Challenges in Anticoagulation Bridging and Emerging Therapies

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Disclosures and Relationships
Dr. Cumbler has no conflicts of interest

Objectives
1. Use individualized risk assessment of thrombo-embolic events and bleeding to design a peri-operative anti-thrombotic bridging regimen
2. Evaluate the role of newly approved antithrombotic therapy in preventing embolic events
3. Identify uncommon side effects of anti-thrombotic medications
Bridging Anticoagulation

Challenge

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

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Pre-Op Bridging Anticoagulation

Embolic Risk

- High

- Bridge

- Medium

- Bridge

- Low

- No bridge?
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

Bleeding Risk

High Risk
- Cardiac surgery
- Vascular surgery
- Neurosurgery
- Major urologic surgery
- Hip/knee replacement
- Use lower dose
- Delay initiation of bridging by 2-3 days

Embolic Risk

<table>
<thead>
<tr>
<th>High</th>
<th>Medium</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full dose anticoagulation</td>
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</tr>
<tr>
<td>Low dose LMWH an option over full dose</td>
<td>Full dose preferred over low dose LMWH</td>
<td></td>
</tr>
<tr>
<td>no bridge or low dose LMWH</td>
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Bleeding Risk
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 embolic 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 use 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

Future Studies to Watch For:
- BRIDGE
- PERIOP 2
Case #4

- A 76 year old man with HTN and DM II presents to the hospital with fatigue, SOB, and palpitations
  - Found to be in atrial fibrillation with rate of 140
  - Rate control achieved with diltiazem

- He is worried about his risk of stroke
- Do you start warfarin….or something else

Emerging Therapy for Anticoagulation

Dabigatran

Connolly SJ et al.
Dabigatran versus Warfarin in Patients with Atrial Fibrillation.
NEJM 2009;361:1139-51

[Image: A gravestone with the word "WARFARIN" and "1948-2010" engraved on it. The text below the gravestone reads "REST IN PEACE."
RE-LY TRIAL

- RCT comparing warfarin to two doses of Dabigatran (110mg and 150mg p.o. BID)
- Non-inferiority trial
- 18,113 patients with atrial fibrillation and risk of stroke
  - 967 centers in 44 countries
- Median follow-up 2 years
- Primary Outcome: Stroke or Systemic Embolism

Findings

- **Stroke/Embolism**
  - 1.7%/yr with warfarin
  - 1.1%/yr with 150mg bid dabigatran
  - **RR = 0.66** (CI 0.53-0.82)
  - P<0.001 for superiority of 150mg bid dose

- **Major Bleeding**
  - 3.4%/yr with warfarin
  - 3.1%/yr with 150mg bid dabigatran
  - No significant difference in bleeding with 150mg bid dose

Non-inferiority trial. FDA does not allow a claim of superiority over warfarin.

Cumulative Hazard Rates for the Primary Outcome of Stroke or Systemic Embolism, According to Treatment Group.

Context
- 2.3 million Americans have A-fib
  - And rising
- Annual risk of stroke with A-fib 4.5%
  - $57.9 billion dollars for this stroke care
- Warfarin reduces stroke risk by 2/3rd
  BUT
- Warfarin is a finicky, dangerous, and difficult medicine to manage

Advantages of Oral Direct Thrombin Inhibitors
- More predictable anticoagulation effect
  - Less interaction with food
  - Less interaction with other drugs
- No monthly monitoring
- RE-LY suggests safe and more effective
  - FDA approved as of October 2010
  - 150mg p.o. bid dosing now available

DOWNSIDE

$230-$270 dollars a month for dabigatran 150mg bid
How Do The Costs Compare?

<table>
<thead>
<tr>
<th>Warfarin</th>
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<tbody>
<tr>
<td>- Direct drug costs</td>
</tr>
<tr>
<td>- INR testing</td>
</tr>
<tr>
<td>- Anticoagulation monitoring</td>
</tr>
<tr>
<td>- Bleeding events</td>
</tr>
<tr>
<td>- Stroke care for events</td>
</tr>
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<td>occurring on treatment</td>
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<table>
<thead>
<tr>
<th>Dabigatran</th>
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<tr>
<td>- Higher direct drug costs</td>
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<tr>
<td>- No monitoring costs</td>
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<tr>
<td>- Same bleeding rate</td>
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<tr>
<td>- Less stroke events</td>
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Monte Carlo Simulation
Patients over 65 with at least 1 CHADS2 points

Total Costs
- Warfarin = $143,193
- Dabigatran 150mg bid = $168,398
- Study assumed daily dabigatran cost of $13

Incremental cost per QALY
- $45,372 for high dose dabigatran

TAKE HOME - Dabigatran more expensive than warfarin
May be more effective thus at current pricing is within
currently accepted cost effectiveness ratios

Dabigatran
Practical Pearls for Use
- Therapeutic within 30-120 min with half life of 12-17 hrs
  - Hold at least 1-2 days before invasive procedures
  - If pre-op bridging needed start LMWH/Heparin 12 hrs after last dose
  - Hold at least 3-5 days if impaired renal function
  - If pre-op bridging needed start LMWH/Heparin 24 hrs after last dose
  - No real need for bridging post-op
- Dose adjust to 75mg p.o. BID for Cr Cl 15-30
  - Efficacy/safety at this dose not well studied
- Dyspepsia can be a limiting side effect
- Caution with use in patients with risk for MI
CASE #4 Continued

- The pt is discharged on dabigatran

- 3 months later he returns with dense left hemiplegia developing 1 hour prior to arrival
  - Head CT negative
  - INR 1.4

- Is he eligible for IV thrombolysis?

What if....

- A patient on dabigatran has a stroke
  - INR is not a reliable measure of degree of anticogulation
  - tPA contraindicated

- A patient on dabigatran begins bleeding
  - No complete reversal agent
  - For serious bleeding would probably use FFP

Side Effects of Antithrombotic Therapy
**CASE #5**
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?

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**Heparin Induced Thrombocytopenia**

```
Heparin

PF4
platelet

κ
Heparin
IgG

Platelet Activation

Thrombocytopenia

Thrombosis

Develops in 30-50% of cases
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**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
“4 T” Score

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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

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Post-operative day #2 platelets are 110,000

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Score of 1 = low risk
No Testing Needed
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

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 proven for medical pts

Substitution of LMWH for UFH
- Both cause hyperkalemia via aldosterone inhibition

Fondaparinux
- Synthetic pentasaccharide binds to antithrombin
- Indirectly inhibits factor X
- Will not cause hyperkalemia
Take Home Points

- Weigh individual risk/benefit of bridging anticoagulation
  - Low risk patients do not require bridging
- Dabigatran may be a game changer for atrial fibrillation….
  - Are you an early adopter?
- "4 Ts" identifies patients in whom HIT should be suspected
- Hyperkalemia as side effect of heparin and LMWH