VTE in Trauma: Then and Now

[The future = tomorrow]

Bill Geerts, MD, FRCPC
Thromboembolism Consultant, Sunnybrook HSC
Professor of Medicine, University of Toronto
## Potential Conflicts

<table>
<thead>
<tr>
<th>Current</th>
<th>None</th>
</tr>
</thead>
</table>

### In the past:
- **Grant support**
- **Program support**
- **Advisory boards**
- **Honoraria for education**

<table>
<thead>
<tr>
<th></th>
<th>Bayer</th>
<th>Boehringer-Ingelheim</th>
<th>Covidien</th>
<th>Leo Pharma</th>
<th>Pharmacia, Pfizer</th>
<th>Rhone Poulenc Rorer/Aventis/Sanofi</th>
</tr>
</thead>
</table>
I admire and applaud you incredible trauma surgeons for your:

- Skills
- Commitment
- Leadership
Outline

- Historical perspective of VTE in trauma and its prevention
- Our current practical approach
VTE in Trauma Literature before 1987: easy
VTE in Trauma Literature since 1987: a challenge
VTE in Trauma: Caveats

1. There is more than 1 way to prevent clinically important VTE in trauma.

2. All of you won’t agree with all my suggestions - that’s OK and that’s why we’re here.
- I started at Sunnybrook with an interest in VTE in trauma
1986 → 2022

- No prophylaxis
- Thrombo-prophylaxis not a priority
- No DVT screening
- No prophylactic IVCF
- No guidelines
Early Perception of Bleeding and VTE Risks in Trauma

Days since Injury

bleeding risk perception

VTE risk perception
<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1886</td>
<td>P Bruns</td>
<td>30 of 35 PE after fractures were fatal</td>
</tr>
<tr>
<td>1927</td>
<td>JS McCartney</td>
<td>142 cases of DVT or PE after trauma - “thrombus always developed at the site of the injury”</td>
</tr>
<tr>
<td>1934</td>
<td>BM Vance</td>
<td>2/3 of fatal PE in NYC followed trauma → 65% after LE fractures; injuries sometimes minor</td>
</tr>
<tr>
<td>1944</td>
<td>Gunnar Bauer</td>
<td>1/3 of all DVT followed leg trauma - “it might seem tempting to try prophylactic treatment with heparin and dicoumarin”</td>
</tr>
<tr>
<td>1948</td>
<td>Gordon Murray</td>
<td>1st used heparin in cardiac surgery - “I hope the day may come when it will be possible to give anticoagulants as a prophylactic to patients susceptible to thrombosis.”</td>
</tr>
</tbody>
</table>
916 autopsies at Birmingham Accident Hospital

DVT found in 81% of unselected trauma deaths

More than 1% of trauma admissions died of PE
Posttraumatic Venous Thrombosis

Robert J. Freeark, MD; John Boswick, MD; and Rostam Fardin, MD, Chicago


- Cook County Hospital Trauma Center
- 124 immobilized patients
- No thromboprophylaxis + bilateral venography

<table>
<thead>
<tr>
<th>Trauma patients</th>
<th>No.</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip fracture</td>
<td>70</td>
<td>41%</td>
</tr>
<tr>
<td>CNS injuries</td>
<td>11</td>
<td>36%</td>
</tr>
<tr>
<td>Extremity fractures</td>
<td>14</td>
<td>29%</td>
</tr>
<tr>
<td>Thoraco-abdominal</td>
<td>9</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>35%</td>
</tr>
</tbody>
</table>
Posttraumatic Venous Thrombosis

Robert J. Freeark, MD; John Boswick, MD; and Rostam Fardin, MD, Chicago


- Cook County Hospital Trauma Center
- 124 immobilized patients
- No thromboprophylaxis + bilateral venography

<table>
<thead>
<tr>
<th>Trauma patients</th>
<th>No.</th>
<th>DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoraco-abdominal</td>
<td>9</td>
<td>22%</td>
</tr>
<tr>
<td>Total</td>
<td>124</td>
<td>35%</td>
</tr>
</tbody>
</table>

“Routine prophylactic treatment with anticoagulation may produce more trouble than it prevents.”
Trauma

- “The risks of thromboembolic diseases and subsequent PE have not been specifically defined for the general trauma population.”
- “The efficacy and safety of the various forms of prophylaxis have not been evaluated in patients with multisystem trauma.”
Venous Thromboembolism in Patients with Major Trauma

Steven R. Shackford, MD, FACS, James W. Davis, MD, Peggy Hollingsworth-Fridlund, RN, Nancy S. Brewer, RCP, David B. Hoyt, MD, FACS, Robert C. Mackersie, MD, San Diego, California

Am J Surg 1990;159:365

719 trauma patients

PCD 76%, LDH 40%

No major risk factors n=542 (75%)

>1 major risk factor n=177

DVT 0 7%

1. Lwr extrem #
2. Pelvic #
3. Age >45 + bedrest >3D
4. Coma
5. Spine #
6. Paraplegia/quadriplegia
7. Complex lwr ext wound
8. Major vein repair
9. Previous VTE
A PROSPECTIVE STUDY OF VENOUS THROMBOEMBOLISM AFTER MAJOR TRAUMA


349 consecutive trauma admissions
ISS > 9, 1989-91

No thromboprophylaxis was used

Bilateral venography
day 7-21

Geerts – NEJM 1994;331:1601
DVT is common in major trauma

- Mean age 39; ISS 27; routine venography

<table>
<thead>
<tr>
<th>No.</th>
<th>DVT</th>
<th>Prox DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>349</td>
<td>58%</td>
</tr>
</tbody>
</table>

* 3 fatal pulmonary emboli

Geerts - NEJM 1994;331:1601
DVT is particularly common in orthopedic trauma

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>DVT</th>
<th>Prox DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>349</td>
<td>58%</td>
<td>18%</td>
</tr>
<tr>
<td>Major injuries:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Face/chest/abd</td>
<td>129</td>
<td>50%</td>
<td>15%</td>
</tr>
<tr>
<td>Head</td>
<td>91</td>
<td>54%</td>
<td>20%</td>
</tr>
<tr>
<td>Spine</td>
<td>66</td>
<td>62%</td>
<td>27%</td>
</tr>
<tr>
<td>L.E. Ortho</td>
<td>182</td>
<td>69%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Geerts - NEJM 1994;331:1601
## DVT Risk Factors in Trauma (N=349)

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05</td>
<td>1.03-1.06</td>
</tr>
<tr>
<td>(1 yr increments)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion</td>
<td>1.74</td>
<td>1.07-2.88</td>
</tr>
<tr>
<td>(yes/no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>2.30</td>
<td>1.08-4.89</td>
</tr>
<tr>
<td>(yes/no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur or tibia #</td>
<td>4.89</td>
<td>2.79-8.33</td>
</tr>
<tr>
<td>(yes/no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord injury</td>
<td>8.59</td>
<td>2.92-25.28</td>
</tr>
<tr>
<td>(yes/no)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*multivariate analysis

*Geerts – NEJM 1994;331:1601*
Risk Factors for VTE in Trauma

- Age
- Pelvic / lower extremity fracture
- Spinal cord injury
- Delay in thromboprophylaxis

- Major head injury
- Major venous injury
- Femoral venous line
- ISS
- Surgery
- Reduced mobility
Prophylaxis in Trauma
### SCDs

| **Advantages** | ▪ Don’t cause bleeding  
▪ May ↓ VTE |
|----------------|--------------------------------------------------|
| **Limitations** | ▪ Uncertain benefit – limited evidence  
▪ Must be bilateral + used continuously  
▪ Poor compliance – staff, patients  
▪ Discomfort / sleep interference  
▪ May delay “effective” prophylaxis (& mobilization)  
▪ ↑ costs |
| **Indications** | 1. Early C/I to LMWH  
2. ? Intraop major surgery  
3. ? High risk + LMWH |
Our Exclusive use of LMWH

- Increased bioavailability, more predictable pharmacokinetics, and longer half-life than heparin
- More evidence for LMWH in trauma (and other high-risk groups) + our RCT
- No greater bleeding
- Essentially eliminates HIT
- LMWH not more costly (at least for us)
Our Exclusive use of LMWH

*May 2022 cost to Sunnybrook without rebates, etc

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin 5,000 U TID</td>
<td>$ 10.65</td>
</tr>
<tr>
<td>Enoxaparin 40 mg daily</td>
<td>$  7.59</td>
</tr>
<tr>
<td>Enoxaparin 30 mg BID</td>
<td>$ 11.39</td>
</tr>
</tbody>
</table>
PREVENTION OF VENOUS THROMBOEMBOLISM IN TRAUMA PATIENTS

M. Margaret Knudson, MD, Frank R. Lewis, MD, Anna Clinton, RN, Keith Atkinson, RVT, and Joseph Megerman, PhD

- 251 patients assigned to 1 of 3 groups based on their injuries and then randomized within groups
- Doppler U/S every 5-7 days
- **Proximal DVT** in 7% without prophylaxis
- **SCDs** effective in neurotrauma (0 vs 13%)
- DVT in other patients: SCDs (7%), LDH (3%)
A COMPARISON OF LOW-DOSE HEPARIN WITH LOW-MOLECULAR-WEIGHT HEPARIN AS PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM AFTER MAJOR TRAUMA

1996;335:701


344 Trauma Patients

Exclusions

Heparin 5,000 U S/C Q12H

Enoxaparin 30 mg S/C Q12H
LMWH was more efficacious than LDH

- P = 0.014
  *Risk Red’n = 30%*

- P = 0.012
  *Risk Red’n = 58%
  NNT=11*

Geerts - NEJM 1996;335:701
Practice Management Guidelines for the Prevention of Venous Thromboembolism in Trauma Patients: The EAST Practice Management Guidelines Work Group

Frederick B. Rogers, MD, Mark D. Cipolle, MD, PhD, George Velmahos, MD, PhD, Grace Rozycki, MD, and Fred A. Luchette, MD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDH</td>
<td>“very little proven efficacy” “cannot be supported” (Level I)</td>
</tr>
<tr>
<td>PCDs</td>
<td>“no benefit of the use over no prophylaxis” “cannot be supported” (Level I)</td>
</tr>
<tr>
<td>LMWH</td>
<td>“strongly considered for use in all high-risk trauma” . . . “when their bleeding risk is acceptable” (Level II)</td>
</tr>
<tr>
<td>Prophylactic IVCF</td>
<td>Consider in very high-risk patients who cannot receive anticoagulant prophylaxis (Level III)</td>
</tr>
<tr>
<td>Screening DUS</td>
<td>May decrease PE and may be cost effective (Level III)</td>
</tr>
</tbody>
</table>
Effectiveness of low-molecular-weight heparin versus unfractionated heparin to prevent pulmonary embolism following major trauma: A propensity-matched analysis

J Trauma Acute Care Surg 2017;82:252

James P. Byrne, MD, William Geerts, MD, Stephanie A. Mason, MD, David Gomez, MD, PhD, Christopher Hoeft, MA, Ryan Murphy, MPH, Melanie Neal, MS,
and Avery B. Nathens, MD, PhD, Toronto, Ontario, Canada

- TQIP database 2012-15
- 153,474 patients with ISS ≥9 + in hospital ≥5 days
- Propensity matching for LMWH or UFH

<table>
<thead>
<tr>
<th></th>
<th>LMWH (n=37,960)</th>
<th>LDH (n=37,960)</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>1.4%</td>
<td>2.4%</td>
<td>0.56 [0.50-0.63]</td>
</tr>
<tr>
<td>1986</td>
<td>2022</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prophylaxis</td>
<td>Low dose heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fixed dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombo-prophylaxis not</td>
<td>Thrombo-prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a priority</td>
<td>highly variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No DVT screening</td>
<td>Selected screening DUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prophylactic IVCF</td>
<td>Selected prophylactic IVCF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No guidelines</td>
<td>EAST, ACCP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
How early should we start prophylaxis?
Timing of LMWH Initiation

- **Delayed start** of LMWH $\rightarrow$ more VTE
- **Early start** of LMWH associated with fewer VTE
- **Early start** of LMWH **not** associated with ↑ bleeding
- Shown in patients with TBI (stable head CT), solid organ injury, pelvic and spine fractures, and SCI

Margolick – Can J Neuro Sci 2018;45:432
Coleman – Am J Surg 2019;218:1065
Skarupa – J Trauma Acute Care Surg 2019;87:1104
Ahlquist – Neurospine 2020;17:407
Hecht – J Trauma Acute Care Surg 2021;90:54
Adjusted Enoxaparin Dosing

- Most (30-80%) trauma patients do not achieve target AXa levels with standard enoxaparin doses
- But low AXa not consistently correlated with ↑ VTE
- And high AXa not associated with ↑ bleeding
- Makes a “simple” decision more complex & costly
- Weight-based dosing avoids need for AXa monitoring

Walker – Ann Pharmacother 2017;51:323
Karcutskie – JAMA Surg 2018;153:144
Kay – Surgery 2018;164:144
Stutsrim – Am Surg 2021;87:77
Taylor – Pharmacotherapy 2021;41:508
Prophylactic **IVC Filter** Use

- Very wide variations in use not explained by patient factors
- Earlier studies used suboptimal prophylaxis
- RCT by Ho et al showed no reduction in PE + mortality
- Increased risk of DVT
- Complication rates are more common than the disease that filters are designed to prevent
- Many filters never removed
- Huge costs

Progressive decrease in filter implantation

- Haut – JAMA Surg 2014;149:194
- Sarosiek – JAMA Surg 2017;152:75
- Ho – NEJM 2019;381:328
A Multicenter Trial of Vena Cava Filters in Severely Injured Patients

Major trauma patients with C/I to anticoag prophylaxis

R

N=240
Australia
Mean age 39
Mean ISS 27

IVCF placed <72 hrs
No IVCF placed

Outcomes at 90 days

<table>
<thead>
<tr>
<th></th>
<th>IVCF (n=122)</th>
<th>Control (n=118)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympt PE / death</td>
<td>17 (13.9%)</td>
<td>17 (14.4%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Death</td>
<td>16</td>
<td>11</td>
<td>0.42</td>
</tr>
<tr>
<td>Symptomatic PE</td>
<td>1 (0.8%)</td>
<td>6 (5.1%)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Ho – NEJM 2019;381:328
**DUS Screening** for Asymptomatic DVT

- Very **wide variations** in practice
- Screening detects **more** DVT
- **Clinical significance** of asymptomatic DVT uncertain
- Generally **not associated** with fewer symptomatic VTE or PE
- More patients with asymptomatic DVT are anticoagulated → **more bleeding**
- Substantial additional **cost**

Pierce – J Trauma 2008;654:932
Haut – J Trauma 2011;70:27
Dietch – Surgery 2015;158:379
Kay – J Trauma Acute Care Surg 2021;90:787
Very wide variations in practice
- Screening detects more DVT

“If you just simply take an aggressive approach to prophylaxis, what’s the added benefit of screening people?”

David Spain – J Trauma Inj Infect Crit Care 2008;65:307

Pierce – J Trauma 2008;654:932
Haut – J Trauma 2011;70:27
Dietch – Surgery 2015;158:379
Kay – J Trauma Acute Care Surg 2021;90:787
<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Citation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP</td>
<td>2012</td>
<td>Gould – Chest 2012;141:e227S</td>
</tr>
<tr>
<td>Western Trauma Assoc</td>
<td>2020</td>
<td>Ley – J Trauma ACS 2020;89:971</td>
</tr>
<tr>
<td>AAST Crit Care Committee</td>
<td>2021</td>
<td>Rappold – Trauma Surg Acute Care Open 2021;9:e000643</td>
</tr>
<tr>
<td>AAST/ACS Committee on Trauma</td>
<td>2022</td>
<td>Yorkgitis – J Trauma ACS 2022;92:597</td>
</tr>
</tbody>
</table>
Conclusions
(and our approach)
Bleeding : Thrombosis Risk Separation = \textit{the Window of Opportunity}

High

Low

bleeding risk

thrombosis risk

Anticoagulant Thromboprophylaxis

trauma

Days since Injury
<table>
<thead>
<tr>
<th>1986</th>
<th>2022</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No prophylaxis</strong></td>
<td><strong>Low dose heparin</strong></td>
</tr>
<tr>
<td><strong>Thrombo-prophylaxis not a priority</strong></td>
<td><strong>Thrombo-prophylaxis highly variable</strong></td>
</tr>
<tr>
<td><strong>No DVT screening</strong></td>
<td><strong>Selected screening DUS</strong></td>
</tr>
<tr>
<td><strong>No prophylactic IVCF</strong></td>
<td><strong>Selected prophylactic IVCF</strong></td>
</tr>
<tr>
<td><strong>No guidelines</strong></td>
<td><strong>EAST, ACCP</strong></td>
</tr>
<tr>
<td><strong>VTE prevention is routine, systematic</strong></td>
<td><strong>No or limited screening DUS</strong></td>
</tr>
<tr>
<td><strong>No prophylactic IVCF</strong></td>
<td><strong>Multiple guidelines</strong></td>
</tr>
</tbody>
</table>
1986 → 2022

- No prophylaxis
- Low dose
- Enoxaparin

Decrease in clinically-important VTE

Why?
1. Better thromboprophylaxis
2. Dramatic improvements in trauma care

Congratulations!

- No guidelines
- EAST, ACCP
- Multiple guidelines
Sunnybrook *Priorities* in Thromboprophylaxis in Trauma

1. Don’t cause bleeding √
2. Prevent major VTE (fatal PE, symptomatic extensive PE, extensive DVT) √
3. Do this consistently and efficiently √
4. Don’t spend too much $ accomplishing this √
5. Don’t make the surgeons, ICU docs “nervous” √√

NOT:
- Prevent every (small) DVT
- Prevent every (small) PE
<table>
<thead>
<tr>
<th>Patient</th>
<th>Enoxaparin dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt &lt;40 kg or CrCl &lt;30 mL/mL</td>
<td>30 mg QHS</td>
</tr>
<tr>
<td>Usual risk – wt 40-100 kg</td>
<td>40 mg QHS</td>
</tr>
<tr>
<td>Usual risk – wt 100-125 kg</td>
<td>40 mg BID</td>
</tr>
<tr>
<td>Usual risk – wt &gt;125 kg</td>
<td>0.5 mg/kg BID</td>
</tr>
<tr>
<td>High risk (SCI, major LEF) – wt 40-100 kg</td>
<td>40 mg QHS → 40 mg BID</td>
</tr>
<tr>
<td>High risk (SCI, major LEF) – wt 100-125 kg</td>
<td>40 mg BID → 60 mg BID</td>
</tr>
<tr>
<td>SC heparin</td>
<td>Formal “avoid heparin policy”</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>AXa monitoring</td>
<td>Never</td>
</tr>
<tr>
<td>Duration of prophylaxis</td>
<td>Discharge from rehab (never after discharge)</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg PO daily</td>
<td>High risk + LOS &gt;1 week</td>
</tr>
<tr>
<td>Doppler U/S screening</td>
<td>Never</td>
</tr>
<tr>
<td>Prophylactic IVC filter</td>
<td>Never</td>
</tr>
</tbody>
</table>
Trauma

Adm

Usual risk

Hosp or rehab discharge

enoxaparin

OR

OR
Final Comments

What have I learned over 35 years?

1. Major trauma patients ARE definitely at increased risk of VTE if we are not active in preventing it.
2. We cannot prevent every symptomatic DVT or PE (but we can prevent almost all major DVT/PE).
3. Bleeding concerns have been over-emphasized in the past (clinically important bleeding is very uncommon with sensible thromboprophylaxis).
4. Uniform, fixed dosing of LMWH is insufficient.
5. Early start of LMWH is safe and effective + QHS.
6. Weight-based dosing.
7. Stop prophylaxis at discharge from rehab.
8. Routine DVT screening not effective (may be harmful).
9. Prophylactic IVC filters not needed.
Heroes in Trauma VTE Prevention

- Gunnar Bauer
- Scott Brakenridge
- Karen Brasel
- Mark Cipolle
- Todd Constantini
- Demetrios Demetriades
- Brent Eastman
- Tim Fabian
- Lazar Greenfield
- Elliott Haut
- A Ho

- Kwok Ho
- David Hoyt
- Peggy Knudson
- Ken Kudsk
- Eric Ley
- Mark Meissner
- Ernest Moore
- Lena Napolitano
- Avery Nathens
- Scott Norwood
- Erik Olson

- Herb Phelan
- Jorge Rodriguez
- Fred Rogers
- Tom Scalea
- Martin Schreiber
- Simon Sevitt
- Steven Shackford
- David Spain
- Deborah Stein
- Alexandre Tran
- George Velmahos
- Many others

- Karen Code, RN
- Val Valenzuela, RN
- Alison Bond, PharmD