DVT Prophylaxis In Critically Ill and Trauma

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Deputy Director NSW Medical Retrieval Unit
Director NSW Institute Trauma & Injury Management
Why is it Important

High prevalence of VTE
- Most hospitalised patients have risk factors
- DVT is common in many patient groups
- Hospital acquired DVT and PE are usually clinically silent.
- Difficult to predict
- Screening is usually ineffective
Why is it important?

- Adverse consequences of VTE
  - Fatal Pulmonary Embolus
  - Costs of investigating and treating symptomatic patients
  - Increased future risk of recurrent VTE
  - Chronic post thrombotic syndrome
## Risk Factors in ICU

<table>
<thead>
<tr>
<th>Baseline Factors</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>4.6 (0.6 – 38.3)</td>
</tr>
<tr>
<td>Past VTE</td>
<td>4.6 (0.9 – 29.4)</td>
</tr>
<tr>
<td>Cancer</td>
<td>3.7 (0.7 – 18.8)</td>
</tr>
<tr>
<td>Immobilisation</td>
<td>2.1 (0.1 – 4.9)</td>
</tr>
</tbody>
</table>
## Absolute risk of DVT

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>DVT Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Patients</td>
<td>10-20%</td>
</tr>
<tr>
<td>General Surgery</td>
<td>15-40%</td>
</tr>
<tr>
<td>Major Gynaec Surgery</td>
<td>15-40%</td>
</tr>
<tr>
<td>Major Uro Surgery</td>
<td>15-40%</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>15-40%</td>
</tr>
<tr>
<td>Stroke</td>
<td>20-50%</td>
</tr>
<tr>
<td>Hip or Knee Arthroplasty</td>
<td>40-60%</td>
</tr>
<tr>
<td>Major Trauma</td>
<td>40-80%</td>
</tr>
<tr>
<td>Spinal Cord Injury</td>
<td>60-80%</td>
</tr>
<tr>
<td>Critical Care Patients</td>
<td>10-80%</td>
</tr>
</tbody>
</table>
## Risk factors and OR for VTE among Trauma patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;40 years</td>
<td>2.29 (2.07-2.55)</td>
</tr>
<tr>
<td>Pelvic Fracture</td>
<td>2.93 (2.01-4.27)</td>
</tr>
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<td>Lower extremity fracture</td>
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</tr>
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<td>Spinal cord injury + paralysis</td>
<td>3.39 (2.41-4.77)</td>
</tr>
<tr>
<td>Head Injury AIS&gt;3</td>
<td>2.59 (2.31-2.90)</td>
</tr>
<tr>
<td>Ventilator days&gt;3</td>
<td><strong>10.62 (9.32-12.11)</strong></td>
</tr>
<tr>
<td>Venous injury</td>
<td>7.93 (5.83-10.78)</td>
</tr>
<tr>
<td>Shock @admission</td>
<td>1.95 (1.62-2.34)</td>
</tr>
<tr>
<td>Major surgical procedure</td>
<td>4.32 (3.91-4.77)</td>
</tr>
</tbody>
</table>
Why is it important?

- Efficacy and Effectiveness of Thromboprophylaxis
  - Highly efficacious in preventing DVT
  - DVT prevention prevents VTE
  - Prophylaxis is cost-effective
- Prophylaxis often omitted
What are the options?

- Mechanical Devices
  - Elastic stockings
  - Compression devices – Pneumatic (IPD), Sequential pneumatic (SCD), Foot Pumps

- Chemical Prophylaxis
  - Heparins
  - Oral anticoagulants???
  - Newer agents?
What are the options?

- Currently available data is unequivocally in favour of Heparin - LDUH or LMWH.
- No evidence for aspirin or other platelet agents
- Some evidence for mechanical devices, especially as adjuncts
Mechanical Devices
RCT of Stockings + Pneumatic Compression in Neurosurgery

- Unblinded RCT of 239 neurosurgery patients
- DVT rates diagnosed by IPG/legscan/venogram lower when patients received stockings + pneumatic compression than no prophylaxis
- Bleeding: none
- PE: none

Turpie et al, Arch Intern Med 1989
## Effects of compression methods of thromboprophylaxis on DVT

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of trials with data</th>
<th>Compression</th>
<th>Control</th>
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<th>% OR (SE)</th>
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<td>2</td>
<td>11/61 (18%)</td>
<td>34/65 (52.3%)</td>
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<td>7.3</td>
<td>77% (19) (2 p &lt; 0.00001)</td>
<td></td>
</tr>
</tbody>
</table>

IPC = intermittent pneumatic compression; GCS = graduated compression stockings.

Chemical DVT Prophylaxis

- Vitamin K antagonists
  - Warfarin

- Antithrombin agonists
  - Unfractionated heparin
  - Low molecular weight heparin

- “Factor Xa” inhibitors*
  - Fondaparinux

- Direct thrombin antagonists
  - Hirudin, argatroban, ximelagran, etc.

- Anti-platelet agents
  - Aspirin, dipyrimadole, clopidogrel, etc.
Heparin Mechanisms

- Anti thrombin activation
  - Occurs when the penta-saccharide chain randomly distributed along the UH or LMWH chain binds to anti thrombin.
  - Anti thrombin then under goes a conformational change that accelerates interaction between anti thrombin, factor Xa and thrombin.
Unfractionated Heparin

- Heterogenous polysaccharide chains
- MW 3,000-30,000 Daltons
- 1/3 dose contains penta-saccharide sequence
- Anti X a: anti II a ratio = 1:1
- Non-specific binding to macrophages, platelets, and endothelial cells makes anticoagulation difficult to predict
Low molecular weight heparin

- Derived from UH molecules
- MW 1000-10,000 daltons
- Penta-saccharide sequence present on roughly 15-25% of LMWH chains
- Predominant anti Xa antagonism
- Anti Xa: anti II a ratio 4:1-5:1
- Less binding to macrophages and endothelial cells - predictable, reliable, safe
Advantages of LMWH over UH

- Decreased "heparin resistance"
  - Pharmaco-kinetics of UH are influenced by its bindings to plasma protein, endothelial cell surfaces, macrophages, and other acute phase reactants
  - LMWH has decreased binding to non anticoagulant-related plasma proteins
Advantages of LMWH over UH

- No need for laboratory monitoring
  - when given on a weight-adjusted basis, the LMWH anticoagulant response is predictable and reproducible
- Higher bioavailability - 90% vs 30%
- Longer plasma half-life
  - 4 to 6 hours vs. 0.5 to 1 hour
  - Renal (slower) vs. Hepatic clearance
Advantages of LMWH over UH

- Less inhibition of platelet function
  - potentially less bleeding risk, but not shown in clinical use
- Lower incidence of thrombocytopenia and thrombosis (HIT syndrome)
  - less interaction with platelet factor 4
  - fewer heparin-dependent IgG antibodies
WHICH HEPARIN?
HOW MUCH?
HOW OFTEN?
Unfractionated Heparin

- Primary agent over many years.
- Data primarily from surgical patients
- 60-70% relative risk reduction in both DVT/PE
- Data supporting UH use in medical patients are more difficult to interpret.
Unfractionated heparin

- Earliest study 30 years back
- Patients with MI, HF and unspecified medical problems
- DVT rates 2.6% and 22.5% in Heparin and placebo groups.
- Similar results in a larger study in 192 patients older than 40 years with pulmonary disease
Low molecular weight heparins

- ENOXAPARIN
- DALTEPARIN
- FRAXIPARIN etc.
ENOXAPARIN

- First trial- 270 patients; 60mg s/c bd vs placebo
- Significant reduction of frequency of DVT
- More injection site hematomas.
- No clinically significant bleeding.
Enoxaparin in Medicine Study Group (EMSG)

- 5000 U UH q 12 h vs Enoxaparin 20 mg s/c bd in 442 elderly ICU patients

- No difference in DVT rates diagnosed by RFUT
Prophylaxis in Medical Patients with Enoxaparin (MEDENOX)

- Targets: Risk of VTE
- Safety and efficacy of 20mg vs. 40mg bd of Enoxaparin
- No difference in incidence of DVT/VTE between placebo and 20mg bd Enoxaparin
- 63% risk reduction with 40mg bd dose.
- Benefit maintained for 110 days.
- No major bleeding/thrombocytopenia.
- No data on 40mg bd Enoxaparin vs. UH
Thrombo-embolism prophylaxis in Internal Medicine with Enoxaparin (PRIME) Group

- Multi-center, double blind, RCT 885 pts-40mg bd Enoxaparin vs. 5000U UH q 8h.
- No statistical difference in incidence of VTE.
- No difference in major bleeding tendencies.
- Fewer injection site haematomas with Enoxaparin.
Thrombo-embolism prevention in cardiopulmonary diseases with Enoxaparin (PRINCE)

- Enoxaparin 40mg bd vs UH 5000 U q8h - 665 patients.
- No difference in DVT prevention rates
- More bleeding in UH group
- Better risk reduction with Enoxaparin in those with CHF.
Prospective Evaluation of Dalteparin Efficacy for Prevention of VTE in Immobilised patients (PREVENT)

- 3706, moderate risk hospitalised patients
  Dalteparin 5000 U vs. Placebo once daily for 14 days
- Assessed for DVT at 21 days
- 2.77% vs 4.96% in favour of Dalteparin
- 45% risk reduction with Dalteparin
- No data in exclusively ICU patients
RCT of UF Heparin vs LMWH in Trauma Patients

- Double-blind RCT of 344 trauma patients with ISS>9
- DVT rates proven by venography were lower in patients receiving LMWH than unfractionated heparin
- Bleeds: 5 with LMWH, 1 with unfractionated

Geerts et al, NEJM 1996
## Prophylaxis recommendations in critically ill patients

<table>
<thead>
<tr>
<th>Bleeding risk</th>
<th>Thrombosis risk</th>
<th>Prophylaxis recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>MODERATE</td>
<td>LDUH 5000 U q 12h</td>
</tr>
<tr>
<td>LOW</td>
<td>HIGH</td>
<td>LMWH qd</td>
</tr>
<tr>
<td>HIGH</td>
<td>MODERATE</td>
<td>GCS or IPC→LDUH when bleeding risk decreases</td>
</tr>
<tr>
<td>HIGH</td>
<td>HIGH</td>
<td>GCS or IPC→LMWH when bleeding risk decreases</td>
</tr>
</tbody>
</table>
Principles of DVT prophylaxis in critically ill patients

- Daily review – change prn
- No interruption for Sx or procedures unless risk of bleeding is high.
- Routine screening for asymptomatic patients not recommended if prophylaxis has been adequate.
- Periodic audits.
DVT Prophylaxis - Recommendations

Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy

William H. Geerts, Graham F. Pineo, John A. Heit, David Bergqvist, Michael R. Lassen, Clifford W. Colwell and Joel G. Ray

*Chest* 2004;126;338-400
DOI 10.1378/chest.126.3_suppl.338S

- Orthopaedic surgery sections of recommendations were formally reviewed by 16 external experts, 10 of whom were orthopaedic surgeons (including several well known orthopaedic traumatologists).
- Recommendations reviewed and supported by the AAOS.
5.1 Trauma

- All trauma patients receive thromboprophylaxis, if possible (Grade 1A).
- Unless contraindicated, use LMWH starting as soon as it is considered safe to do so (Grade 1A).
- Recommend against the use of vena cava filters as primary prophylaxis in trauma patients (Grade 1C).
- Recommend continuation of prophylaxis through the completion of inpatient rehab (Grade 1C+), and suggest continued prophylaxis after discharge with LMWH or VKA in patients with impaired mobility (Grade 2C).
Initial prophylaxis consideration

CRITICAL CARE ADMISSION

? BLEEDING RISK

HIGH
• Mechanical Prophylaxis.
• Delay prophylaxis till risk resolves
• Screen for proximal DVT with Doppler in high risk pts

USUAL
• LDUH
• LMWH
• Combined with mechanical prophylaxis
To summarize......

- All ICU & Trauma patients have a combination of risk factors for VTE.
- Balanced assessment and decision making crucial.
- LMWH preferred in those with multiple risk factors vs. risk bleeding
- Adherence to guidelines and regular audits needed for better results.
PROphylaxis for ThromboEmbolism in Critical Care Trial (PROTECT)

- Effect of LMWH vs. UH on primary outcome of DVT diagnosed by USG
- LMWH vs. UH on secondary outcomes of PE, HIT and Bleeding.
- Expected enrolment 3600
- Expected completion June 2009.
What’s new?
Synthetic oligo-saccharides

- Result of breakthrough in polysaccharide chemistry.
- Fondaparinux-selective inhibitor of factor Xa.
- Approved for use in orthopaedic surgery.
- Also found to be beneficial in ACS and in VTE.
- Efficacy at least as good as Enoxaparin; better safety profile.
Arixtra for Thromboembolism Prevention in a Medical Indications Study (ARTEMIS)

- 849 acutely ill medical patients bedridden for >4 days
- Multinational, double blind
- 2.5mg Fondparinux vs placebo once daily.
- Venography at 6 and 14 days
- 5.6 vs 10.6% with OR 49.5% for DVT
- No PTE in fondparinux group vs 1.2% in placebo group
- Similar bleeding rates
## Properties of conventional anticoagulants

<table>
<thead>
<tr>
<th>Property</th>
<th>Vit.K antagonism</th>
<th>UH</th>
<th>LMWH</th>
<th>Fondaparinux</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Synthetic</td>
<td>Animal</td>
<td>Animal</td>
<td>Synthetic</td>
</tr>
<tr>
<td>Structure</td>
<td>Homogenous</td>
<td>Heterogenous</td>
<td>Heterogenous</td>
<td>Homogenous</td>
</tr>
<tr>
<td>Target</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Multiple</td>
<td>Single</td>
</tr>
<tr>
<td>Prot. binding</td>
<td>Albumin</td>
<td>AT III +pl.prot</td>
<td>AT III +pl.prot</td>
<td>AT III</td>
</tr>
<tr>
<td>Administration</td>
<td>Daily</td>
<td>Q 8h</td>
<td>Q12h</td>
<td>Daily</td>
</tr>
<tr>
<td>Monitor coagulation</td>
<td>Frequent</td>
<td>Frequent</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Interactions</td>
<td>Many</td>
<td>None known</td>
<td>None known</td>
<td>None known</td>
</tr>
<tr>
<td>HIT Ab cross reactivity</td>
<td>100%</td>
<td>80%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>
Direct Thrombin Inhibitors (DTI)

- Parenteral
  - Hirudin
  - Bivalirudin
  - Argatroban
- Oral
  - Ximelagatran - studied in DVT
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<td>77% (19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>180/1,834 (8.6%)</td>
<td>435/1,839 (23.7%)</td>
<td></td>
<td>115.5</td>
<td></td>
<td>67% (6)</td>
</tr>
</tbody>
</table>

- **CareFlight** logo on the left:
  - Pneumatic compression; compression stockings.

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## Effects of compression methods of thromboprophylaxis on PE

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of trials with data</th>
<th>Compression</th>
<th>Control</th>
<th>Stratified statistics</th>
<th>OR and CI compression: control</th>
<th>% OR (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>PE</td>
<td></td>
<td>O–E Variance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression (mono-therapy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS</td>
<td>3</td>
<td>0/123 (0%)</td>
<td>4/90 (4.4%)</td>
<td>– 1.8  0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPC</td>
<td>8</td>
<td>14/590 (2.4%)</td>
<td>18/618 (2.9%)</td>
<td>– 1.6  7.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foot pump</td>
<td>1</td>
<td>0/28 (0%)</td>
<td>0/32 (0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>14/741 (1.9%)</td>
<td>22/740 (3%)</td>
<td>– 3.4  8.5</td>
<td>33% (28)</td>
</tr>
</tbody>
</table>

% OR (SE) = 33% (28)

2 p > 0.1; NS

Compression better Compression worse

Treatment effect 2 p = 0.006

## DVT & Trauma – Risk Factors

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<th>Risk factor</th>
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<td>Spinal cord injury with paralysis ($n = 2852$)</td>
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<td>Head injury (AIS score $\geq 3$) ($n = 52,197$)</td>
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<td>Ventilator days $&gt; 3$ ($n = 13,037$)</td>
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<tr>
<td>Venous injury ($n = 1450$)</td>
<td>7.93 (5.83–10.78)</td>
</tr>
<tr>
<td>Shock on admission (BP &lt; 90 mm Hg) ($n = 18,510$)</td>
<td>1.95 (1.62–2.34)</td>
</tr>
<tr>
<td>Major surgical procedure ($n = 73,974$)</td>
<td>4.32 (3.91–4.77)</td>
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P $< 0.001$ for all factors.

AIS, Abbreviated Injury Scale; BP, blood pressure.

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Why Is Prophylaxis Omitted?

- Lack of awareness
- Diversion of attention
- Concerns regarding safety of regimens
  - Neurosurgical – Brain, Spinal
- More daily injections
- Cost