Challenges of VTE Prophylaxis in Orthopaedics

I have a potential conflict with this presentation due to receiving research funds from:
- Bayer Healthcare
- Medical Compression Systems
- Boehringer Ingelheim

I will be discussing drugs not yet approved by the FDA:
- Rivaroxaban
- Dabigatran

Deep Venous Thrombosis (DVT)
- Rate without prophylaxis:
  - 40 – 80%
- ~90% symptomatic pulmonary emboli originate from lower extremity DVT

Risk for DVT/VTE

<table>
<thead>
<tr>
<th>Surgery/Condition</th>
<th>Risk of all DVT if untreated</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Surgery</td>
<td>25%</td>
</tr>
<tr>
<td>THR</td>
<td>54%</td>
</tr>
<tr>
<td>TKR</td>
<td>64%</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>28%</td>
</tr>
<tr>
<td>Trauma</td>
<td>30-60%</td>
</tr>
<tr>
<td>Acute spinal cord injury</td>
<td>80%</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>55%</td>
</tr>
<tr>
<td>Medical condition</td>
<td>16%</td>
</tr>
<tr>
<td>Cancer</td>
<td>50%</td>
</tr>
<tr>
<td>Pediatrics</td>
<td>3-15%</td>
</tr>
</tbody>
</table>

Geerts et al; Chest 2001, 2004

Prevalence of DVT in Orthopaedic Surgery Without Prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>DVT</th>
<th>Proximal DVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>42 – 57%</td>
<td>18 – 36%</td>
</tr>
<tr>
<td>Knee</td>
<td>41 – 85%</td>
<td>5 – 22%</td>
</tr>
<tr>
<td>Hip Fx Surgery</td>
<td>46 – 60%</td>
<td>23 – 30%</td>
</tr>
</tbody>
</table>

Geerts, et al., Chest 2008

Prevalence of PE in Orthopaedic Surgery Without Prophylaxis

<table>
<thead>
<tr>
<th></th>
<th>Symptomatic</th>
<th>Fatal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>0.9 – 28%</td>
<td>0.1 – 2.0%</td>
</tr>
<tr>
<td>Knee</td>
<td>1.5 – 10%</td>
<td>0.1 – 1.7%</td>
</tr>
<tr>
<td>Hip Fx Surgery</td>
<td>3 – 11%</td>
<td>0.3 – 7.5%</td>
</tr>
</tbody>
</table>

Geerts, et al., Chest 2008
What are We Attempting to Prevent?

- Pulmonary Death
- Symptomatic and Asymptomatic PE
- DVT Proximal and Distal
- Chronic Pulmonary Hypertension
- Post-Thrombotic Syndrome

Ideal Prophylactic Methods

- Effective (clinically proven)
- Low risk of side effects
- Practical for use
  - Easy to administer and monitor
- Cost effective

No single modality meets ideal requirements or is appropriate for every patient condition

Orthopaedists have single and additive mechanical and pharmacological protocols, with different time frames of patient exposure

Traditional Prophylactic Therapy Modalities

- Pharmacological
- Mechanical

Pharmacological Agents

- Aspirin
- Warfarin
- LMWH
- Pentasaccharide
- Direct Thrombin Inhibitor

Coagulation Cascade

Black arrows denote "activation"
Red lines ending in vertical lines imply "inhibition"
Aspirin

- Acetylsalicylic acid
- Cyclooxygenase inactivator
- Arachidonic acid + cyclooxygenase = thromboxane A2; vasoconstriction, platelet aggregation

Aspirin Alone

- Number of trials report no significant benefit from ASA VTE prophylaxis
- Others found ASA inferior to other modalities

Aspirin Combinations

- Combined with
  - Early mobilization
  - Regional anesthesia
  - Foot pumps
  - Improved surgical techniques
- Reported in AAOS guidelines as acceptable for preventing fatal PE

Warfarin

- Dose
  - INR 2-3 (PT 1.3-1.5xControl)
- Action
  - Inhibits proper synthesis of Vitamin K-dependent coagulation factors (II, VII, IX, X)
- Onset of action
  - 4-5 days

Low Molecular Weight Heparins (LMWH)

- Enoxaparin (Lovenox®)
- Dalteparin (Fragmin®)
- Approval
  - FDA approved for TJA
  - FDA approved for THA

Warfarin

- Advantages
  - Given orally
  - Inexpensive
- Disadvantages
  - Continuous lab monitoring
  - Dose adjustment
  - Time to reach peak function
  - Affected by other drugs and food
What is LMWH?

- Fragments of unfractionated heparin produced by either chemical or enzymatic depolymerization
- Mean molecular weights from 4,000 to 6,500 daltons

Predictable Concentrations

No need to monitor coagulation times in patients with normal presurgical coagulation parameters

Fondaparinux

Synthetic Pentasaccharide

- Highly potent and indirect selective inhibitor of factor Xa
- First product of a new generation obtained by chemical synthesis
- Devoid of antithrombin activity
- Does not potentiate ADP or collagen induced platelet aggregation

Fondaparinux vs. Enoxaparin

Results

North American Studies

<table>
<thead>
<tr>
<th></th>
<th>TKA</th>
<th>THA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>N=361</td>
<td>N=788</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>N=363</td>
<td>N=797</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>TKA</th>
<th>THA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>12.5%*</td>
<td>6.2%#</td>
</tr>
</tbody>
</table>

*p<0.05


Symptomatic VTE after In-hospital prophylaxis for TJR

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Op No.</th>
<th>Prophylaxis</th>
<th>Duration</th>
<th>Symptomatic VTE, no. (%)</th>
<th>Fatal PE no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson, 1997</td>
<td>THR 249</td>
<td>Warfarin</td>
<td>9.8 d</td>
<td>3 (1.2)</td>
<td>0</td>
</tr>
<tr>
<td>Leclerc, 1998</td>
<td>THR 1142</td>
<td>LMWH</td>
<td>9.0 d</td>
<td>49 (4.3)</td>
<td>0</td>
</tr>
<tr>
<td>Colwell, 1999</td>
<td>THR 1516</td>
<td>LMWH</td>
<td>7.5 d</td>
<td>55 (3.6)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Holt, 2000</td>
<td>THR 1494</td>
<td>Warfarin</td>
<td>7.0 d</td>
<td>56 (3.7)</td>
<td>2 (0.1)</td>
</tr>
</tbody>
</table>

LMWH Prophylaxis After THA following hospital prophylaxis

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patients</th>
<th>Placebo</th>
<th>LMWH</th>
<th>Placebo</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergqvist, 1996</td>
<td>225</td>
<td>37</td>
<td>18</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Plane, 1996</td>
<td>173</td>
<td>19</td>
<td>7</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Dahl, 1997</td>
<td>218</td>
<td>32</td>
<td>19</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Spiro, 1997</td>
<td>435</td>
<td>23</td>
<td>8</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Lassen, 1998</td>
<td>215</td>
<td>12</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Hull, 2000</td>
<td>533</td>
<td>37</td>
<td>20</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Combined</td>
<td>1887</td>
<td>27</td>
<td>14</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>
Mechanical Devices
- Primary attraction is lack of bleeding potential
- Types of devices
  - Graduated compression stockings (GCS)
  - Intermittent pneumatic compression devices (IPC)
  - Venous foot pump (VFP)

Intermittent Pneumatic Compression Regimen
- Applied preoperatively and during surgical procedure
- Continued postoperatively until patient is ambulatory
  - No clinically significant side effects.
  - Bleeding no greater than placebo trials or 4%

Mechanical Thromboprophylaxis
- Methods do not even have to demonstrate they provide any protection against VTE to be approved and marketed
- Unsubstantiated assumption that all are effective and equivalent

Mechanical Compression Devices
- Nearly complication free
- Time worn = effectiveness
- Ensure do not actually impede ambulation

Mobile Compression Device (MCD)*
- Miniature
- Portable
- Battery Powered
- Can be worn out of bed and out of hospital

Synchronized Flow Technology (SFT)
- Triggers compression in synchronization with respiratory rate
- Provides natural phasic venous flow
- Patient compliance monitored by device
- Patient compliance clearly visible on device screen

*ActiveCare ® +SFT
**Hemodynamic Study**

*ActiveCare+SFT* vs *SCD Express*
Peak venous velocity with Calf sleeves (n=11)

- **Popliteal**
  - ActiveCare+SFT: 450
  - SCD Express: 260
  - 66% improvement

- **Common Femoral Vein**
  - ActiveCare+SFT: 520
  - SCD Express: 130
  - 72% improvement

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**Multi-Center Randomized Prospective Study**

- All primary total hip arthroplasties
- Exclusion
  - Self-reported or documented hx DVT or PE
  - Routine use of anticoagulant or antiplatelet drug
- Patients signed HSC approved consent

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**Large Prospective Randomized Multi-centered Clinical Trial**

- United States of America
- 9 sites in U.S.
- Hosp Special Surg, NY
- Siani Hosp, Baltimore, MD
- Cleveland Clinic, OH
- Indiana Research Found., IN
- Mayo Clinic, MN
- Ortho & Neuro Center of Cascades, OR
- Loma Linda Univ, CA
- Kerlan Jobe Ortho Clinic, CA
- SCORE at Scripps Clinic, CA

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**Methods**

- Prospective randomized study
- MCD group
  - Compression device ± aspirin 81 mg daily
- LMWH group
  - Enoxaparin 30 mg twice daily in hospital
  - Enoxaparin 40 mg once daily after discharge

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**Methods**

- Treatment for 10 days with MCD or LMWH
- Bilateral duplex ultrasound on day 10 – 12
- Compliance rate checked on MCD

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**Methods**

- 3 months postop – clinical exam
- Signs and symptoms
  - DVT
  - PE
**Results**

- No fatal PE or deaths
- Major bleeding
  - MCD 0%
  - LMWH 5.6%*

\*p = .0007

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**MCD Compliance**

Compliance = 86%
Mean days worn = 11 (2 – 14)
Mean hours worn = 219 (4 – 850)
Average daily ~ 20 hrs/day

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**Strength of any recommendation depends on two factors**

1. Trade-off between benefits and risks
2. Strength of methodology leading to estimates of treatment effect

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**Evaluation of Safety vs. Efficacy**

- **Bleeding**
- **DVT/PE**

All MD’s – Orthopaedists

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**Evaluation of Safety vs. Efficacy**

- **Bleeding**
- **DVT/PE**

Orthopaedists
Definition of Practice Guidelines

Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

Guidelines for Guidelines

- Validity
- Reliability/Reproducibility
- Clinical Applicability
- Clinical Flexibility
- Clarity
- Multidisciplinary Process
- Scheduled Review
- Documentation

National Standards for Prevention and Care of VTE: Proposed VTE Performance Measures

VTE Risk Assessment/Prophylaxis

1. Documentation of VTE risk assessment and prophylaxis within 24 hours of hospital admission if prophylaxis indicated.
2. Documentation of VTE risk assessment and prophylaxis within 24 hours of ICU admission if prophylaxis indicated.

(Nov 2009)

www.JointCommission.org/PerformanceMeasurement

NQF / JCAHO National Standards for the Prevention and Care of VTE

Policy Statement:

“Every healthcare organization shall have a written policy appropriate for its scope, that is evidence-based and drives continuous quality improvement related to venous thromboembolism (VTE) risk assessment, prophylaxis, diagnosis and treatment.”

VTE Measures

For surgical patients:

1. Has recommended VTE prophylaxis* been ordered;
2. Has recommended prophylaxis* actually been commenced within 24 hours after surgery.

http://www.medqic.org/ * Grade 1 ACCP recommendations

Goal: To reduce preventable surgical morbidity and mortality 25% by 2010.

http://www.medqic.org/
**Rivaroxaban:**
An Oral Direct Factor Xa Inhibitor

- Direct, competitive Factor Xa inhibitor
- Rapid onset within 2-4 hours
- High bioavailability: >80%
- No dosage adjustment for gender, age, extreme body weight
- Half-life: 7-11 hours
- Approved in Canada, Europe


**Dabigatran Etexilate:**
An Oral Direct Thrombin Inhibitor

- Specific, competitive, reversible thrombin inhibitor
- Rapid onset within 2 hours
- Low bioavailability: 3.5-5%
- Half life: 12-17 hours
- Approved in Canada, Europe


**New Oral Anticoagulants:**

**Strengths**
- Oral administration
- No laboratory monitoring
- Few drug interactions
- Rapid onset
- Won’t cause HIT
- Potential major impact on clinical: more patients get prophylaxis practice

**Limitations**
- Limited indications
- No hip fracture data
- No specific reversibility agents
- New; short track record

**Research → Practice**

- Evaluation
  - Changes in outcomes
  - Economic
- Education
  - All caregivers
  - Ongoing
- Practice guidelines & standard orders
- Periodic check of outcomes - QA