DVT In Trauma, The **Good**, The **Bad**, The **Future**

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The University of Arizona, Tucson, AZ
Nothing to Disclose
VTE Prophylaxis In Trauma Patients

PubMed.gov

(VTE prophylaxis) AND (Trauma)

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User Guide

RESULTS BY YEAR

1996  2021

The diagram shows an increase in publications related to VTE prophylaxis in trauma patients from 1996 to 2021.
Each year in the United States:

- Incidence is up to **900,000** individuals
- More than **100,000** Deaths
- **1/3** died within 30 days of diagnosis
Hidden burden of venous thromboembolism after trauma: A national analysis

Rattan, Rishi MD; Parreco, Joshua MD; Eidelson, Sarah A. MD; Gold, Joann; Dharmaraja, Arjuna; Zakrison, Tanya L. MD, MPH; Dante Yeh, D. MD; Ginzburg, Enrique MD; Namias, Nicholas MD

Based on Nationwide Readmissions Database (NRD):

- Total yearly cost of 30-day readmission with VTE = $114.4 million.
- Total yearly cost of 1-year readmission with VTE = $256.9 million.
The Good
• The Mechanism:
How to be “The Good”? 

Prophylaxis vs Treatment

Timing

Agent

Dosing

Adjustments
Prophylaxis vs Treatment

Venous Thromboembolism After Trauma

Knudson, M Margaret; Ikossi, Danagra G

- Detection of VTE → Difficult
- Better to concentrate on → Prevention
Optimal Timing
When is It Safe to Start VTE Prophylaxis After Blunt Solid Organ Injury? A Prospective Study from a Level I Trauma Canter

Morgan Schellenberg, Kenji Inaba, Subarna Biswas, Patrick Heindel, Elizabeth Benjamin, Aaron Strumwasser, Kazuhide Matsushima, Lydia Lam & Demetrios Demetriades

- Prospective study
- 118 adult patients
- Early (≤48 h) vs Late (>48)
- Early (≤48 h) → DVT
- Early (≤48 h) ↔ Bleeding
Optimal Timing of Initiation of Thromboprophylaxis after Nonoperative Blunt Spinal Trauma: A Propensity-Matched Analysis

- Isolated severe pelvic fractures + Early VTEp → Survival ↑ & VTE ↓

- Nonoperative Spinal Trauma + Early VTEp → VTE ↓
  - No difference between UFH and LMWH

- Venous Injuries and Post-operative VTEp initiation
  - Only delay in starting VTE chemoprophylaxis (30%/day) independently predicted VTE

Elizabeth Benjamin, Alberto Aiolfi, Gustavo Recinos, Kenji Iinaba, Demetrios Demetriades

Frank, Brian MD; Maher, Zoë MD; Hazelton, Joshua P. DO; Resnick, Shelby MD; Dauer, Elizabeth MD; Goldenberg, Anna DO; Lubitz, Andrea L. MD; Smith, Brian P. MD; Saillant, Noelle N. MD; Reilly, Patrick M. MD; Seamon, Mark J. MD

2019

2018
Optimal Timing

Early VTEp → Graph → Skull + No Change

THE EARLIER, THE BETTER!
Optimal Prophylaxis Agent

- **LMWH**
- **DOACs**
- **Anti-platelets**
- **UFH**
Efficacy and Safety of Low Molecular Weight Heparin Versus Unfractionated Heparin for Prevention of Venous Thromboembolism in Trauma Patients
A Systematic Review and Meta-analysis

Tran, Alexandre MD, MSc; Fernando, Shannon M. MD, MSc; Carrier, Marc MD, MSc; Siegal, Deborah M. MD, MSc; Inaba, Kenji MD; Vogt, Kelly MD, MSc; Engels, Paul T. MD; English, Shane W. MD, MSc; Kanji, Salmaan PharmD; Kyeremanteng, Kwadwo MD, MHA; Lampron, Jacinthe MD, MPH; Kim, Dennis MD; Rochwerg, Bram MD, MSc

Adult trauma patients + **LMWH** → Superior for VTE prevention + **mortality**
Compared to UFH
Optimal Prophylaxis Agent

Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin for Nonoperative pelvic fractures + DOACs → ↓ DVT without ↑ Bleeding

Compared to LMWH

Mohammad Hamidi, Muhammad Zeeshan, Joseph V Sakran, Narong Kulvatunyou, O’Keeffe, Ashley Northcutt, El Rasheid Zakaria, Andrew Tang, Bellal Joseph

Pharmacological Thromboembolic Prophylaxis in Traumatic Brain

LMWH + severe TBI → ↑ survival and ↓ DVT

Compared to UFH

Benjamin, Elizabeth MD, PhD, FACS; Recinos, Gustavo MD; Aiolfi, Alberto MD; Inaba, Kenji MD, FACS; Demetriades, Demetrios MD, PhD,

The survival benefit of low molecular weight heparin over unfractionated heparin in pediatric trauma patients

LMWH → ↑ Survival ↓ DVT ↓ Hospital LOS

Compared to UFH

Muhammad Khurrum, Samer Asmar, Marion Henry, Michael Ditillo, Mohamad Chehab, Andrew Tang, Letitia Bible, Lynn Gries, Bellal Joseph
Optimal Prophylaxis Agent

LMWH > UFH

DOACs? Anti-platelets?
How About the Optimal Dosing?
Optimal Dosing

Dose Adjusting Enoxaparin is Necessary to Achieve Adequate Venous Thromboembolism Prophylaxis in Trauma Patients

Todd W. Costantini, MD, Emily Min, PharmD, Kevin Box, PharmD, Vy Tran, PharmD, Robert D. Winfield, MD, Dale Fortlage, BS, Jay Doucet, MD, Vishal Bansal, MD, and Raul Coimbra, MD, PhD

Study Design:

- 61 trauma patients
- Receiving prophylactic enoxaparin
- Outcome: Peak plasma anti-Xa levels

Enoxaparin 30 mg twice daily

70% Subtherapeutic anti-Xa levels

Suggesting inadequate VTE prophylaxis
Wh-wh-wh-what are we gonna do?
Weight-based enoxaparin dosing and deep vein thrombosis in hospitalized trauma patients: A double-blind, randomized, pilot study

Annika BickfordKay PA-C, MPAS, Sarah Majercik MD, MBA, FACS, Jeffrey Sorensen MStat, Scott C. Woller MD, Scott M. Stevens MD, Thomas W. White MD, FACS, CNSC, David S. Morris MD, FACS, Margaret Baldwin PharmD, Joseph R. Bledsoe MD

Adjustments

Weight-based enoxaparin dosing in trauma patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>ST group (n = 124)</th>
<th>WB group (n = 110)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE in-hospital</td>
<td>12 (9.7%)</td>
<td>6 (5.5%)</td>
<td>0.335</td>
</tr>
<tr>
<td>VTE 90-day</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
<td>1</td>
</tr>
<tr>
<td>Major bleed 90-day</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
<td>1</td>
</tr>
<tr>
<td>Mortality 90-day</td>
<td>1 (0.8%)</td>
<td>0 (0.0%)</td>
<td>1</td>
</tr>
</tbody>
</table>

MAY provide better protection
Venous thromboembolism prophylaxis in the trauma intensive care unit: an American Association for the Surgery of Trauma Critical Care Committee Clinical Consensus Document

Joseph F Rappold, Forest R Sheppard, Joseph Cuschieri, Eric Ley, Erika Rangel, Anupamaa J Seshadri, P Michetti
Adjustments

Routine enoxaparin prophylaxis

Commonly initiated at a dose of 0.5 mg/kg or 30 mg for patients weighing 50-60 Kg

Weight-based enoxaparin prophylaxis

40 mg for patients weighing 61–99 kg and 50 mg for patients weighing >100kg

Suggestion:

More investigation is needed in trauma patients with obesity, especially since these patients often have an elevated risk of VTE.
Optimal Dose of Enoxaparin in Critically Ill Trauma and Surgical Patients

Rutherford, Edmund J. MD; Schooler, Wesley G. MD; Sredzienski, Edward MSPharm; Abrams, Jeffrey E. MD; Skeete, Dionne A. MD

- 17 patients
- 40 mg enoxaparin daily
- Outcome: Anti-Xa activity after the Third dose
- 15 (88%) of patients had subtherapeutic Anti-Xa Levels

Increased interval of administration (daily dosing)
Pharmacokinetics and pharmacodynamics of the prophylactic dose of enoxaparin once daily over 4 days in patients with renal impairment

Todd W. Costantini, MD, Emily Min, PharmD, Kevin Box, PharmD, Vy Tran, PharmD, Robert D. Winfield, MD, Dale Fortlage, BS, Jay Doucet, MD, Vishal Bansal, MD, and Raul Coimbra, MD, PhD

In anti-Xa exposure of enoxaparin, there is a significant increase in severe renal impairment compared to mild and moderate renal impairment.
Where Are We Now?
## Latest Guideline

### American Association for the Surgery of Trauma/American College of Surgeons - Committee on Trauma Clinical Protocol for inpatient venous thromboembolism prophylaxis after trauma

**Initiation of VTE Prophylaxis**

- **If a patient has multiple injuries or risk factors for bleeding, the most restrictive dosing policy should be applied.**

**Prophylaxis Timing**

**Agent**

**Dosing Adjustments**

**Risk Stratification**

- **Modified Berne-Norwood Criteria**
- **Low Risk**
  - No Moderate or High Risk Criteria
  - 24 hours if CT stable
- **Moderate Risk**
  - Subdural or epidural Hematomas > 8mm
  - Contusion or intracerebral Hemorrhage >2cm
  - Multiple Contusions to a single lobe
  - Subarachnoid Hemorrhage with abnormal CT angiogram
  - Evidence of Progression at 24 hours
  - 72 hours if CT stable
- **High Risk**
  - ICP Monitor Placement
  - Cerebral Edema
  - Evidence of Progression at 72 hours
  - Consider screening duplex or IVC filter

**Yes**

- Traumatic Brain Injury?

**No**

- Spinal Fracture / Cord Injury?

**Yes**

- Signs of ongoing hemorrhage?

**No**

- Mechanical Prophylaxis**

**Yes**

- Enoxaparin 30mg BID

**No**

- Enoxaparin 40mg BID

- Enoxaparin 5mg/kg BID

**BMI > 30?**

**Yes**

- Heparin 5000u q6hrs

**No**

- Heparin 7500u q6hrs

**Age > 65 years OR**

- **CrCl < 30 mL/min OR**

- **Weight < 50kg OR**

- **pregnant?**

**Signs of ongoing hemorrhage?**

**No**

- Enoxaparin 30mg BID

**Yes**

- Adjust per Anti-Xa level

**BMI > 30?**

**Yes**

- Heparin 5000u q6hrs

**No**

- Heparin 7500u q6hrs

**2022**

**Prophylaxis**

**Yorkgitis, Brian K. PA-C, DO, FACS; Berndtson, Allison E. MD, FACS; Cross, Alisa MD; Kennedy, Ryan MD, FACS; Kochuba, Matthew P. MD; Tignanelli, Christopher MD, MS, FACS; Tominaga, Gail T. MD, FACS; Jacobs, David G. MD, FACS; Marx, William H. DO, FACS; Ashley, Dennis W. MD; Ley, Eric J. MD; Napolitano, Lena MD, FACS, FCCP, FCCM; Costantini, Todd W. MD, FACS**
A Quick 5-Year Analysis of ACS-TQIP

Incidence of VTE per 100,000 Trauma Patients (2015-2019)

- DVT
- PE
What are the Obstacles?

- TBI patients
- Complications
- Underuse!
- ACS Trauma Verification Level
- Surgery Duration
AH, YOU GET A FEW SIDE EFFECTS.
Complications related to deep venous thrombosis prophylaxis in trauma: a systematic review of the literature

Indraneel Datta, Chad G Ball, Lucas Rudmik, S Morad Hameed & John B Kortbeek

- Bleeding
- HIT
- Pharmacologic
- Inferior Vena Cava Filtration
- Mechanical Compression Devices

- Local soft tissue injury
- Bleeding
- Patient non-compliance
- Migration
- IVC occlusion
- Vessel penetration
## Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Type of LMWH</th>
<th>No. Patients</th>
<th>Non-Fatal Bleeding</th>
<th>Fatal Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geerts et al. 1996[10]</td>
<td>Randomized</td>
<td>Enoxaparin</td>
<td>171*</td>
<td>5 (2.9%)</td>
<td>0</td>
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<td></td>
<td>UH 5,000 U SC BID vs. LMWH 30 mg SC BID</td>
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<td></td>
<td>Multi-system trauma &amp; ISS ≥ 9</td>
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<tr>
<td>Knudson et al. 1996[20]</td>
<td>Randomized</td>
<td>Enoxaparin</td>
<td>120</td>
<td>6 (5%)</td>
<td>0</td>
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<tr>
<td></td>
<td>LMWH 30 mg SC BID vs. SCD or Avi bilaterally</td>
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<tr>
<td></td>
<td>Multi-system trauma &amp; AIS ≥ 3 with ISS &gt; 10</td>
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<tr>
<td>Ginzburg et al. 2003[19]</td>
<td>Randomized</td>
<td>Enoxaparin</td>
<td>218</td>
<td>13 (6%)</td>
<td>0</td>
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<tr>
<td></td>
<td>LMWH 30 mg BID vs. IPC bilaterally</td>
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<tr>
<td></td>
<td>Multi-system trauma &amp; ISS ≥ 9</td>
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<tr>
<td>Green et al. 1990[17]</td>
<td>Randomized</td>
<td>Logiparin</td>
<td>20</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>UH 5,000 U SC TID vs. LMWH 3500 U SC QD</td>
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<tr>
<td></td>
<td>Spinal cord trauma &amp; complete motor paralyis</td>
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<tr>
<td>Spinal Cord Injury Thromboprophylaxis Investigators 2003[18]</td>
<td>Randomized</td>
<td>Enoxaparin</td>
<td>230</td>
<td>6 (2.6%)</td>
<td>0</td>
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<tr>
<td></td>
<td>UH 5,000 U SC TID + IPC vs. LMWH 30 mg SC BID</td>
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<tr>
<td></td>
<td>Spinal cord trauma</td>
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<tr>
<td>Kurtoglu et al. 2004[13]</td>
<td>Randomized</td>
<td>Enoxaparin</td>
<td>60</td>
<td>2 (3.3%)</td>
<td>0</td>
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<tr>
<td></td>
<td>LMWH 40 mg QD vs. IPC bilaterally</td>
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<tr>
<td></td>
<td>Head and Spinal Trauma</td>
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<tr>
<td></td>
<td>Spinal Cord Trauma Bleeding Risk</td>
<td>8/310 (2.6%)</td>
<td>0%</td>
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<tr>
<td></td>
<td>Combined Total Bleeding Risk</td>
<td>32/819 (3.9%)</td>
<td>0%</td>
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</tbody>
</table>

* 344 patients randomized and assessed for bleeding whereas only 265 patients had venograms adequate for DVT analysis ISS, Injury Severity Score; SCD, Sequential Compression Device; IPC, Intermittent Pneumatic Compression
Venous thromboembolism (VTE) prophylaxis in severely injured patients: an international comparative assessment

Amy C. Gunning, Ronald V. Maier, Doret de Rooij, Luke P. H. Leenen & Falco Hietbrink

- International Multicenter Study (US & Netherlands)
- Significant variation in timing of VTEp by region
  - Netherlands and the United States
- Early thromboprophylaxis Protocol → VTE prevention
  - All severely injured adults
- VTEp → No effect on the major bleeding rates
  - Outcomes: - VTE Incidence - Hemorrhagic complications
VTE prophylaxis in TBI patients

- Risk of developing DVT in TBI patients
- Stable RHCT → Minimal risk of progression with prophylaxis

- TBI patients → LMWH > UFH
- VTEp Initiation after 72 hrs → Greater than 3-fold in VTE
- Early VTEp within 48 hrs → Safe & effective

Patients with TBI + Timely VTEp → Favorable Outcomes
VTE prophylaxis in TBI patients

Association of Venous Thromboembolism Prophylaxis After Neurosurgical Intervention for Traumatic Brain Injury With Thromboembolic Complications, Repeated Neurosurgery, and Mortality
James P. Byrne, MD, PhD; Christopher D. Witiw, MD, MS; James M. Schuster, MD, PhD; et al

- TBI + Neurosurgical intervention + Early VTEp \(\rightarrow\) VTE & repeated neurosurgery

Optimal timing of initiation of thromboprophylaxis in spine trauma managed operatively: A nationwide propensity-matched analysis of trauma quality improvement program
Muhammad Zeeshan, Muhammad Khan, Terence O'Keeffe, Nina Pollack, Mohammad Hamidi, Narong Kulvatunyou, Joseph V Sakran, Lynn Gries, Bellal Joseph

Operative Spinal Trauma + Early VTEp \(\rightarrow\) DVT without the risk of bleeding
Is early chemical thromboprophylaxis in patients with solid organ injury a solid decision?

David Skarupa, Kamil Hanna, Muhammad Zeeshan, Firas Madbak, Mohammad Hamidi, Zaid Haddadin, Ashley Northcutt, Lynn Gries, Narong Kulvatunyou, Bellal Joseph

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No CTP (n = 23,160)</th>
<th>Early CTP (n = 4,819)</th>
<th>Late CTP (n = 8,208)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
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</tr>
<tr>
<td>Failure of NOM, % (n)</td>
<td>4% (926)</td>
<td>4.6% (221)</td>
<td>4.2% (344)</td>
<td>0.16</td>
</tr>
<tr>
<td>Postprophylaxis pRBC transfusions received, % (n)</td>
<td>—</td>
<td>3.9% (188)</td>
<td>3.8% (312)</td>
<td>0.21</td>
</tr>
<tr>
<td>Mortality, % (n)</td>
<td>2.4% (556)</td>
<td>2.0% (96)</td>
<td>2.3% (189)</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hospital LOS: median [IQR], d</td>
<td>5 [3–7]</td>
<td>6 [4–12]</td>
<td>8 [6–18]</td>
<td>0.02</td>
</tr>
<tr>
<td>DVT, % (n)</td>
<td>5.4% (1,250)</td>
<td>1.9% (91)</td>
<td>4.1% (336)</td>
<td>0.01</td>
</tr>
<tr>
<td>PE, % (n)</td>
<td>2.9% (671)</td>
<td>1.0% (48)</td>
<td>1.8% (147)</td>
<td>0.01</td>
</tr>
<tr>
<td>DVT and PE, % (n)</td>
<td>1.1% (255)</td>
<td>0.1% (5)</td>
<td>0.3% (25)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

IQR, interquartile range.
Inability to predict subprophylactic anti–factor Xa levels in trauma patients receiving early low-molecular-weight heparin

Imran, Jonathan B. MD; Madni, Tarik D. MD; Clark, Audra T. MD; Rizk, Paul; Huang, Emily; Minshall, Christian T. MD, PhD; Taveras, Luis R. MD; Cunningham, Holly B. MD; Eastman, Alexander L. MD, MPH; Koshy, Jojo P. PharmD; Kacir, Cory D. PharmD; Cripps, Michael W. MD, MSCS

- 124 Trauma patients on LMWH
- 31% had subprophylactic anti-Xa levels
- Among those with subprophylactic anti-Xa:
  - 92% had increased dosage
  - But only 75% reached prophylactic levels
Is there a difference between Trauma Center Verification Levels?
Incidence of VTE (DVT, PE) Among Different ACS Trauma Verification Levels (2019)

- Level I: 0.6%
- Level II: 0.4%
- Level III: 0.1%
Prolonged operating room time in emergency general surgery is associated with venous thromboembolic complications

Joseph V Sakran, Hiba Ezzeddine, Elliott R Haut, Nicole Lunardi, Ambar Mehta, Rachel L Choron, Jennifer Reid, Muhammad Zeeshan, Mohammad Hamidi, Bellal A Joseph

- Prolonged operation time → ↑ risk of developing VTE following EGS
- Operating time of ≥100 min → ↑ risk of developing a VTE.

What About Operatively Managed Trauma Patients?
VTE prophylaxis – Trauma surgery perspectives

The Future
Venous thromboembolism chemoprophylaxis regimens in trauma and surgery patients with obesity: A systematic review

Shaikh, Saamia MDc, JD; Boneva, Dessy MD, FACS; Hai, Shaikh MD, FACS; McKenney, Mark MD, MBA, FACS; Elkbuli, Adel MD, MPH

Weight-based chemoprophylaxis

- **Not** associated with a ↓ in VTE
- Associated with ↑ bleeding complications
Thrombelastography versus AntiFactor Xa levels in the assessment of prophylactic-dose enoxaparin in critically ill patients

Philbert Y Van, S David Cho, Samantha J Underwood, Melanie S Morris, Jennifer M Watters, Martin A Schreiber

TEG is superior to Anti Xa Levels in predicting VTE development after receiving enoxaparin prophylaxis.
How do new agents play into this?

DOACs?

Apixaban?
Rivaroxaban?
Dabigatran?

AntiPlatelets
Aspirin?
What About VTE among Trauma Patients with Cancer?

Analysis of TQIP (2017-19):

- Trauma patients with Cancer → more likely to suffer from DVT
- Despite no significant differences in rates of VTE prophylaxis
The Future

Impact of marijuana on venous thromboembolic events: Cannabinoids cause clots in trauma patients
Stupinski, Jack MD; Bible, Letitia MD; Asmar, Samer MD; Chehab, Mohamad MD; Douglas, Molly MD; Ditillo, Michael DO; Gries, Lynn MD; Khurrum, Muhammad MD; Joseph, Bellal MD

Positive blood alcohol is associated with reduced risk of VTE in trauma patients

What About Other Unstudied Substances?
Altered venous function and deep venous thrombosis following proximal femoral fracture

D Wilson, E.A Cooke, M.A McNally, H.K Wilson, A Yeates, R.A.B Mollana

How Long?

- Hypercoagulability can persist for six weeks after trauma
- Venous function impairment up to 42 days following surgery
The Long-Term Risks of Venous Thromboembolism Among Non-Operatively Managed Spinal Fracture Patients: A Nationwide Analysis”

Mauricio Avila, MD; Omar Obaid, MD; Letitia Bible, MD; Adam Nelson, MD; Raul Reina, MD; Michael Ditillo, DO; Tanya Anand, MD, MPH; Lourdes Castanon, MD; Randall Friese, MD; Bellal Joseph, MD

VTE risk and associated mortality remain high for 6 months after non-operatively managed traumatic spinal fractures.
M.I.S.T

The Most Important Slide of the Talk

IT ALL COMES DOWN TO THIS
MORE RESEARCH IS NEEDED
Thank You!

@TopKniFe_B

bjoseph@surgery.arizona.edu