Challenges in Anticoagulation and Thromboembolism

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No Conflicts of Interest

Objectives

1. Discuss data on prevention and treatment of upper extremity venous thrombosis
2. Use individualized risk assessment of thrombo-embolic events and bleeding to design a peri-operative anti-thrombotic bridging regimen
3. Identify uncommon side effects of anti-thrombotic medications

Upper Extremity DVT

- 10% of all DVTs occur in the upper extremities
- Symptomatic upper ex DVT will complicate 12% of CVCs
  - Asymptomatic clot in up to 2/3 pts with central lines

Upper Extremity DVT
Risk Factors

Primary
- 20%
  - Strenuous arm exercise
  - Effort thrombosis
  - Anatomy
- Thoracic outlet syndrome

Secondary
- 80%
  - Cancer
  - Surgery/trauma to arm
  - Cast immobilization
  - Central Line
  - Pacemaker
  - Thrombophilia
  - OCPs

Does prophylaxis with warfarin work?

- New research demonstrates fixed dose warfarin to prevent CVC related DVTs in cancer patients is ineffective
- No significant reduction in DVT rates
  - 6% in no-warfarin
  - 6% in warfarin group
  - Subgroup analysis suggested possible benefit in adjusted dose warfarin compared to fixed dose
- No improvement in mortality

Randomized Placebo-Controlled Study of Low-Dose Warfarin for the Prevention of Central Venous Catheter Associated Thrombosis in Patients With Cancer: Results of the WARFARIN for the Prevention of CVC Thrombosis (WARP) Study.
Journal of Clinical Oncology 2005;23:4063-4069

Upper extremity DVTs are not benign

- Risks of upper extremity DVT
  - Post-phlebitic syndrome
    - 20-27%
  - Recurrence
    - 1 in 10
  - PE in up to 36%
    - Line related has higher risk
  - Death
    - 10-50% mortality rate
    - Largely due to underlying disease

Clinical outcomes of patients with an upper extremity deep vein thrombosis: results from the RIETE registry.
Chest 2008;133(1):143-148
Treatment

- Treatment improves outcomes
  - 12% PE rate with physical measures only
  - 7% PE rate with anticoagulation
  - 1% PE rate with thrombolysis

- Recommendations for non-cancer associated DVT are to treat with UFH/LMWH or fondaparinux followed by oral anticoagulation for at least 3 months

- For patients with catheter associated DVT the CHEST guidelines do NOT recommend removal so long as the line is functioning and needed

Treatment of VTE in Cancer Patients

- LMWH is the preferred agent for initial and long term treatment of VTE in cancer patients

- CLOT trial:
  - 17% recurrent VTE rate with oral anticoagulation
  - 9% recurrent VTE rate in LMWH group
  - 52% RRR (p=0.002)

Bridging Anticoagulation
Challenge

- Many pts needing procedures are on chronic anticoagulation
  - Quarter of a million annually

- The hospitalist is frequently asked to determine how to:
  - Minimize risk of bleeding with the procedure
  - Prevent peri-op thromboembolic events

Fundamental Concept

**Balance of Risks**

- Chance of thrombosis
- Severity of potential event
  - Periop VTE= 4-9% fatal
  - Mechanical heart valve thrombosis = 15% mortality
  - Periop embolic stroke = 70% disability or death

- Chance of bleeding
  - 1 in 10 major surgeries will bleed if INR>2
  - Once bleeding occurs, longer delays to restart anticoagulation

- Ability to achieve hemostasis
How to Reverse Warfarin

Three options:
- Hold Warfarin 5 days – INR<1.5 in 93% of pts
- Vitamin K – low dose (2.5-5mg)
- Fresh Frozen Plasma
  - Plus low dose Vitamin K

How to Bridge

Pre-Op

No Bridge

Full therapeutic heparin
  - Requires hospitalization
  - Stop 4 hrs before procedure

Full therapeutic LMWH
  - Allows home therapy
    - Last dose >24 hours before procedure
    - Reduce final dose by 50% if using therapeutic LMWH

Pre-Op Bridging Anticoagulation

<table>
<thead>
<tr>
<th>Embolic Risk</th>
<th>Bridge</th>
<th>Bridge</th>
<th>No bridge?</th>
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<tbody>
<tr>
<td>High</td>
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</table>
High Risk

**Thromboembolism >10%**
- Mechanical mitral valves
- Older aortic valve devices
- Afib with CVA in last 3 months or CHADS2 of 5-6
- VTE in last 3 months or severe thrombophilia
  - Delay elective surgery if VTE in last month

Moderate Risk

**Thromboembolism 4-10%**
- Modern mechanical AVR + other risk factors
- Afib with CHADS2 of 3-4
- VTE 3-12 months ago, recurrent VTE, or common thrombophilias
- Active cancer

Low Risk

**Thromboembolism <4%**
- Modern mechanical AVR without other risk factors
- Afib with CHADS2 of 0-2
- Prior VTE more than a year ago
How to Bridge Post-Op
- Resume oral anticoagulation 12-24 hrs post-op
  - Expect 2 days to restore INR > 1.5
  - 5 days to full therapeutic
- Add prophylactic dose heparin/LMWH
- Start full therapeutic heparin/LMWH
  - New guidelines allow delay of full bridging for patients at high surgical bleeding risk

Bleeding Risk
- High Risk
  - Cardiac surgery
  - Vascular surgery
  - Neurosurgery
  - Hip/knee replacement
  - Major urologic surgery
- Use lower dose
- Delay initiation of bridging by 2-3 days
Case 1
Mechanical Heart Valve
A 72 y/o woman with a modern mitral bi-leaf mechanical heart valve is to have ankle surgery.
How would you handle the perioperative anticoagulation?
- High risk for embolism
- Intermediate risk for bleeding
- Rec hold warfarin 5 days with full dose LMWH preop
- Full dose bridging postop
  - Full dose LMWH or therapeutic UFH
  - Start 24 hrs post-op
- Resume warfarin POD1

Case 2
Atrial Fibrillation
45 y/o with Afib and HTN scheduled for nephrectomy
- Low risk for embol event
  - CHADS2=1 point so 1.5% annual risk
  - Predicts 0.004% daily risk of embolic event
  - Actual rate may be 10X higher (surgery is prothrombotic)
  - Taking this into account- 8 day risk is only 0.3%
- High risk for Bleeding
- Rec hold warfarin 5 days pre-op without bridge
- No bridging post-op or using prophylactic dose LMWH
- Restart warfarin POD1 (if good hemostasis)
Case 3
Prior VTE

- 67 year old man with history of PE 4 months ago is scheduled for lap choly for gallstone pancreatitis
- Intermediate risk for venous embolic event
- Intermediate risk for bleeding
- Rec Hold Warfarin 5 days pre-op—Full dose LMWH bridge
- Starting low dose LMWH day after surgery
- If no bleeding increase to therapeutic LMWH in 2-3 days
- Restart warfarin POD1

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<th>Embolic Risk</th>
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<th>Low</th>
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| Full dose anticoagulation delayed 2-3 days | Low dose LMWH vs full dose delayed 2-3 days
Low dose LMWH delayed 2-3 days | Full dose anticoagulation may delay until day 2
No bridge |

Future Studies to Watch For:
- BRIDGE
- PERIOP 2

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Full dose anticoagulation may delay until day 2
Full dose anticoagulation starting 24 hours post procedure

Low dose LMWH or no bridge
High |
| Medium |
| Low |

Low dose LMWH or no bridge
Low dose LMWH or no bridge

(Consider low dose initially)
Side Effects of Antithrombotic Therapy

You are seeing a 56 y/o male following total knee arthroplasty. Enoxaparin 40 mg SQ QD started on POD #1.

- Pre-operative platelet count was 200,000
- Post-operative day #1 platelets were 160,000
- Post-operative day #2 platelets are 110,000
- Should you suspect heparin induced thrombocytopenia?

Heparin Induced Thrombocytopenia

- Antibodies bind platelet factor 4 and heparin
- Induces pro-thrombotic state
  - Thrombocytopenia
  - Thrombosis
- Thrombosis develops in 30-50% of cases
**HIT**

- Platelets drop >50% or less than 150,000
- Heparin exposure usually precedes plt drop by 5-10 days
- Diagnosis difficult in situations where thrombocytopenia is caused by other mechanisms
  - Trauma
  - Post-operative
    - Particularly CABG

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### “4 T” Score

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<td>Timing of fall</td>
<td>Early onset day 5-10</td>
<td>Onset &gt; day 10 or unclear time</td>
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<td><strong>Thrombosis</strong></td>
<td>New thrombus</td>
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<td>No other cause evident</td>
<td>Possible alternative cause</td>
<td>Diffuse other cause</td>
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6-8 = High Risk  
4-5 = Intermediate Risk  
<3 = Low Risk
Pearls

- Low risk score (<3) has low probability of HIT and testing not needed
- Intermediate and High risk scores (>3) merit testing

Pre-operative platelet count was 200,000
Post-operative day #1 platelets were 160,000
Post-operative day #2 platelets are 110,000

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Score of 1 = low risk
No Testing Needed

But why is the potassium elevated?

- Unfractionated Heparin inhibits aldosterone production
  - Acts only at glomerulosa so other steroids are spared
    - Aldosterone suppression impairs K+ excretion by kidneys
    - End result can be hyperkalemia

Heparin-Induced Hyperkalemia. Diabetes Research and Clinical Practice 2008;80:e7-8
How often does this happen

- Heparin, even in prophylactic doses, leads to hyperkalemia in about 7% of patients in the first 2 wks

- LMWH also causes hyperkalemia
  - K+ >5.0 in 9% of patients on LMWH by day#3

Switch to SCDs

- Not as effective DVT prevention as chemoprophylaxis
- SCDs used far more in US (22%) compared to other countries (0.2%)
- Unlike the surgical literature, SCDs not as proven in medical pts

Substitution of LMWH for UFH

- Both cause hyperkalemia via aldosterone inhibition

Fondaparinux

- Synthetic pentasacharide binds to antithrombin
- Indirectly inhibits factor X
- Will not cause hyperkalemia

Take Home Points

- Upper Extremity DVT should be treated for ≥ Months
  - Catheter removal not required if still functioning

- LMWH preferred over warfarin for VTE in cancer patients

- Weigh individual risk/benefit of bridging anticoagulation peri-operatively
  - Low risk patients do not require bridging

- "4 Ts" can identify patients in whom HIT should be suspected

- Hyperkalemia is a rare but under-recognized side effect of heparin and LMWH