Injury, Int. J. Care Injured 50 (2019) 697–702

Contents lists available at ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

# Timing of venous thromboprophylaxis in isolated severe pelvic fracture: Effect on mortality and outcomes☆

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ARTICLE INFO

*Keywords:*
Low molecular weight heparin
Pelvic fracture
Venous thromboembolic event

ABSTRACT

Introduction: Optimal timing of pharmacological thromboprophylaxis (VTEp) in patients with severe pelvic fractures remains unclear. The high risk of venous thromboembolic (VTE) complications after severe pelvic fractures supports early VTEp however concern for fracture-associated hemorrhage can delay initiation. Patients with pelvic fractures also frequently have additional injuries that complicate the interpretation of the VTEp safety profiles. To minimize this problem, the study included only patients with isolated severe pelvic fractures.

Materials and methods: The Trauma Quality Improvement Program was used to collect patients with blunt severe pelvic fractures (AIS > 3) who received VTEp with unfractionated heparin (UH) or low-molecular-weight heparin (LMWH). Patients with head, chest, spine, and abdominal injuries AIS > 3, or those with angio or operative intervention prior to VTEp were excluded. The study population was stratified according to timing of VTEp, early (<48 h) and late (>48 h). Outcomes included in-hospital mortality and VTE.

Results: 2752 patients were included in the study. Overall, 2007 patients (72.9%) received early VTEp, while 745 (27.1%) received late VTEp. LMWH was administered in 2349 (85.4%) and UH in 403 (14.6%).

Late VTEp was associated with significantly higher incidence of VTE (4.3% vs. 2.2%, p = 0.004). Logistic regression identified late VTEp as an independent risk factor for VTE (OR 1.93, p = 0.009) and mortality (OR 4.03, p = 0.006). LMWH was an independent factor protective for both VTE and mortality (OR 0.373, p < 0.001, OR 0.266, p = 0.009, respectively).

Conclusion: In isolated severe pelvic fractures, early VTEp is independently associated with improved survival and fewer VTE. LMWH may be preferred over UH for this purpose.



## Introduction

Venous thromboembolic events (VTE) are a significant concern in the trauma population with an increased risk of associated morbidity and mortality. Patients with pelvic fractures are at an even higher risk of thrombus formation due to prolonged immobility and a hypercoagulable state, with DVT rates as high as 61% [1–3]. Conversely, bleeding after pelvic trauma is common, dependent upon fracture patterns, and hemorrhage control can often require complex interventions.

VTE prophylaxis with unfractionated heparin (UH) or low molecular weight heparin (LMWH) is known to decrease the risk of VTE after trauma and early initiation of prophylaxis has been shown to be superior after a variety of injuries in the prevention of subsequent VTE events [4–7]. The optimal timing of initiation of VTE prophylaxis after pelvic fracture trauma, however, remains uncertain.

The purpose of this study was to determine the optimal timing and method of VTE prophylaxis after severe pelvic trauma using a large volume database.

## Materials and methods

After IRB approval from the University of Southern California, the Trauma Quality Improvement Program (TQIP) database from the American College of Surgeons from 2013 to 2014 was used for this study.

The study included all adult patients (≥16 years old) with isolated severe blunt pelvic fracture, who received either UH or LMWH (Fig. 1). Patient with bleeding disorders, alternative or no prophylaxis, and those with missing data, regarding type or timing

☆ Presented at the 76th Annual Meeting for the American Association for the Surgery of Trauma and Clinical Congress of Acute Care Surgery.

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https://doi.org/10.1016/j.injury.2019.02.009
0020-1383/

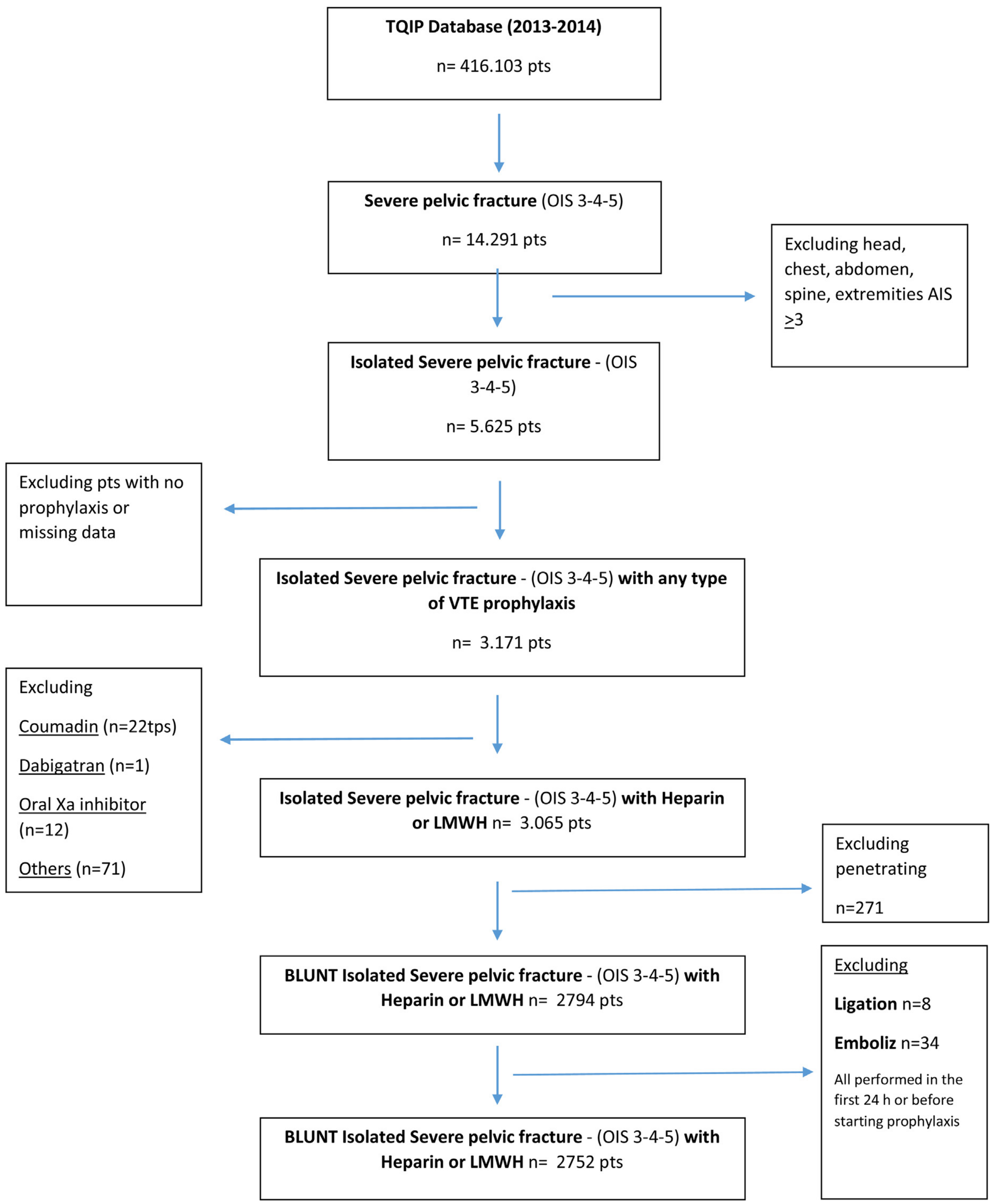


**Fig. 1.** Flowchart of patients included.

of prophylaxis, were excluded. Severe pelvic fractures were defined as patients with pelvic Abbreviated Injury Scale (AIS) score of 3 or higher. Patients with isolated injuries were then extracted by excluding those with head, chest, abdomen, spine, or extremity AIS $\geq$ 3. In addition, patients that underwent pelvic embolization or operative ligation of the internal iliac arteries prior to initiation of VTE prophylaxis were excluded.

Analyzed variables included patient demographics, comorbidities, mechanism of injury, AIS for each body area, vital signs in the emergency department, need for transfusion in the first 24 h, type of pharmacological prophylaxis, time from admission to prophylaxis initiation, pelvic angioembolization, and surgical procedures. Outcomes included in-hospital mortality, ventilation days, ICU length of stay, hospital length of stay, and complications including deep vein thrombosis (DVT), pulmonary embolism (PE), venous thromboembolism (VTE), and overall thromboembolic event (TE).

The study population was stratified according to timing of prophylaxis initiation: early prophylaxis (EP) was considered $\leq$48 h from admission and late prophylaxis (LP) was defined as >48 h.

### Statistical analysis

Continuous variables were reported as medians with interquartile range (IQR) while categorical variables were reported as percentages. Continuous variables were dichotomized using clinically relevant cut off points. Univariate analysis was performed to identify differences between the two study groups (early vs. late prophylaxis). The Mann-Whitney U test was used to compare medians for continuous data points while Fisher Exact or Pearson's chi-squared test were used to compare proportions for categorical variables.

Variables with $p < 0.2$ in univariate analysis were included into a forward stepwise logistic regression to identify independent predictors for overall mortality and complications. Multicollinearity testing was performed to identify correlation between variables. The accuracy of the test was calculated using the area under the curve with 95% confidence interval. Variables with p value <0.05 were considered significant. The statistical analysis was performed using SPSS for windows version 23.0 (SPSS Inc. Chicago, IL).

## Results

During the study period, 2752 patients with isolated severe pelvic fracture were included in the study for final analysis (Fig. 1). Overall, 2007 patients (72.9%) received EP, while 745 (27.1%) received LP. Based on patient demographics, these populations were similar, however the EP group was more likely to be stable on admission, have lower grade injury, and require fewer transfusions (Table 1). LMWH was administered in 2349 patients (85.4%), while 403 (14.6%) received UH.

Overall mortality was 0.7% with a higher mortality observed in the LP group (1.5% vs. 0.3%, $p = 0.001$) on unadjusted analysis (Table 2). Overall complications were more common in the LP group (14.7% vs. 7.3%, $p < 0.001$). The incidence of DVT was statistically similar between groups (2.6% vs. 1.9%, $p = 0.264$),

**Table 1**
**Demographics.** Isolated severe pelvic fracture patients ant timing of VTE prophylaxis starting.

| | Total (n=2752) | ≤48 hours (n=2007) | >48 hours (n=745) | p-value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Gender, male | 1632 (59.3%) | 1166 (58.1%) | 466 (62.6%) | 0.04 |
| Age, years | 48 (30-62) | 47 (29-62) | 49 (33-62) | 0.33 |
| Mechanism of injury | | | | |
| MVC | 1074 (39.0%) | 778 (38.8%) | 296 (39.7%) | 0.64 |
| MCC | 329 (12.0%) | 227 (11.3%) | 102 (13.7%) | 0.09 |
| AVP | 339 (12.3%) | 239 (11.9%) | 100 (13.4%) | 0.28 |
| Fall | 919 (33.4%) | 696 (34.7%) | 223 (29.9%) | 0.02 |
| Assault | 91 (3.3%) | 67 (3.3%) | 24 (3.2%) | 0.88 |
| **Comorbidities** | | | | |
| Overall | 1534 (55.7%) | 1100 (54.8%) | 434 (58.3%) | 0.11 |
| Current smoker | 587 (21.3%) | 433 (21.6%) | 154 (20.7%) | 0.61 |
| Chronic renal failure | 14 (0.5%) | 10 (0.5%) | 4 (0.5%) | 1 |
| CVA | 28 (1.0%) | 20 (1.0%) | 8 (1.1%) | 0.86 |
| MI | 29 (1.1%) | 18 (0.9%) | 11 (1.5%) | 0.19 |
| Hypertension | 762 (27.7%) | 540 (26.9%) | 222 (29.8%) | 0.13 |
| Obesity | 340 (12.4%) | 240 (12.0%) | 100 (13.4%) | 0.3 |
| Respiratory disease | 167 (6.1%) | 117 (5.8%) | 50 (6.7%) | 0.39 |
| Steroid use | 17 (0.6%) | 15 (0.7%) | 2 (0.3%) | 0.18 |
| Cirrhosis | 20 (0.7%) | 12 (0.6%) | 8 (1.1%) | 0.19 |
| Diabetes mellitus | 274 (10.0%) | 192 (9.6%) | 82 (11.0%) | 0.26 |
| CHF | 48 (1.7%) | 34 (1.7%) | 14 (1.9%) | 0.74 |
| Cancer | 13 (0.5%) | 10 (0.5%) | 3 (0.4%) | 1 |
| **ED vitals** | | | | |
| sbp | 130 (116-145) | 131 (117-146) | 128 (112-143) | <0.001 |
| SBP <90 mmHg | 88 (3.2%) | 47 (2.4%) | 41 (5.6%) | <0.001 |
| HR >120 bpm | 179 (6.6%) | 114 (5.8%) | 65 (8.8%) | 0.004 |
| GCS <9 | 48 (1.8%) | 19 (1.0%) | 29 (3.9%) | <0.001 |
| **Pelvic AIS** | | | | |
| 3 | 2047 (74.4%) | 1541 (76.8%) | 506 (67.9%) | <0.001 |
| 4 | 629 (22.9%) | 433 (21.6%) | 196 (26.3%) | 0.009 |
| 5 | 76 (2.8%) | 33 (1.6%) | 43 (5.8%) | <0.001 |
| **Type of Heparin** | | | | 0.001 |
| UH | 403 (14.6%) | 322 (16.0%) | 81 (10.9%) | |
| LMWH | 2349 (85.4%) | 1685 (84.0%) | 664 (89.1%) | |
| **Transfusion in the first 24 hours (Unit)** | | | | |
| PRBC >2 | 119 (8.5%) | 48 (4.9%) | 71 (17.0%) | <0.001 |
| PRBC ≥6 | 60 (4.3%) | 18 (1.8%) | 42 (10.0%) | <0.001 |

Highlights denote p value < 0.05.

**Table 2**
Outcome comparison between patients with early and late VTE prophylaxis.

| | Total (n=2752) | ≤48 hours (n=2007) | >48 hours (n=745) | p-Value |
|---|---|---|---|---|
| **Mortality** | 18 (0.7%) | 7 (0.3%) | 11 (1.5%) | 0.001 |
| **Ventilation days*** | 3 (1-7) | 2 (1-4) | 4 (2-8.5) | <0.001 |
| **ICU stay, days*** | 3 (2-6) | 3 (2-5) | 4 (2-7) | <0.001 |
| **Hospital length of stay*** | 7 (5-11) | 6 (4-10) | 9 (6-15) | <0.001 |
| **Complications^** | | | | |
| Overall | 246 (9.4%) | 137 (7.3%) | 109 (14.7%) | <0.001 |
| Infectious | 162 (6.2%) | 94 (5.0%) | 68 (9.1%) | <0.001 |
| Thromboembolic event | 82 (3.1%) | 46 (2.5%) | 36 (4.8%) | 0.002 |
| DVT | 54 (2.1%) | 35 (1.9%) | 19 (2.6%) | 0.26 |
| PE | 24 (0.9%) | 8 (0.4%) | 16 (2.2%) | <0.001 |
| VTE | 74 (2.8%) | 42 (2.2%) | 32 (4.3%) | 0.004 |
| Stroke/CVA | 4 (0.2%) | 4 (0.2%) | 0 (0.0%) | 0.58 |
| MIO_infarction | 5 (0.2%) | 1 (0.1%) | 4 (0.5%) | 0.025 |
| ARDS | 15 (0.6%) | 4 (0.2%) | 11 (1.5%) | <0.001 |
| Acute kidney injury | 25 (1.0%) | 9 (0.5%) | 16 (2.2%) | <0.001 |
| Cardiac arrest | 10 (0.4%) | 5 (0.3%) | 5 (0.7%) | 0.16 |
| Deep SSI | 15 (0.6%) | 9 (0.5%) | 6 (0.8%) | 0.39 |
| Organ/space SSI | 6 (0.2%) | 3 (0.2%) | 3 (0.4%) | 0.36 |
| Superficial SSI | 15 (0.6%) | 5 (0.3%) | 10 (1.3%) | 0.002 |
| Pneumonia | 44 (1.7%) | 22 (1.2%) | 22 (3.0%) | 0.001 |
| UTI | 95 (3.6%) | 61 (3.3%) | 34 (4.6%) | 0.10 |
| Catheter blood stream related complication | 3 (0.1%) | 0 (0.0%) | 3 (0.4%) | 0.02 |
| Sepsis | 17 (0.6%) | 10 (0.5%) | 7 (0.9%) | 0.28 |

Highlights denote p value < 0.05.

however PE (2.2% vs. 0.4%, p < 0.001) and VTE (4.3% vs. 2.2%, p = 0.004) rates were higher in the LP group. No bleeding complications, pelvic angioembolization, internal iliac artery ligation, or other surgical hemostatic procedures after VTE initiation were noted.

Forward stepwise logistic regression analysis was performed in order to identify independent risk factors for VTE and mortality. After correcting for pelvic fracture severity, age, comorbidities, hypotension, GCS, and type and timing of VTE prophylaxis, LP was found to be an independent risk factor for VTE events (OR 1.93, p = 0.009; Table 3). This increased risk of VTE was most pronounced in PE rate with LP patients having a significantly higher rate of PE (OR 5.52, 95% CI 2.27–13.43, p < 0.001; Table 4). EP was not associated with increased mortality and, in fact, mortality risk was higher in those with LP (OR 4.03, p = 0.006; Table 5).

Interestingly, on regression analysis, patients treated with LMWH were less likely to have VTE events (OR 0.373, p < 0.001) and, in addition, LMWH conferred a survival advantage over UH (OR 0.266, p = 0.009).

## Discussion

Trauma patients have clearly been shown to be at increased risk for VTE events and pharmacologic VTE prophylaxis has been shown to reduce this risk [1,6,8]. Despite this, there is little literature to guide the timing of initiation of VTE prophylaxis for specific injuries. Patients with severe pelvic fractures represent a specific subset of the trauma population, as these patients often require prolonged immobilization and the injury pattern may put these patients at increased risk of VTE. Conversely, hemorrhage

**Table 3**
Independent risk factors for Venous Thromboembolism (DVT + PE).

| | VTE | | |
|---|---|---|---|
| | adj p | OR | 95% CI for OR |
| Age > 50 | 0.57 | 1.16 | (0.706 - 1.891) |
| Hypotension | 0.76 | 1.18 | (0.403 - 3.455) |
| GCS<9 | 0.11 | 2.43 | (0.821 - 7.206) |
| Pelvic AIS 3 | Reference | 1 | |
| Pelvic AIS 4 | 0.62 | 1.15 | (0.661 - 2.007) |
| Pelvic AIS 5 | 0.03 | 2.77 | (1.103 - 6.978) |
| Overall comorbidities | 0.91 | 1.03 | (0.624 - 1.7) |
| Unfractioned Heparin | Reference | 1 | |
| LMWH | <0.001 | 0.37 | (0.219 - 0.634) |
| Less 48 hours | Reference | 1 | |
| More 48 hours | 0.009 | 1.93 | (1.183 - 3.158) |

Highlights denote p value < 0.05.

**Table 4**
Independent risk factors for PE.

| | PE | | | | |
|---|---|---|---|---|---|
| | adj p | OR | 95% CI for OR | | |
| Age > 50 | 0.82 | 0.91 | (0.377 | - | 2.175) |
| Hypotension | 0.76 | 0.71 | (0.086 | - | 5.91) |
| GCS<9 | 0.79 | 1.33 | (0.167 | - | 10.547) |
| Pelvic AIS 3 | Reference | 1 | | | |
| Pelvic AIS 4 | 0.97 | 0.98 | (0.349 | - | 2.759) |
| Pelvic AIS 5 | 0.05 | 3.93 | (1.027 | - | 15.017) |
| Overall comorbidities | 0.86 | 0.92 | (0.374 | - | 2.277) |
| Unfractioned Heparin | Reference | 1 | | | |
| LMWH | <0.001 | 0.17 | (0.072 | - | 0.41) |
| Less 48 hours | Reference | 1 | | | |
| More 48 hours | <0.001 | 5.52 | (2.265 | - | 13.431) |

Highlights denote p value < 0.05.

**Table 5**
Independent risk factors for Mortality.

| | Mortality | | | | |
|---|---|---|---|---|---|
| | adj p | OR | 95% CI for OR | | |
| Age >50 | 0.008 | 7.82 | (1.708 | - | 35.787) |
| Hypotension | 0.25 | 2.46 | (0.525 | - | 11.482) |
| GCS<9 | 0.06 | 5.17 | (0.965 | - | 27.635) |
| Pelvic AIS 3 | Reference | 1 | | | |
| Pelvic AIS 4 | 0.33 | 1.69 | (0.592 | - | 4.799) |
| Pelvic AIS 5 | 0.74 | 1.44 | (0.169 | - | 12.242) |
| Overall comorbidities | 0.27 | 2.06 | (0.569 | - | 7.454) |
| Unfractioned Heparin | Reference | 1 | | | |
| LMWH | 0.009 | 0.27 | (0.098 | - | 0.718) |
| Less 48 hours | Reference | 1 | | | |
| More 48 hours | 0.006 | 4.03 | (1.483 | - | 10.922) |

Highlights denote p value < 0.05.

after pelvic fracture is not always easily accessible or simply controlled and therefore physicians may be reluctant to start prophylaxis early. This study was designed to evaluate the optimal timing of VTE prophylaxis after severe pelvic fracture and found that early initiation of prophylaxis, $\leq$48 h after admission was associated with decreased VTE complications and improved mortality. Further, LMWH was likely the preferred agent over UH for prophylaxis.

These data support the use of early prophylaxis after severe pelvic fractures to reduce the risk of VTE and mortality. Although there are no clear consensus guidelines for timing of initiation of pharmacologic prophylaxis after pelvic fracture, these data of improved outcomes with early initiation are supported in the literature for other traumatic injuries. After traumatic brain injury, early prophylaxis has been shown to be both safe and effective [7,9]. Using the TQIP database, Byrne and colleagues performed a propensity score matched analysis of patients with isolated traumatic brain injury which found that early pharmacologic VTE prophylaxis was associated with decreased rates of DVT and PE [7]. In a retrospective study of 705 patients with blunt spine trauma requiring operative stabilization, PE rates were significantly lower in patients that consistently received preoperative VTE prophylaxis [10]. Rostas et al, in a 5 year retrospective study of patients with blunt liver and spleen injuries, found that early pharmacologic prophylaxis with LMWH was safe and associated with lower rates of VTE [11]. No studies have been published addressing the timing and type of prophylaxis in pelvic fractures.

The decision of when to start VTE prophylaxis after trauma differs significantly based on the injury pattern of the patient. The extent of associated head injury or degree of solid organ injury influences the level of concern for early hemorrhage. In order to minimize these confounding factors, we chose to analyze a population of blunt trauma patients with isolated severe pelvic fractures allowing a highly selective comparison of similarly injured patients.

Overall VTE rates were higher in patients with LP, however these results were most pronounced in the PE rates with a more than 5x higher rate of PE in patients with LP. The reliability of DVT rate as a predictor of PE events has been questioned. DVT rates may be difficult to interpret in the TQIP database overall and specifically in this population. The most common method for DVT diagnosis is with lower extremity ultrasound, identifying thrombus in the femoral, popliteal, or calf veins. Although some studies suggest that pelvic thrombi are not as common in patients with fatal PE [12], in the subset of patients with severe pelvic fractures, pelvic vein thrombosis are likely a significant contributor to PE rates that is not captured in DVT rate alone. Further complicating interpretation is a potential surveillance bias. Ultrasound surveillance protocols have fallen out of favor and are not consistently performed across the country. In a comparison study between two hospitals with similar trauma populations, one with a surveillance protocol and the other without, the reported DVT rate was 5x higher in the center with routine ultrasound [13]. Finally, there is a growing body of evidence to support the concept of primary pulmonary artery thrombosis after trauma [8,12,14], possibly due to a proinflammatory, prothrombotic state.

These data also suggest that LMWH may be preferable to UH for pharmacologic prophylaxis after severe pelvic fracture conferring both a survival advantage as well as decreasing the rate of VTE. These findings are consistent with previously reported database analyses in patients with severe traumatic brain injury, which found improved outcomes with the use of LMWH [7,15]. A potential mechanism for the neuroprotective properties of LMWH after brain injury has been described using a murine model showing a reduction in cerebral edema and leukocyte recruitment after treatment with LMWH [16,17]. Using the Michigan TQIP database, Jacobs et al [18] recently showed that general trauma patients treated with LMWH was superior to UH in reducing VTE rates (OR 0.67) and mortality (OR 0.64). Although the reduction in VTE was most pronounced in the less injured patients, the survival advantage was seen in those with higher injury severity scores, a subset of patients in which an anti-inflammatory effect may be more beneficial.

This study has several limitations. Although the ability to extract isolated injuries is a strength, this is a retrospective analysis, including all of the limitations that come with this design. The database records the time of initiation of pharmacologic VTE prophylaxis, however there is no data regarding held doses after initiation. Additionally, this study used mortality as an indicator of safety as well as performing a search for angioembolizaiton or operative interventions after VTE prophylaxis was started. These were used as a proxy however the database does not provide sufficient information on hemorrhagic events to determine safety with any additional granularity. Finally, the vast majority of the patients with severe pelvic fractures in our cohort had AIS 3 injuries thus limiting significant additional statistical analysis of the different subgroups.

## Conclusions

In isolated severe pelvic fractures, early initiation of VTE prophylaxis, and specifically LMWH, is associated with improved outcomes including lower VTE rates and decreased mortality. These data support consideration of early initiation of pharmacologic VTE prophylaxis with LMWH after severe pelvic fractures in the appropriate clinical setting.

## Conflicts of interest

The authors have no conflicts of interest to disclose regarding this manuscript.

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