Management of the Patient with VTE: A Case-Based Approach

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Disclosures

• Ms. Heffline: No relationships to disclose.
• Dr. Rudd: No relationships to disclose.
Objectives

• Identify prevalence rates of venous thromboembolism (VTE), including rates for morbidity and mortality.
• Discuss professional guidelines that stress methods for assessing risk in patients with VTE and provide algorithms for patient management.
• Review clinical trial data for approved therapies for the effective and safe management of patients with, and at risk for the recurrence of VTE.
• Describe methods for ensuring effective communications with patients and caregivers as a means of improving adherence and self-care in patients with VTE.
Definition of VTE

- Distal DVT
- Proximal DVT
- Asymptomatic PE
- Symptomatic PE
- Fatal PE
- Post-phlebitic syndrome
Incidence of VTE

- Incidence
  - 600,000 venous thromboembolic events annually
- At least 50,000 perhaps 200,000 will die PE
- Morbidity – 90% originate in the legs
- Mortality -estimated that one in 100 patients admitted to a hospital dies because of PE

- www.dvt.org accessed February 2015
Case Study

• 43 y/o female Ms. C
  – Family history of VTE (mother with PE after open cholecystectomy)
  – Pending colon resection for colon mass
  – Worked as cosmetologist for 23 years
  – 2 children delivered by C-section, previous TAH
  – Osteoarthritis of both knees, no other co-morbidities
Prevention

• “DVT prophylaxis will reduce the incidence of DVT during the postoperative period by two-thirds and will prevent death from pulmonary embolism in 1 patient out of every 200 major operations”

• “10 to 25 percent of all deaths in hospital involve emboli in the lung, many of which are extensive enough to be considered as having caused the death of the patient”

• [www.dvt.org](http://www.dvt.org), accessed February 2015
Fatal PE
Prevention – Assess Risk Factors

• Accidental Trauma
• Surgical Patients
  – orthopedic surgery (hips and knees)
  – major surgery lasting longer than 30 minutes
Major Surgeries

- Hysterectomies: 617,000
- Cesarean section: 1.3 million
- Reduction of fracture: 671,000
- Insertion of coronary artery stent: 454,000
- Coronary artery bypass graft: 395,000
- Total knee replacement: 719,000
- Total hip replacement: 332,000
- TOTAL: 27 - 51 million

http://www.cdc.gov/nchs/fastats/inpatient-surgery.htm
Prevention – Assess Risk Factors

- Age (risk rises steadily from age 40)
- Obesity
- Malignancy
- History of DVT or PE
- Immobilization (bed rest, paralysis of legs, plaster casts, prolonged travel)
- Pregnancy and puerperium
- Oral contraceptive/hormone use
- Extensive dissection at surgery
Clinical Conditions Predisposing

• Dehydration
• Varicose veins
• Cardiac problems (e.g. cardiac failure and myocardial infarction)
• Stroke
• Nephrotic syndrome
• Thrombocytosis
• Primary proliferative polycythemia
• Systemic lupus erythematosus
• Infection
• Inherited thrombotic disorders
  – Protein C, S or AT III deficiency & Factor V Leiden or Prothrombin Gene Mutation
Prevention

• Hydration

• Early ambulation

• Compression
  – Anti-embolic stockings
  – Sequential compression device/foot pump

• Pharmacological Agents
  – Heparin, LMWH, warfarin, TSOACs
Management of VTE

• Bedrest or not?
• Compression stockings or not?
• Pain relief – NSAIDS or not?
• Anticoagulation
  – Drugs of choice
  – Duration of therapy
Non-pharmacologic Treatment

• Early Ambulation
  – Anderson et al. - no significant difference between ambulation and bed rest for risk of developing a PE or development and progression of a new DVT in any of the studies
  – Partsch et al - Immediate mobilisation with compression in acute stage of DVT reduces the incidence and the severity of PTS

• Elevation of affected limb (Core Curriculum for Vascular Nursing, 2014)
Non-Pharmacologic Treatment

• Compression stockings
  – GCS effective in diminishing risk of DVT in hospitalized patients with strong evidence use in general and orthopaedic
  – evidence for effectiveness in medical patients limited to one trial

• Pain Management
  – Chest (2012) guidelines suggest avoiding NSAID’s
  – May be best option for early acute pain due to inflammation
  – Do not use long term
Review of Guidelines – VTE Prevention

• **Non-Orthopedic Surgical Patients**
  – Very Low Risk (< 0.5%): No pharmacologic or Mechanical
  – Low Risk (~1.5%): Mechanical Prophylaxis (IPC)
  – Moderate Risk (~3%): LMWH or “LDUFH” or IPC
  – High Risk (≥ 6\(^{\wedge}\)): (LMWH or LDUFH) + Mechanical

  – Rogers &/or Caprini score helpful to risk assess
  – **Duration:** Clinical Judgment except
    • Abdominal/Pelvic Cancer Surgery = 4 weeks
Review of Guidelines – VTE Prevention

• **Non-Surgical (Medical) Patients**
  – “Acutely Ill at increased risk of thrombosis”
    • LMWH or “LDUFH” BID/TID
    • Only During Hospitalization
  – Low Risk: Early Ambulation
  – Increased Risk of VTE and Bleeding: Mechanical
  – Critically Ill: LMWH or “LDUFH” BID/TID
  – Outpatients with Cancer: No routine prophylaxis

– Significantly heterogeneity in risk assessment for VTE
  • Consider Padua Prediction Score or other validated tool
CMS/TJC Core Measures in VTE Prevention

- **Hospital Inpatient Quality Measures**
  - Establishes evaluative standards for VTE Prophylaxis
    - VTE prophylaxis within 24 hours
    - All patients must be risk assessed
    - Delineates “acceptable” options for PHARMACOLOGIC prophylaxis
    - Sets standards for MECHANICAL prophylaxis use
  - These standards vary by “TYPE” of patient
    - ie. Orthopedic Surgery, Surgery and Medically Ill
  - Impacts “Value Based Purchasing” & Reimbursement
Some of the places we can go wrong...

• Initiation
  – Wrong Dose
  – Drug-drug & Drug-disease Interactions
  – “Suboptimal” Drug
    • Indication, Patient selection, etc.

• Maintenance
  – No monitoring (yes, that’s right...)
  – Drug-drug & Drug-disease Interactions

• Transitions of Care
  – Are we stopping/starting correctly?
Case Study

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• Question 1: Is VTE prophylaxis indicated?
  1. Yes
  2. No
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• Question 2: Which VTE prophylaxis strategy is best?
  1. Heparin 5000 units subq every 8 hours
  2. Enoxaparin 40mg subq every 24 hours
  3. Apixaban 2.5mg po every 24 hours
  4. Compression Stockings with Early Ambulation
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**Therapy IS indicated:**
LMWH 40mg subq q24h > Heparin 5000 units subq q8h

**Baseline Labs:** Creatinine, CBC with Platelets
Choosing An Agent for VTE Prevention

• **Caveats:**
  – LMWH preferred for Cancer Patients
  – Orthopedics:
    • LMWH special dosing, TSOACs, warfarin, aspirin (?), TSOACs
  – Prophylaxis in Medically Ill
    • Think LMWH (40mg subq q24h), Heparin, warfarin
  – Obese patients may need higher doses
    • Heparin 5000 units subq q8h, Enoxaparin 40mg subq q12h
How About VTE treatment?
Review of Guidelines – VTE Treatment

• **Therapy Starts Immediately**
  
  – Goal 1: “Therapeutic” in 24 hours
  – Outpatient treatment is preferred
  – Stockings to aid in Post-Phlebitic Syndrome
  – Minimum duration: 3 months, then reassess
    
    • Patients may need 6-12 months
    • Lifelong therapy for (> 1 VTE) or (VTE + active Cancer)

  – Therapeutic Options:
    
    • LMWH for Cancer patients
    • Warfarin + Parenteral (LMWH/UFH) x 5 days
    • TSOACs (with parenteral “bridge”)

Chest 2012;141;e419S-e494S. DOI 10.1378/chest.11-2297
Pharmacologic Treatment

• Tried and True plus **Novel** Oral Anticoagulants (NOACs)
• Inhibit free & clot bound Xa/IIa = decreased clot propagation & growth
Pharmacologic Treatment of VTE

With the approval of TSOACs – this increases options and “potentially” eliminates need to “bridge” with parenteral agent...
# Meta-Analysis of TSOACs vs. Warfarin for VTE Treatment

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<tr>
<th>Outcome</th>
<th>TOAC %</th>
<th>VKA %</th>
<th>Absolute Risk Difference</th>
<th>NNT with TSOAC</th>
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<td>Recurrent VTE</td>
<td>2 (1.6-2.4%)</td>
<td>2.2 (1.8-3.0%)</td>
<td>-0.24 (-0.6 to 0.11)</td>
<td>417</td>
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<td>Fatal PE</td>
<td>0.07 (0.04-0.1%)</td>
<td>0.07 (0.0-0.24%)</td>
<td>0.01 (-0.06 to 0.08)</td>
<td>10,000</td>
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<td>Overall Mortality</td>
<td>2.4 (1.5-3.2%)</td>
<td>2.4 (1.7-3.1%)</td>
<td>-0.10 (-0.47 to 0.28)</td>
<td>1,000</td>
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<td>Major Bleeding</td>
<td>1.1 (0.6-1.6%)</td>
<td>1.7 (1.2-2.2%)</td>
<td>-0.67 (-1.13 to -0.21)</td>
<td>149</td>
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<td>Clinically relevant non-major bleeding</td>
<td>6.6 (3.9-9.5%)</td>
<td>8.4 (6.9-9.8%)</td>
<td>-0.14 (-0.31 to 0.03)</td>
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<td>Non-fatal ICH</td>
<td>0.09 (0-0.12%)</td>
<td>0.25 (0-0.42%)</td>
<td>-0.14 (-0.31 to 0.03)</td>
<td>714</td>
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<td>Major GI bleed</td>
<td>0.35 (0.17-0.71%)</td>
<td>0.53 (0.23-0.67%)</td>
<td>-0.16 (-0.42 to 0.11)</td>
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<td><strong>CYP Metabolism</strong></td>
<td>75% via 3A4</td>
<td>~20%</td>
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## TSOACs - Indications & Dosing

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<th>Warfarin</th>
<th>Apixaban (Eliquis)</th>
<th>Dabigatran (Pradaxa)</th>
<th>Rivaroxaban (Xarelto)</th>
<th>Edoxaban (Savaysa)</th>
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<tr>
<td>Stroke Prevention (Non-Valvular AF)</td>
<td>Individualized Dosing</td>
<td>5mg po BID (REDUCE for age &gt; 80y, Scr &gt; 1.5mg/dl or &lt; 60kg)</td>
<td>150mg po BID</td>
<td>20mg po Daily with a Meal</td>
<td>60mg po daily ONLY if CrCl &lt; 95ml/min</td>
</tr>
<tr>
<td>Stroke Prevention (Valvular AF and/or Valvular Heart Disease/Replacement)</td>
<td>Not FDA Approved</td>
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<td>Not FDA Approved</td>
<td></td>
</tr>
<tr>
<td>VTE Prevention (s/p THR, TKR)</td>
<td>2.5 mg ORALLY twice daily beginning 12 to 24 hours after surgery</td>
<td>Not FDA Approved</td>
<td>10mg po daily</td>
<td>Not FDA Approved</td>
<td></td>
</tr>
<tr>
<td>VTE Treatment</td>
<td>10mg po BID x 7 days, then 5mg po BID</td>
<td>Parenteral tx x 5-10 days, then 150mg po BID</td>
<td>15mg po BID x 21 days, then 20mg po daily</td>
<td>Parenteral tx x 5-10 days, then 60mg po daily</td>
<td></td>
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</tbody>
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Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per manufacturer), Ridgefield, CT, 2014.
TSOACs: Special Considerations

- Age
- Concurrent ASA Use
- P’kinetics of “Special Populations”
- Drug-Drug Interactions
- Time-in-Therapeutic Range
TSOACs: Special Considerations

- **Age**
  - Apixaban
    - DVT & PE = 55.8 +/- 15.6
  - Dabigatran
    - DVT & PE = 55 +/- 15.8
  - Rivaroxaban
    - DVT & PE = 57.9 +/- 7.3

- Steady-State Serum Concentrations are variable & strongly age-dependant!
- This dramatically impacts ADE rate!
  - Rivaroxaban: Higher rates of major bleeding if $\geq 75$ years (GI bleeding 2.81% vs. 1.66%, $p = 0.0002$, NNH = 87)
  - Apixaban: Major bleeding 3x & ICH 2.5x higher in patients $\geq 75$ ($p <0.0001$)
- “Tailoring...dose might improve benefit-risk”
Biostatistics: 101, continued

Could we be over/under dosing 36% of our patients???
TSOACs: Special Considerations

• Concurrent Aspirin Use
  – Apixaban
    • APPRAISE-2 trial: Terminated prematurely
    • Increased rates of major bleeding (HR 2.36, 95% CI 2.06-2.70)
    • Increased rates of ICH (HR 4.06, 95% CI 1.15-14.38)
  – Rivaroxaban
    • Aspirin use > 100mg/day excluded

– All Three Agents warn of risks of concurrent use.
TSOACs: Special Considerations

- **Pharmacokinetics in Special Populations**
  - **Obese**
    - Trials cap at weights between 150-170kg
    - Apixaban reports 20% increase in AUC in patients < 50kg
    - Apixaban reports a 23% decrease in AUC in patients > 120 kg

- **Renal Dysfunction**
  - No clinical trials have been conducted in patients with ClCr < 30ml/min
  - Dose Adjustments are the results of Pharmacokinetic Modeling
## FDA Labeled Dose Adjustments

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<tr>
<td>Stroke Prevention</td>
<td>Based upon Patient Response</td>
<td>Dose Adjust (↓50% ) if 2 criteria are met: age &gt;= 80 years weight &lt;= 60kg Scr &gt;= 1.5mg/dL ESRD on HD: no adjustment</td>
<td>Dose Adjust (↓50% ) if: ClCr 15-30ml/min. Avoid if &lt; 15ml/min.</td>
<td>Dose Adjust(↓25% ) if: ClCr 15-50ml/min. Avoid if &lt; 15ml/min.</td>
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<td>(Non-Valvular AF)</td>
<td>Target INR = 2.0-3.0</td>
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TSOACs: Special Considerations

- **Drug-Drug Interactions**
  - Notably Less than Warfarin, but still present
    - P-glycoprotein
    - Cytochrome P450 interactions
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<th>Drug</th>
<th>MOA</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
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<tr>
<td>Rifampin, Carbamazepine,</td>
<td>Potent P-glycoprotein Inducer &amp;</td>
<td>Avoid</td>
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</tr>
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<td>Phenytoin</td>
<td>Strong CYP3A4 Inducer</td>
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</tr>
<tr>
<td>PPIs</td>
<td>Decreased GI Acidity (raises pH)</td>
<td>Not Addressed (No issue)</td>
<td>Not Addressed (AUC decreases by 30%)</td>
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<tr>
<td>Amiodarone, Verapamil</td>
<td>P-glycoprotein Inhibitor &amp; Moderate CYP3A4 Inhibitor</td>
<td>Not Addressed</td>
<td>AF: “Do not extrapolate from other agents” - No change in dose.</td>
<td>Avoid if CI Cr 15-80 mL/min</td>
</tr>
<tr>
<td>Amiodarone DOUBLEs</td>
<td>Serum concentrations of dabigatran</td>
<td></td>
<td>AUC increases: Amiodarone= 60% Verapamil 200%</td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>P-glycoprotein Inhibitor &amp; Strong CYP3A4 Inhibitor</td>
<td>Reduce dose by 50% to 2.5mg po BID**</td>
<td>AF: For CI Cr 30-50ml/min: Dose reduction suggested.</td>
<td>Avoid</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>P-glycoprotein Inhibitor &amp; Moderate CYP3A4 Inhibitor</td>
<td>Not Addressed</td>
<td>For CI Cr &lt; 30ml/min: Avoid</td>
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Product Information: PRADAXA(R) oral capsules, dabigatran etexilate mesylate oral capsules. Boehringer Ingelheim Pharmaceuticals, Inc. (per manufacturer), Ridgefield, CT, 2014.


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TSOACs: Special Considerations

• **Time In Therapeutic Range**
  – Usual Medical Care Literature Standard: 50-60%
  – VTE treatment Trials: 55-60%
  – Anticoagulation Management Services: > 70%

  – Impact of Improved TTR unknown in VTE
    • In A. Fib trials, warfarin becomes safer/more effective
So How does all apply back in Clinical Practice?
Case Study

- Colon resection
  - Mass adenocarcinoma, margins clear, no metastasis, surgery prolonged due to extensive adhesions
- Slow to ambulate due to stiffness in knees
- Prolonged NPO period after surgery due to ileus
- Develops R calf pain and tenderness on POD#3 – U/S confirms DVT R leg from the femoral vein mid-thigh through the popliteal with complete occlusion of the vessel
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• Question 3: Is Thrombolytic therapy indicated?
  1. Yes
  2. No
Thrombolysis for DVT

• Used selectively to dissolve thrombus
  – Extensive Proximal DVT (ilio-femoral)
  – Large PE
  – Phlegmasia cerulean dolens

• Candidate selection
  – Recent surgery/trauma
  – Age
  – Active/Recent bleeding issues
  – Severe hypertension
Interventional Management

• DVT Thrombectomy
• Vena Cava filter placement
• Saphenofemoral junction ligation
Education for Patients/Families

- **Treatment**
  - Activity
  - How to use compression stockings
  - Elevation as necessary
- **Post procedure care following intervention**
- **Guidelines for follow up vascular studies**
- **Long-term complications**
  - Postphlebitic syndrome
  - Ulcerations
Education for Patients/Families

• Implications of pharmacologic therapy
  – Continuous use of medication
  – Drug/food interactions

• Potential for recurrence
Websites for Further Study

- www.svn.net
- www.dvt.org
- www.veinforum.org
- www.intersocietal.org
References


References