VTE Chemoprophylaxis in the Surgical Patient

When do the benefits outweigh the risks?

Lawrence Dennen, MD
2 April 2008
Oh what to do, what to dooo?
The Agency for Healthcare Research and Quality


- Number One safety intervention based on strength of evidence
- “Appropriate use of prophylaxis to prevent VTE in patients at risk.”
History of this VTE events

- **1884** Rudolph Virchow
  - Vascular endothelial damage
  - Stasis of blood flow
  - Hypercoagulable state in the blood

- **1950’s** Surgical patients had increased risks for thrombotic events

- **1962** Published reports that UF Heparin greatly reduced the risks of these events

- **1986** 1st consensus statement by American College of Chest Physicians Prevention of Venous Thromboembolism

- **1991** Hospitalized medical patients have similar risks to moderate risk surgical patients
Our Track Record

- 38 years of documented understanding of problem and evidence of effective strategies to prevent VTE related death
- 15 years of published consensus recommendations

Data shows only 50.5% of high risk abdominal surgery patients received VTE prophylaxis during hospitalization

Arch Intern Med 2000
Regulatory & Government Involvement:

- Every hospital must develop a formal strategy to address the prevention of thromboembolic complications
  - Approach 1: Evaluate the risk VTE in each patient
  - Approach 2: Implement group specific prophylaxis routinely for group
Why have we not embraced VTE Chemical Prophylaxis?

- Confusing and contradicting results of trials
- Many patients with high risks also have terminal illness
- Many VTE complications present after surgical discharge
- Incidence of devastating pulmonary embolus is low
- No tangible evidence of patient benefit
- Fear of bleeding complications
Natural History

- Begins in deep veins of calf at valve cusps
  - Most present intra-operatively (50%)
  - Half of these resolve spontaneously in 72 hours
  - Rarely result in clinical symptoms
  - Low risk for PE
  - 1 in 6 develop PTS
Natural History

- Extends into proximal leg venous system
  - Commonly extends despite anticoag Rx
  - Resolution is slow = 1 yr. 38% complete
    55% partial
  - 60% of these patients have PTS
Natural History

- **Develops Pulmonary Embolism**
  - Asymptomatic PE are very common with proximal DVT’s
  - Highest risk is 3-7 days post-op
  - Symptoms less common in young, more common in chronically ill and elderly
  - Symptoms depend on:
    - Extent of thrombosis
    - Adequacy of collateral vessels
    - Severity of vascular occlusion inflammatory response
    - Capacity of patient to tolerate insult
Natural History

- Results in Fatal Pulmonary Embolism
  - 200,000 deaths/year in USA
  - Clinical diagnosis of PE established rarely in those dying of PE
  - 10% fatal within 1 hour preventing initiation of treatment, 25% within 7 days
  - 50% of symptomatic patients have right ventricular dysfunction which correlates to high short term mortality
Epidemiology

- No identifiable gender differences
- May have some seasonality (winter > summer)
- Exponential increase with age over 40 years
  - 25-35 year old = 30 cases (per 100,000 population)
  - 70-79 year olds = 300-500 cases (per 100,000 population)
- Significant variation with race (per 100,000 population)
  - African Americans > Caucasians > Hispanic > Asian Pacific Islanders

  29  23  14  6
Risk Factors for VTE

Absolute:
1. Major abdominal or thoracic procedure
   - Operative time > 30 minutes using general anesthesia
   - Very little high quality data on laparoscopic procedures
2. Spinal cord injury or paralysis of one limb
3. Isolated long bone fracture, hip fracture, or pelvic fracture
4. Multiple trauma without any of above fractures
5. Procedures / hospitalizations for malignancy
   - Breast, colon, lung, rectum
   - Brain, pancreas, ovary
   - After chemotherapy has been administered
6. Active myocardial infarction
7. Class III/IV heart failure

Anderson, Spencer, Circulation, June 2003
# Relative Risk Factors

## Moderate Risk Factors

1. Age > 40 years
2. Within 2 weeks post partum
3. Prior VTE episode
   - PE >> DVT
4. Bed rest > 7 days
5. Exogenous Estrogen Therapy
   - BCP (3-4), HRT (2-4), Prostrate Rx
6. Inflammatory Bowel Disease
7. Known Antiphospholipid Antibody Syndrome
   - Anticardiolipin Antibody
   - Lupus Anticoagulant
8. Hereditary Conditions
   - Only 10% of all VTE cases
   - 50% of spontaneous cases in age < 35 years

## Weak Risk Factors

1. Obesity
2. Long duration air travel
3. Varicose veins
4. Pregnancy
5. Presence of central venous catheters
6. Nephrotic syndrome
Hereditary Conditions

- Antithrombin deficiency (AT-III)
- Protein C or Protein S deficiency
- Activated protein C resistance (Factor V Leiden)
- Prothombin G20210A mutation variant
- Decreased levels of plasminogen / plasminogen activators
- Increased concentration of coagulation factors VIII, IX, XI
- Myeloproliferative disorders
  - Polycythemia vera
  - Primary thrombocytosis
# Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Description</th>
<th>Calf DVT (%)</th>
<th>Proximal DVT (%)</th>
<th>Clinical PE (%)</th>
<th>Fatal PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Minor surgery patients &lt; 40</td>
<td>2</td>
<td>0.4</td>
<td>0.02</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>No risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Risk</td>
<td>Minor surgery plus risk factor</td>
<td>10-20</td>
<td>2-4</td>
<td>1-2</td>
<td>0.1-0.4</td>
</tr>
<tr>
<td></td>
<td>Major surgery age 40-60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MI / CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>Major surgery age &gt; 60</td>
<td>20-40</td>
<td>4-8</td>
<td>2-4</td>
<td>0.4-1.0</td>
</tr>
<tr>
<td></td>
<td>Major surgery age 40-60 with risk factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very High Risk</td>
<td>Major surgery age &gt; 40</td>
<td>40-80</td>
<td>10-20</td>
<td>4-10</td>
<td>0.2-5.0</td>
</tr>
<tr>
<td></td>
<td>with multiple risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multiple trauma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spinal cord injury w/paralysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GEERTS et al, Chest 2001
## Low Dose Unfractionated Heparin (LDUH)

<table>
<thead>
<tr>
<th>#</th>
<th>n</th>
<th>Incidence</th>
<th>CI</th>
<th></th>
<th>n</th>
<th>Incidence</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>284/3265</td>
<td>8.70%</td>
<td>(7.8-9.7)</td>
<td>DVT</td>
<td>853/3382</td>
<td>25.2%</td>
<td>(23.8 - 26.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12</td>
<td>22/1564</td>
<td>1.40%</td>
<td>(0.9-2.2)</td>
<td>Prox. DVT</td>
<td>113/1788</td>
<td>6.4%</td>
<td>(5.3 - 7.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>20</td>
<td>22/4215</td>
<td>0.52%</td>
<td>(0.33-0.8)</td>
<td>All PE</td>
<td>52/4228</td>
<td>1.2%</td>
<td>(0.93 -1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24</td>
<td>10/4699</td>
<td>0.21%</td>
<td>(0.11-0.4)</td>
<td>Fatal PE</td>
<td>34/4772</td>
<td>71.0%</td>
<td>(0.50 - 1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Intermittant Pneumatic Compression**

<table>
<thead>
<tr>
<th>#</th>
<th>n</th>
<th>Incidence</th>
<th>CI</th>
<th></th>
<th>n</th>
<th>Incidence</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>31/313</td>
<td>9.90%</td>
<td>(6.9-13.9)</td>
<td>DVT</td>
<td>61/300</td>
<td>20.3%</td>
<td>(16 - 25.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Clagett, Reisch, Ann Surg 1988
Additional Conclusions

- Intermittent Pneumatic compression devises outside of clinical trials - suboptimal
  - Right size/fit
  - Compliance with use recommendations
- Proximal DVT and PE endpoint conclusions cannot be reached for IPC.
  Little data for medical patients
- Comparison IPC to LDH is not statistically significant for any advantage
- Dextran (D70, D40) - effective in reducing DVT, PE, fatal PE
- Elastic GPS- effective in reducing (+FUT) DVT but not in any other measurement for VTE
- Aspirin was not effective
Overview of Data for LMWH

- Mega-analysis adding nearly 25,000 additional patients to Clagett et al studies
- Heavily concentrated toward LMWH especially Enoxaparin and Dalteparin
- Fifty-nine studies comparing LMWH with placebo
  - Statistically significant reduction DVT (72%), clinical PE (75%), clinical VTE (71%) and non-significant (46%) reduction overall mortality
- Fifty-one studies comparing LMWH to UFH
  - No statistically significant differences in efficacy at all endpoints
  - If consider just double blind studies, there is no difference between LMWH and UFH

(Mismetti et al, BR J Surg, 2001)
Complications of Chemoprophylaxis for VTE

- Wound hematoma
- Major bleeding
- Thrombocytopenia (0.3%)
- Hypersensitivity reaction
- Inability to use spinal / epidural anesthesia
## Meta-Analysis of Bleeding Complications

<table>
<thead>
<tr>
<th></th>
<th>LMWH</th>
<th>No Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound hematoma</td>
<td>11.79%</td>
<td>6.26%</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>2.98%</td>
<td>1.33%</td>
</tr>
<tr>
<td>Transfusion requirement</td>
<td>9.83%</td>
<td>5.95%</td>
</tr>
</tbody>
</table>

Mismetti, Br J Surgery 2001
What are the Recommendations?

Low Risk
- Minor OR procedure
- Age < 40 yo
- No additional risk factors
  - Early Ambulation

Moderate Risk
- Minor surgery but age 40-60 yo or additional risk factors
- Major surgery with age < 40 yo and no risk factors
  - LMWH < 3400 units SQ Daily
  - LDUH 5000 units SQ BID
What are the Recommendations?

High Risk

- Minor OR procedure but > 60 yo or with additional risk
- Major surgery, age > 40 yo with additional risk
  - *LMWH > 3400 units SQ Daily*
  - *LDUH 5000 units SQ TID*

Very High Risk

- Multiple risk factors
  - *Combine chemoprophylaxis with GPS or IPS*
Data on Laproscopic Procedures

- Paucity of epidemiologic or prospective data
  - Modest thrombogenic activation, stimulation of fibrinolysis, venous pooling
  - Laparoscopic cholecystectomy
Recommendations for Laproscopic Procedures

- European Association for Endoscopic Surgery
- Society of American Gastrointestinal Surgery
- American College of CHEST Physicians
  - Patients without risk factors: early ambulation
  - Patients with risk factors: LDUH, LMWH, IPC or GLS
Responsibility

You cannot escape the responsibility of tomorrow by evading it today.

--Abraham Lincoln
QUESTIONS?