Clinical Practice Management Guideline for Venous Thromboembolism Prevention

**Goals**

1. Identify patients at risk for developing venous thromboembolism after a traumatic mechanism.
2. Utilize the medication and dosing appropriate for chemoprophylaxis in the traumatically-injured patient to prevent venous thromboembolism events.
3. Identify patient cohorts that are affected by pharmacologic prophylaxis.
4. Adjust pharmacologic dosing according to patient cohort to limit complications with chemoprophylaxis.

**Background**

Deep vein thrombosis and pulmonary embolism, collectively known as venous thromboembolism (VTE), affect an estimated 900,000 people per year.\(^1\) Deep vein thrombosis occurs when a blood clot forms in an extremity, which can cause limb swelling, skin ulceration, venous incompetence, and thrombophlebitis. Additionally, a pulmonary embolism occurs when the clot travels to the lungs, which can lead to hemodynamic instability, cardiac arrest, and sudden death.\(^2\) Trauma patients are at an increased risk for developing VTE due to hypercoagulability, and even with pharmacologic prophylaxis, up to 25% of trauma patients can still develop a VTE.\(^3,4\)

CHEST® guidelines, with regards to VTE prophylaxis in the trauma patients, state that low-dose unfractionated heparin (LDUH) or low-molecular weight heparin (LMWH) may be used for VTE prophylaxis.\(^10\) However, a systematic review of the literature by the Eastern Association for the Surgery of Trauma (EAST) noted that LDUH was inferior to LMWH for VTE prophylaxis.\(^11\) As such, LMWH (e.g. enoxaparin) is considered the standard drug of choice for VTE prophylaxis in this patient population. Dosing of such being either 40mg daily or 30mg every twelve hours, both administered subcutaneously.

In recent studies, it has been elucidated that standard doses of enoxaparin may not be adequate to protect trauma patients from VTE.\(^5,6\) In a study conducted by Singer et al., 65.4% of trauma patients had sub-prophylactic levels of plasma anti-Xa, indicating that standard enoxaparin dosing is insufficient for the trauma patient population.\(^5\) Because of this, many institutions have begun to use weight-based dosing in conjunction with measuring anti-Xa levels to ensure that their patients are adequately protected against VTE. On review of our institution’s data, it has been noted that there is trend to decreased incidence of VTE with weight-based dosing compared to the standard 30mg every twelve hours.
VTE Risk Factors\textsuperscript{17,18,19}

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
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<tbody>
<tr>
<td>Age &gt; 60 yrs</td>
<td>Age 40-60 yrs</td>
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<tr>
<td>Malignancy (present or previous)</td>
<td>Varicose veins</td>
</tr>
<tr>
<td>Severe head injury (GCS &lt; 8)</td>
<td>Coagulopathy</td>
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<tr>
<td>Central venous access</td>
<td>Inflammatory bowel disease</td>
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<tr>
<td>Injury Severity Score (ISS) (\geq 15)</td>
<td>Oral contraceptive use or hormone replacement therapy</td>
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<tr>
<td>Morbid obesity (BMI (\geq 40))</td>
<td>Swollen legs (current)</td>
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<tr>
<td>Spinal fractures/Spinal Cord Injury</td>
<td>Immobilization (\leq 2) days</td>
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<tr>
<td>History of VTE</td>
<td>Minor surgery planned</td>
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<tr>
<td>Pelvic fractures</td>
<td>Tranfusion of 4U pRBCs in 1st 24hrs</td>
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<tr>
<td>Immobilization &gt; 2 days</td>
<td>Pregnancy</td>
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<td>Long bone fractures</td>
<td></td>
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<tr>
<td>Heparin-induced thrombocytopenia</td>
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<td>Hip dislocation</td>
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Special Populations

Traumatic Brain Injury (TBI)

Another area where lack of clarity exists in VTE prophylaxis is in the TBI patient. Despite the fact that head injury is an independent risk factor for developing VTE in trauma patients\textsuperscript{25}, delays to prophylaxis initiation persist due to concerns for expansion of intracranial bleeding. Presently, the Brain Trauma Foundation states (as Level III evidence) recommends the use of LMWH or LDUH in conjunction with mechanical prophylaxis in patients with TBI.\textsuperscript{26} However, they have no recommendations for preferred agent, dosing, or timing due to insufficient evidence.\textsuperscript{26} The issue behind the lack of standardization is the unknown time frame for which VTE prophylaxis can be initiated. If the prophylaxis is given too soon, there is an increased risk for progression of the intracranial hemorrhage, and if it is given too late the patient is at an increased risk for a VTE.\textsuperscript{8} The group out of Parkland Memorial Hospital has created a TBI risk stratification protocol known as the “Parkland Protocol” based on the work presented by Berne and Norwood.\textsuperscript{2,9,24} This was an effort to account for the heterogeneity of the TBI population.\textsuperscript{24} The protocol classifies TBI patients into a low, medium, or high risk arm on the first iteration of the protocol.\textsuperscript{2,24} It has since been modified into a low-risk and high-risk arm on further data analysis at the home institution.\textsuperscript{9} Patients with low-risk TBI are given enoxaparin 24 hours after their injury, while high-risk patients are given enoxaparin 72 hours after injury if the CT scan remains stable. With the modification of the protocol, Parkland has also removed the use of inferior vena cava filter placement in these patients due to change in practice.\textsuperscript{9} However at Augusta University Medical Center (AUMC), there are a number of patients who develop symptomatic VTE after the 72hr period and have decided to keep this aspect of the protocol.
with regards to management at this institution. To date, only the low risk arm has been tested.\(^\text{20}\) While there was some progression of the TBI noted with initiation of enoxaparin at 24hrs post-injury, none were clinically significant (i.e. didn’t require intervention).\(^\text{20}\)

**Spinal cord injury**

Spine fractures with or without associated spinal cord injury represent a patient subset with an increased risk of developing a VTE. The reported incidence is as high as 31% after spinal surgery. The increased risk is multifactorial in nature due to concomitant injuries, immobility, and lack of pharmacologic prophylaxis due to concerns of post-operative bleeding. Reported incidence of post-operative epidural spinal hematoma is 1%.\(^\text{22}\) Despite this, the perception of spine surgeons is that this incidence is 5-10%, leading to the delays in chemoprophylaxis initiation at 48 hours.\(^\text{22}\) Presently, there are studies that demonstrate decreased incidence of VTE when chemoprophylaxis is initiated < 48 hours after surgery without bleeding complications.\(^\text{21,22}\) However, there was heterogeneity in these studies with regards to the chemoprophylaxis used. Furthermore, there is no study to date that evaluates enoxaparin chemoprophylaxis use in this population and post-operative bleeding complications.

**Solid organ injury**

As a patient cohort, the overall incidence of VTE is low (1.2%). Patients without signs of active hemorrhage, coagulopathy, hemodynamic instability, or hypothermia have no contraindications to pharmacologic prophylaxis according to available studies.\(^\text{23}\) The studies that do evaluate for timing assess for either 48 hours or 72 hours post-injury. Heterogeneity was also noted in these studies with regards to type of prophylaxis used. Another study evaluated enoxaparin usage in patients with isolated solid organ injury and timing to initiation (< 48hrs, 48-72hrs, ≥72hrs).\(^\text{23}\) No bleeding complications were noted in either arm, however VTE were noted in the intermediate (48-72hrs) and late (≥72hrs) groups.

**Pediatrics**

While VTE is a well-documented complication in adult patients with traumatic injury, it is a rare event in the pediatric trauma population.\(^\text{12,13}\) In general, the incidence of VTE in the pediatric population is very low, but like the adult population, the incidence rises in the trauma cohort.\(^\text{13}\) The overall incidence of VTE in pediatric trauma patients is < 1% with a mortality rate of 2.2%.\(^\text{12,13}\) In survivors, morbidity associated with the diagnosis (e.g. post-thrombotic syndrome, bleeding, recurrent VTE) can be as high as 50%. These complications lead to increased costs due to testing, monitoring, and treatment, both short-term and long-term. Despite the low incidence, there has been a noted increase in the incidence in the past decade (~70%).\(^\text{16}\) There have been attempts to ascertain the best method to address this issue. A group in 2012 noted a statistically significant decrease in VTE incidence when patients with high risk factors for VTE received pharmacologic prophylaxis.\(^\text{15}\) In 2016, a consensus statement of expert panelist across various pediatric specialties that care for this population was published. While there wasn’t a near consensus with regards to age, it was recommended that patients ≤ 12 yrs old should not receive prophylaxis.\(^\text{14}\) It also stated to consider pharmacologic prophylaxis in patients ≥ 13 who...
can walk but have noted risk factors.\textsuperscript{14} This is further corroborated in the practice management guideline written by the Pediatric Trauma Society (PTS) with the EAST.\textsuperscript{16} The only difference is the age of pharmacologic prophylaxis is $\geq 15$ yrs old unless the patient is post-pubertal with an ISS $> 25$.\textsuperscript{16}
Protocol for Enoxaparin Dosing (Adult)

- Enoxaparin is to be initiated within 12hrs of hospital admission unless patient has an injury for which initiation is delayed (please refer to specific algorithm for sub-group). The dose is to begin at 0.5mg/kg subcutaneously every twelve hours. Dosing is to be rounded to the closest measurable dose.

- Chemoprophylaxis (LMWH or LDUH) will not be held prior to surgery per CHEST® guidelines. However, if it needs to be held due to the nature of the procedure, it will be held no earlier than 12hrs prior to surgery for LMWH (8hrs for LDUH) prior to surgery. Furthermore, it will be resumed no more than 12hrs post-operatively unless the patient falls under the ‘Special Populations’ cohort.

- Anti-factor Xa activity levels are monitored to assess whether or not the patient is in the appropriate range for prophylaxis.
  - Monitoring anti-factor Xa activity levels:
    1. Sample should be drawn after 3 doses of enoxaparin at steady state.
    2. Peak level is recommended and should be drawn 4-6 hours post-dose. Goal range 0.2-0.6 units/mL.
    3. Trough level is preferred in renally-impaired patients on enoxaparin. Sample should be drawn immediately before next dose. Goal trough level < 0.4 units/mL.

- If the anti-factor Xa activity level is within the range, no follow-up levels are required unless there is a change in renal function or weight.
  - Acute kidney injury (AKI) can be defined as: increase in serum creatinine of 0.3mg/dL in < 48hr or increase in serum creatinine of ≥ 1.5 times baseline, or urine output less than 0.5mL/kg/hr for 6hrs.
  - Acute kidney failure (AKF) can be defined as: increase in serum creatinine of ≥ 3 times baseline, or urine output of <0.3mL/kg/hr for ≥ 24hrs or anuria for ≥ 12hrs.
  - 15% change in weight not due to anasarca or fluid overload.

- Anti-factor Xa activity levels that are < 0.2 units/mL are considered sub-therapeutic and will require an increase in enoxaparin dosing. An increase of 0.1 mg/kg per dose may be considered until target peak levels are achieved. Levels that are > 0.6 units/mL, a decrease of 0.1 mg/kg per dose may be considered until target peak level is achieved.
  - Anti-Xa levels out of range will require more frequent monitoring until the dose is within range.
  - Anti-Xa levels are recommended in settings of changing renal function.

- Pharmacokinetic Parameters: The maximum anti-Xa effect of enoxaparin occurs 3 to 5 hours after a subcutaneous (SC) injection. The half-life of the anti-Xa effect after an enoxaparin dose at steady state is approximately 7 hours.
• Enoxaparin will not be administered in patients with creatinine clearance < 30 mL/min. These patients instead will be given LDUH (5000-7500U subcutaneous every eight hours) instead.

Protocol for Enoxaparin Dosing (Pediatric ≥ 13 yrs old)
• Enoxaparin is to initiated at 0.5mg/kg subcutaneously every twelve hours when appropriate for patient sub-group (please refer to specific algorithm for sub-group). Dosing is to be rounded to the closest measurable dose.
• Chemoprophylaxis (LMWH or LDUH) will not be held prior to surgery per CHEST® guidelines. However, if it needs to be held due to the nature of the procedure, it will be held no earlier than 12hrs prior to surgery for LMWH (8hrs for LDUH) prior to surgery. Furthermore, it will be resumed no more than 12hrs post-operatively unless the patient falls under the ‘Special Populations’ cohort.
• Anti-factor Xa activity levels monitoring is not required. However, a level will be drawn in the event a VTE is diagnosed.
• If there is a change in renal function or weight. Enoxaparin will not be used. LDUH will be used instead.
  ▪ Acute kidney injury (AKI) can be defined as: increase in serum creatinine of 0.3mg/dL in < 48hr or increase in serum creatinine of ≥ 1.5 times baseline, or urine output less than 0.5mL/kg/hr for 6hrs.
  ▪ Acute kidney failure (AKF) can be defined as: increase in serum creatinine of ≥ 3 times baseline, or urine output of <0.3mL/kg/hr for ≥ 24hrs or anuria for ≥ 12hrs.
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• Enoxaparin will not be administered in patients with creatinine clearance < 30 mL/min. These patients instead will be given LDUH (5000-7500U subcutaneous every eight hours) instead.
References


VTE Prophylaxis Algorithm

Trauma Activation leading to hospital admission?

- YES
- NO

Presence of special considerations (TBI, SCI, Solid Organ Injury, Pediatrics)?

- YES
- NO

Start pharmacologic & mechanical prophylaxis at admission

Cr. Cl. < 30 mL/min?

- YES
- NO

Start enoxaparin at appropriate dosing

Admission weight?

- < 100kg
- > 100kg

Start heparin 5000U subcutaneous q8hrs

Start heparin 7500U subcutaneous q8hrs

Initiate mechanical prophylaxis. Please refer to the injury-specific or patient-specific algorithm to ascertain when pharmacologic prophylaxis is to begin.
**Please refer to appropriate algorithm regarding timing of chemoprophylaxis initiation as this will vary depending on the patient’s injury or injuries.**
**TBI VTE Prophylaxis Algorithm**

1. Subdural hematoma \( \leq 8 \text{mm} \)?
2. Epidural hematoma \( \leq 8 \text{mm} \)?
3. Largest single contusion \( \leq 2 \text{cm} \)?
4. No more than one contusion per lobe?
5. Isolated intraventricular hemorrhage?
6. Isolated subarachnoid hemorrhage?

- **YES**

- **NO**

**Craniotomy or EVD/ICP monitor?**

- **YES**

1. Repeat CT scan stable by 24 hours after injury?

   - **YES**

   - **NO**

   **LOW RISK TBI**

   - **YES**

   - **NO**

   **HIGH RISK TBI**

   - **YES**

   **Repeat CT scan stable by 72 hours after injury?**

     - **YES**

     **Initiate chemoprophylaxis (72hrs)**

     - **NO**

     Delay chemoprophylaxis until hemorrhage pattern stable.

     Consider placement of a prophylactic inferior vena cava filter until prophylaxis can be initiated.
SCI VTE Prophylaxis Algorithm

Spinal cord injury with hemorrhage?

YES

Surgical Stabilization?

NO |

Hold prophylaxis for 48hrs post-injury.
If patient undergoes surgical stabilization, initiate prophylaxis 48hrs post-operatively.

YES |

Surgical Stabilization?

NO |

Start prophylaxis in 48 hours.

YES |

Initiate prophylaxis at time of admission.

Initiate prophylaxis at time of admission. Resume 48hrs post-operatively.
Solid Organ Injury VTE Prophylaxis Algorithm

Solid organ injury with active hemorrhage?

YES

Hemorrhage control (i.e. surgery, embolization)

1. Hemodynamic instability?
2. Base deficit/acidosis?
3. Coagulopathy present?
4. Hypothermia?

YES

Complete resuscitation, correct coagulopathy, active warming.

NO

Initiate prophylaxis within 24-48 hours.