Clinical Controversies in Perioperative Medicine

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Disclosures

- No financial relationships with pharmaceutical industry
- No discussion of unapproved medications
- Non-FDA approved indications for medications to be presented
Clinical Controversies in Perioperative Medicine

Should we provide bridging anticoagulation?
- Atrial Fibrillation, Prosthetic valves, Venous clots

How long should we delay surgery:
- After ischemic stroke?
- After drug-eluting stent implantation?

Is there still a role for perioperative beta-blockers?

Managing Perioperative Anticoagulation

An orthopedic surgeon asks your advice on how to manage anticoagulation in two patients who had hip replacements:
- One patient has atrial fibrillation due to HTN
- The other patient has a mechanical AVR
- Neither has any other relevant comorbidity

1. Bridge for AVR only
2. Bridge for AF only
3. Bridge both
4. Bridge neither
Benefits & Harm of Bridging Perioperative Anticoagulation

Death or disability from thromboembolism averted by bridging

Death or disability from perioperative bleeding caused by bridging

Meta-analysis of Cohort Studies

<table>
<thead>
<tr>
<th></th>
<th>Bridged</th>
<th>No Bridge</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embolic Event</td>
<td>1.1%</td>
<td>0.9%</td>
<td>0.8 (0.4-1.5)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>11%</td>
<td>2%</td>
<td>5.4 (3.0-9.7)</td>
</tr>
<tr>
<td>Serious Bleeding</td>
<td>3.7%</td>
<td>0.9%</td>
<td>3.6 (1.5-8.5)</td>
</tr>
</tbody>
</table>

BRIDGE Trial

Patients:
- 1884 patients on warfarin for atrial fib or flutter
- CHADS-2 score ≥ 1
- Excluded patients with mechanical valve or stroke within 12 weeks and cardiac & neurologic surgery

Intervention:
- Randomized to bridging with LMWH or placebo

Outcome:
- 30-day risk of arterial thromboembolism & bleeding

Douketis JD et al. NEJM, 2015; 373:823-33

BRIDGE Trial

<table>
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<tr>
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<th>Bridged</th>
<th>No Bridge</th>
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<tbody>
<tr>
<td>Embolic Event</td>
<td>0.3%</td>
<td>0.4%</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>3.2%</td>
<td>1.3%</td>
<td>NNH = 53</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>21%</td>
<td>12%</td>
<td>NNH = 12</td>
</tr>
</tbody>
</table>

Douketis JD et al. NEJM, 2015; 373:823-33
BRIDGE Trial for Atrial Fibrillation

Conclusions:
- Bridging did not reduce risk of embolism
- Bridging increases bleeding risk

Caveats:
- Few patients with high CHADS-2 score (mean = 2.3)

My take-away:
- Don’t bridge majority of atrial fibrillation
- Carefully consider bridging if stroke risk is very high (CHADS-2 score 5 or 6, rheumatic atrial fibrillation)

What About Mechanical Valves?

- BRIDGE trial confirmed common practice for atrial fibrillation
- Trial excluded patients with mechanical prosthetic valves
- General perception valves carry higher risk of thromboembolism & require bridging
Thromboembolic Risks with Atrial Fibrillation

CHADS-2 Score:
- Score 0 - 2: < 5% stroke risk / yr
- Score 3 - 4: 5-10%
- Score 5 - 6: > 10%

Ansell J. Chest. 2004;126:204S-233S.

Thromboembolic Risks with Mechanical Valves

Effect of Mechanical Valve Location & Design on Thromboembolic Risk

Valve Location:
- Aortic: RR = 1.0
- Mitral: RR = 1.8

Valve Design:
- Caged Ball: RR = 1.0
- Tilting Disk: RR = 0.7
- Bi-leaflet: RR = 0.6


<table>
<thead>
<tr>
<th>Atrial Fib.</th>
<th>Mechanical Valve</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 = 5-6; recent CVA; rheumatic AF</td>
<td>Any MVR; older (caged-ball or tilting disc) AVR; recent CVA</td>
<td>Bridge with heparin</td>
</tr>
<tr>
<td>CHADS2 = 3-4</td>
<td>Bileaflet AVR plus other stroke risk factor(s)</td>
<td>???</td>
</tr>
<tr>
<td>CHADS2 = 0-2</td>
<td>Bileaflet AVR without AF or other stroke risk factor</td>
<td>No heparin bridge</td>
</tr>
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</table>
### Perioperative Anticoagulation: My Approach to AF and Valves

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<td>CHADS$_2$ = 5-6; recent CVA; rheumatic AF</td>
<td>Any MVR; older (caged-ball or tilting disc) AVR; recent CVA</td>
<td><strong>Consider bridging</strong></td>
</tr>
<tr>
<td>CHADS$_2$ = 3-4</td>
<td>Bileaflet AVR plus other stroke risk factor(s)</td>
<td><strong>No bridge</strong></td>
</tr>
<tr>
<td>CHADS$_2$ = 0-2</td>
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### How About Venous Clots?

A retrospective cohort study

- 1178 patients on warfarin for DVT or PE

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<th>Bridged</th>
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<th>Hazard Ratio</th>
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</thead>
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<tr>
<td>Recurrent VTE</td>
<td>0%</td>
<td>0.2%</td>
<td>ns</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0.2%</td>
<td>2.7%</td>
<td>17 (4-75)</td>
</tr>
</tbody>
</table>

Clark NP et al. *JAMA Int Med*, 2015; 175:1163
How About Venous Clots?

Conclusions:
• Recurrent VTE is rare & bridging didn’t affect risk
• Bridging increases bleeding

Caveats:
• Retrospective study with possible confounders
• Few patients were considered high-risk for recurrence

My practice:
• Bridge or place temporary IVC filter only in high-risk group

Thromboembolic Risk with DVT & PE

Risk of Recurrent VTE

Time Since Venous Thromboembolic Event

Clark NP et al. JAMA Int Med, 2015; 175:1163
### Venous Clots: 2012 ACCP Guideline

<table>
<thead>
<tr>
<th>Risk of Recurrent VTE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Risk:</strong> VTE &lt; 3 months ago; Severe thrombophilia</td>
<td>Bridge</td>
</tr>
<tr>
<td><strong>Medium Risk:</strong> VTE 3-12 months ago; recurrent VTE; VTE  with cancer other thrombophilia</td>
<td>Case-by-case decision</td>
</tr>
<tr>
<td><strong>Low:</strong> Single VTE &gt; 12 months ago</td>
<td>No bridge</td>
</tr>
</tbody>
</table>

### Venous Clots: My Approach

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<th>Recommendation</th>
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<td><strong>High Risk:</strong> VTE &lt; 3 months ago; Severe thrombophilia</td>
<td>Consider bridging or IVC filter</td>
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<tr>
<td><strong>Medium Risk:</strong> VTE 3-12 months ago; recurrent VTE; VTE with cancer other thrombophilia</td>
<td>No bridge</td>
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<tr>
<td><strong>Low:</strong> Single VTE &gt; 12 months ago</td>
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Delaying Surgery After Stroke

You admit a 63-year-old man with an acute stroke that is managed without thrombolysis. Brain MRI incidentally detects a large meningioma. The neurosurgeon wants to resect the tumor in 2 weeks. Because of his stroke, you recommend delaying surgery for:

A. 1 month
B. 3 months
C. 6 months
D. 9 months
E. At least a year

Delaying Surgery After Stroke

Question: How does time between stroke and surgery affect the risk of cardiovascular complications?

Danish cohort study of all adults undergoing elective noncardiac surgery from 2005-2011:

- 7137 patients had prior stroke (1.5% of total cohort)
- Outcome: 30-d postop Major Adverse Cardiac Events (MACE): nonfatal MI, ischemic stroke, cardiovascular death
- Looked at effect of time since stroke on MACE rate

Jorgenson ME et al. JAMA 2014; 312:269-277
Delaying Surgery After Stroke

How Long to Wait after CVA?

Conclusions:
- Surgery after CVA associated with greater cardiac risk
- Risk falls over 9 months, biggest drop after first 3 months

Caveats:
- Nonrandomized, observational study

My take-away:
- Delay surgery for at least 3 months if at all possible
- Delay for 9 months if truly elective
Surgery After Drug Eluting Stent

A 75-y.o. man sustains an unstable cervical spine fracture. He is clinically stable, but had a drug-eluting stent placed 7 months ago for stable angina. The neurosurgeon wants to operate, but putting him in a halo vest is less desirable alternative approach.

What do you recommend?

1. Operate now
2. Wait 12 months after DES

Perioperative Cardiac Complications in Patients with Coronary Stents

Question: How do stent type and time until surgery affect risk of cardiac complications?

Study Design: Retrospective cohort analysis

- Over 25,000 pts who had noncardiac surgery between 6 weeks & 2 years after BMS or DES placement
- Identify risk factors for cardiac complications (all-cause mortality, MI, revascularization)

Effect of Stent Type & Time After Implantation

Time of surgery after PCI didn’t matter after first 6 months

Guidelines for DES

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC / AHA</td>
<td>Wait 12 months before elective surgery…but maybe 6 months is ok if delay is harmful</td>
</tr>
</tbody>
</table>
| ACCP      | • Wait 6 months before surgery  
        | • If < 6 months, continue DAPT |
| ESC       | • Wait 12 months before surgery  
        | • 6 month delay OK for new-generation DES |
Is There Still a Role for Perioperative Beta-Blockers?

While use of perioperative beta-blockade has declined due to safety concerns, I would still consider their use in surgical patients with:

1. Very high cardiac risk
2. Need to start additional HTN drug anyway
3. Both
4. Neither

Perioperative Beta-blocker Timeline

1996-1999: Small studies showing huge benefit, no risk
Early 2000's: Recommendations for aggressive use
2005: Re-analysis suggests less benefit, some risk
2008: POISE mega-trial shows increased mortality
2009: DECREASE IV shows great benefit, low risk
2011-2012: DECREASE studies discredited for fraud
2014: ACC/AHA guideline revised
2014 ACC / AHA Guideline for \(\beta\)-blockers

Definite indications to continue if… (Level I)
- Already using \(\beta\)-blocker to treat angina, HTN, arrhythmia

Reasonable to consider initiation if… (Level 2b)
- High clinical risk (RCRI score \(\geq 3\))
- Ischemia seen on preoperative stress test
- Compelling indication for long-term beta-blockade

Who Does It Help? Who Does it Harm?

Question: What subsets of patients are more likely to be helped or harmed by perioperative beta-blockers?

Cohort study of 314,114 patients having noncardiac surgery at 119 VA hospitals (2008-2013):
- Beta-blocker use determined from hospital pharmacy data
- Outcome: 30-d postop mortality
- Stratified by number of cardiac risk factors (0-4):
  - CAD, Diabetes, SCr > 2, Surgery in major body cavity

Friedell ML et al. JAMA Surg, 2015; 150(7):658-63
### Who Does It Help? Who Does it Harm?

<table>
<thead>
<tr>
<th>Number of Risk Factors*</th>
<th>Odds Ratio for Mortality (β-blocker vs. No β-blocker)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.19 (1.05-1.35)</td>
</tr>
<tr>
<td>1 or 2</td>
<td>0.95 (0.87-1.03)</td>
</tr>
<tr>
<td>3 or 4</td>
<td>0.63 (0.43-0.93)</td>
</tr>
</tbody>
</table>

* CAD, Diabetes, SCr > 2, Surgery in major body cavity

Friedell ML et al. JAMA Surg, 2015; 150(7):658-63

### β-Blockers for HTN in Surgical Patients

**Question:** Does treating hypertension with beta-blocker increase perioperative cardiac complications?

Danish cohort study of all adults undergoing elective noncardiac surgery from 2005-2011:

- 55,320 patients had h/o HTN on at least two HTN drugs
- Excluded patients with known cardiac disease
- Outcome: 30-d postop Major Adverse Cardiac Events (MACE): nonfatal MI, ischemic stroke, cardiovascular death

Jorgenson ME et al. JAMA Int Med, 2015; Published online October 5, 2015.
Treating uncomplicated HTN with beta-blocker associated with increased risk in surgical patients

<table>
<thead>
<tr>
<th></th>
<th>β-blocker</th>
<th>Other drugs</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>1.3%</td>
<td>0.8%</td>
<td>209</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>1.9%</td>
<td>1.3%</td>
<td>164</td>
</tr>
</tbody>
</table>

All comparisons P < .001

Jorgenson ME et al. JAMA Int Med, 2015; Published online October 5, 2015.

Is There Still a Role for Perioperative Beta-Blockers?

Conclusions:
• Beta-blockers increase mortality in low-cardiac risk pts
• Potential benefit in high-cardiac risk patients

Caveats:
• Observational studies, many possible confounders

My take-away:
• I’m pretty much done with perioperative beta-blockade
Conclusions

• Bridging anticoagulation for most patients with AF, mechanical valves, VTE is not indicated
• Possible exceptions CHADS2 = 5-6, MVR, acute VTE
• Recent stroke predicts postoperative cardiac complications, especially within first 3 months
• While waiting 12 months to go to OR after DES is standard, 6 months may be adequate
• Perioperative beta-blockers? Stick a fork in it.

Thank You!

quinny.cheng@ucsf.edu
Additional Material

Managing New Oral Anticoagulants

<table>
<thead>
<tr>
<th>Last dose of drug prior to high bleeding risk surgery</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 50</td>
<td>3 Days Before</td>
<td>3 Days Before</td>
<td>3 Days Before</td>
</tr>
<tr>
<td>CrCl 30-50</td>
<td>5 Days Before</td>
<td>3 Days Before</td>
<td>4 Days Before</td>
</tr>
</tbody>
</table>

-- Rapid onset of action & no reversal agent
-- No need to bridge
**Preoperative Bridging Protocol**

Discuss plan with surgeon & anesthesiologist

Stop warfarin 5 days before surgery
  - If INR 2.5 - 4.5, stop warfarin 6 days before

Start therapeutic dose LMWH (off-label indication) or
IV UFH 36 hrs after last warfarin dose

Stop LMWH 24 hrs before surgery; stop IV UFH at
least 4 hrs before surgery

Check INR on AM of surgery (typical target < 1.5)


**Postoperative Bridging Protocol**

Minor procedures:
  - Restart LMWH or IV UFH 24 hrs after surgery if hemostasis
    is adequate (individualize timing)

Major surgery or high bleeding risk:
  - Delay restarting therapeutic LMWH or IV UFH dose for 48-72
    hours if hemostasis is adequate (individualize timing)

Restart warfarin 12-24 hrs after surgery

Stop LMWH or IV UFH when INR therapeutic for 24 hrs