile (RAP), a tool proposed by Greenfield et al[13] and validated in a large retrospective cohort by Hegsted et al.[14] Patients were classified as low, moderate, or high risk. By trauma service protocol, all high-risk patients received LMWH as well as mechanical prophylaxis if not contraindicated and were screened using US at 3-day intervals. Low- and moderate-risk patients had US screening after 1 week and received LMWH prophylaxis at the discretion of the attending surgeon. If patients had below-knee superficial thrombosis, they were screened at 3-day intervals for evidence of proximal progression. Repeat duplex in high-risk patients was performed by protocol. Mechanical prophylaxis was utilized for all low-, moderate-, and high-risk patients and consisted of SCD. PE was detected by computed tomography angiography or postmortem examination. The accuracy of the data abstraction was tested by inter-rater reliability on 2% of the patient charts and agreement was quantified by calculating observed agreement, Cohen's kappa coefficient, and prevalence-adjusted bias-adjusted kappa coefficient (PABAK). For each individual, we determined the risk of VTE according to categorical placement in low-, moderate-, and high-risk groups as determined by the RAP. Logistic regression was performed to determine the odds ratio of developing VTE based on the risk group. We then determined the proportion of individuals in each risk category that received prophylactic LMWH, which we considered as any amount $\geq 1$ dose for the purpose of this study. Within each risk category we determined the relative risk (RR) and number needed to treat (NNT) to prevent VTE or PE, using univariate logistic regression.

## Results

In the cohort of 2,281 patients, there were 2,077 blunt and 204 penetrating injuries, 1,596 male and 685 female, with a mean age of 45.2 years and a mean ISS of 15.5. In the cohort, 254 (11.1%) patients developed VTE. This analysis included 1,211 patients at low risk, 979 patients at moderate risk, and 91 patients at high risk. Analysis of data reliability showed a high level of agreement among the

**Table 3** Patients by risk category

| | Lovenox | No Lovenox | Ratio |
|---|---|---|---|
| Low | 126 | 1,068 | .44 |
| Moderate | 311 | 655 | 1.77 |
| High | 38 | 50 | 2.84 |

Patients who received LMWH compared to those who did not by risk category.

LMWH = low molecular weight heparin.

**Table 4** Venous thromboembolic events (values in parentheses represent proportion within that risk group and treatment group)

| Event | Lovenox | No Lovenox | *P* value |
|---|---|---|---|
| Moderate and high risk | | | |
| VTE | 56 (.16) | 148 (.21) | .08 |
| DVT | 55 (.16) | 140 (.19) | .15 |
| PE | 2 (.01) | 22 (.03) | .01 |
| PE death | 0 (.00) | 5 (.01) | |
| High risk | | | |
| VTE | 10 (.26) | 28 (.53) | .02 |
| DVT | 10 (.26) | 27 (.51) | .03 |
| PE | 0 (.00) | 4 (.08) | |
| PE death | 0 (.00) | 3 (5.66) | |

Venous thrombotic events among patients receiving LMWH and those who did not. Associated *P* values in right-hand column.
DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; VTE = venous thromboembolism.

abstractors. Binary data had observed agreement of 98%, mean kappa of .83, and mean PABAK of .94, and categorical data had an overall observed agreement of 97%, mean kappa of .88, and mean PABAK of .96. Comparing age, sex, and ISS scores of patients who received LMWH to those who did not, we see that there is no significant difference between age and sex of the 2 groups, and that patients who received LMWH have a significantly higher ISS score (Table 1). Logistic regression of the risk categories showed that patients at high risk have a significantly higher chance of developing VTE (odds ratio = 31.8, $P < .001$, 95% confidence interval: 16.8 to 61.1) (Table 2). LMWH was given to 126 (10.6%) of the patients at low risk, 311 (32.2%) of those at moderate risk, and 38 (43.2%) of those at high risk (Table 3). The ratio of patients who received prophylactic LMWH to those who did not receive LMWH in each of the risk categories low, moderate, and high were .44, 1.77, and 2.84 ($P < .001$), respectively (Table 3). This demonstrates that the proportion of patients given LMWH was higher in the high-risk group and lower in the low-risk group. In the high-risk group, the incidence of VTE was significantly lower among those patients who received LMWH than those who did not (.26 vs .53, $P = .02$) (Table 4). This trend continued when the moderate-risk group was included (.16 vs .21, $P = .08$), but was not significant. Among patients at moderate and high risk combined, prophylactic LMWH was associated with a significant reduction in PE (RR = .19, NNT = 40.4, $P = .01$) and a reduced incidence of DVT which was not statistically significant (RR = .81, NNT = 27.3, $P = .15$) (Table 5). Among high-risk patients only, LMWH significantly lowered the incidence of DVT (RR = .52, NNT = 4.1, $P = .03$).

## Comments

The overall VTE incidence rate of 11% in this study was remarkably lower than the 58% reported by Geerts et al.[1] The low prevalence of VTE in this study is even more remarkable considering the aggressive use of US and computed tomography directed by the trauma program screening protocol, which would be expected to identify asymptomatic DVT not diagnosed using clinical criteria. The findings of this study support the conclusion made by Adams et al[12] that an aggressive screening and prophylaxis

**Table 5** Relative risk of adverse outcome

| | Moderate and high risk | High risk |
|---|---|---|
| VTE | | |
| Relative risk | .78 (.59–1.03) | .50 (.28–.90) |
| Odds ratio | .74 (.53–1.04) | .32 (.13–.79) |
| Number needed to treat | 22.32 | 3.77 |
| DVT | | |
| Relative risk | .81 (.61–1.08) | .52 (.29–.94) |
| Odds ratio | .78 (.55–1.09) | .34 (.14–.85) |
| Number needed to treat | 27.34 | 4.06 |
| PE | | |
| Relative risk | .19 (.04–.79) | |
| Odds ratio | .18 (.04–.78) | |
| Number needed to treat | 40.35 | |

Relative risk, odds ratio, and number needed to treat in high-risk group and moderate and high-risk groups combined.
DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

protocol are an effective method for reducing VTE incidence in trauma patients. Knudson et al[8] have previously demonstrated similar results for the addition of LMWH to existing mechanical methods of VTE prophylaxis, and the combination of LMWH and SCD was associated with a significant decrease of DVT incidence in trauma patients. The Knudson study was limited by the small number of patients enrolled in that study and the use of historical controls, and because of this it was unclear whether LMWH prophylaxis was superior to optimal mechanical compression.[8] The retrospective cohort by Knudson preceded the development of a risk stratification tool such as the RAP by Greenfield et al, which is the only risk stratification tool validated in trauma patients and allows for more precise identification of patients at risk of developing VTE.[14] This retrospective cohort analysis of 2,281 patients is the largest study examining the efficacy of LMWH thromboprophylaxis in trauma patients. The only other similar large-scale study performed by Adams et al[12] failed to isolate the effect of LMWH in preventing VTE and instead looked at a combination of LMWH along with aggressive US screening in reducing VTE incidence. Our study went one step further by determining the effect of LMWH in reducing DVT and PE in high- and moderate-risk patients. Using the RAP for risk stratification, we were able to conclude that prophylactic treatment with LMWH was associated with significant reduction of VTE incidence in high-risk trauma patients, and PE incidence was significantly reduced for patients at high and moderate risk who received LMWH. Although not statistically significant, the incidence of VTE in the high- and moderate-risk groups combined strongly trended toward effective reduction in the prevalence of VTE in this cohort.

Limitations to this study include its retrospective nature, the possible confounding of unmeasured variables, as well as limited long-term follow-up of outpatients. Further studies examining the efficacy of LMWH in preventing VTE in moderate-risk patients are warranted to resolve the trend toward effective risk reduction which was observed in our study. Formal cost analysis is in order to justify using LMWH in low- and moderate-risk patients. Additionally, we believe that risk stratification by RAP can be attributed to the resulting low number needed to treat in order to prevent VTE among high-risk patients. In conclusion, risk-stratified utilization of LMWH prophylaxis is associated with the reduction of VTE in trauma patients.

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## Discussion

**Slate Wilson, M.D.:** The authors, using the RAP, have been able to define those patients most likely to benefit from enoxaparin, a Xa inhibitor, and have made us aware of the significance of its use in the high risk patients. It should be noted that the doses of enoxaparin were for prophylaxis not therapeutic. SCD's were also used in all patients.

Extensive and, I feel, proper use of Duplex US was used in both the high risk (every 3 days) and lower risk categories (at 1 week).

Whereas in patients at high risk the use of prophylactic enoxaparin was statistically significant, in patients in the moderate and low risk profiles the use of prophylactic enoxaparin showed a trend toward reduction of VTE, and the authors, rightly, question the cost/benefit ratio of using this expensive drug in lower risk patients.

The Risk Assessment Profile (RAP) in stratifying patients into the above risk profiles takes into consideration baseline patient risk factors such as age, obesity, hypercoagulopathy states, alcoholism, as well as iatrogenic factors such as length of operation, and number of blood transfusions. It also includes the injuries scores AIS for brain and spinal cord, chest, abdomen, and grade of extremity fractures. There are 16 factors in all.

I have a few questions for the authors:

1. Were these all hospitalized patients, and how long did you follow them?

2. What, in your opinion, is the role of SCDs alone in the low profiled patients? It might reduce the cost of caring for these patients.
3. Many patients in the modern era of damage control, multiple staged operations (particularly orthopedic) must be bound to change the risk profile of many patients. Do you advocate re-RAPing patients after such procedures and adjusting doses or ultrasound frequency?
4. Have you considered the use of thromboelastography, a point of service study, in your follow-up care, particularly in patients undergoing multiple procedures or receiving multiple blood transfusions or in septic situations? Possibly TEG might aid determining the risk of DVT.
5. Did you use the "standard" score of 5 to profile patients into the high risk group? That is worrisome to since, at over 75, if I even tip over after 2 martinis, I'm automatically in the high risk profile. Not sure I like that idea, and I promise to be careful for the rest of the meeting. In Victoria though, I believe enoxaparin would be free of charge and materialize out of the ether.