Updates & Controversies in Perioperative Medicine

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Perioperative Medicine Workshops

12:40 – 2:00:
Preoperative Cardiac & Pulmonary Evaluation
• Clinical assessment, preoperative testing, and approaches to risk reduction

2:10 – 3:30:
Tough Cases in Perioperative Medicine
• Common questions and dilemmas in the management of medical problems in surgical patients
Updates in Perioperative Medicine

1. Screening & treatment for postoperative myocardial injury

2. Anticoagulating postoperative atrial fibrillation

3. Managing medications around surgery
   - Stress-dose steroids
   - ACE-inhibitors & ARBs
   - Direct-acting oral anticoagulants
You get signout about a patient with CAD and HFpEF who had a colectomy last week. Your fellow hospitalist tells you:

“He had no cardiac symptoms, but I checked a postop troponin anyway because his RCRI was 3. It peaked at 0.2 ng/mL, but I didn’t do anything based on this result.”

How do you respond?

1. I wouldn’t have ordered a screening troponin
2. I’ll just optimize his secondary risk reduction regimen
3. I’ll order a stress test or refer to cardiology for possible cath
4. I’ll start long-term anticoagulation
5. Meh – I’ll ignore it too and inform the PCP
Perioperative Myocardial Injury

Findings from POISE (beta-blocker) trial:

- 5% of these “elevated risk” patients had postop MI, defined as elevated biomarker + ECG changes
- Most MI occurred by POD #3 (74% within 48 hr)
- Postoperative MI predicted 5-fold mortality
- Majority of postoperative MI were asymptomatic
- Silent MI had similar mortality as symptomatic MI
## Postop Biomarkers Predicts Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Biomarker</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>POISE (2011)</td>
<td>Troponin or CK-MB</td>
<td>2.5x mortality with isolated biomarker elevation</td>
</tr>
<tr>
<td>VISION (2012)</td>
<td>Troponin-T</td>
<td>4x mortality with any Tn-T elevation</td>
</tr>
<tr>
<td>Meta-analysis of 14 earlier studies (2011)</td>
<td>Troponin</td>
<td>3x mortality with elevation</td>
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Arguments Against Screening

Insufficient Sensitivity:
• Screening only identified 21% of patients who died in POISE

Too late to do anything:
• Nearly 2/3 of deaths in patients with MI occurred by POD 3
• Many deaths in MI patients are not cardiac-related
• Elevated troponin just identifies obviously crashing patients

No known effective intervention:
• Don’t order the test unless it will change management
Non-FDA Approved Indication

MANAGE
Management of myocardial injury after non-cardiac surgery
**Question:** Does the direct thrombin inhibitor dabigatran improve outcomes in patients with elevated postop troponin?

**Patients:** 1754 patients who evidence of myocardial injury after noncardiac surgery (MINS), defined as elevated postop troponin either with clinical, ECG or imaging evidence of new ischemia or no other explanation (e.g., PE, sepsis, atrial fib)

**Intervention:** Dabigatran 110 mg bid vs. placebo for up to 2 yrs

**Outcome:** CV mortality, nonfatal MI, stroke, peripheral arterial thrombosis, and symptomatic PE

Amputation and symptomatic proximal DVT added post hoc
## MANAGE Trial Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran</th>
<th>Placebo</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary cardiac or vascular outcome</td>
<td>11%</td>
<td>15%</td>
<td>25 (p = .012)</td>
</tr>
<tr>
<td>Mortality – CV</td>
<td>6%</td>
<td>7%</td>
<td>NS</td>
</tr>
<tr>
<td>Mortality – All cause</td>
<td>11%</td>
<td>13%</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>4%</td>
<td>5%</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding complications</td>
<td>3%</td>
<td>4%</td>
<td>NS</td>
</tr>
</tbody>
</table>

[https://doi.org/10.1016/S0140-6736(18)30832-8](https://doi.org/10.1016/S0140-6736(18)30832-8)
Limitations of MANAGE trial:

- Design problems (changing sample size & outcomes)
- Outcomes too broad and individually no significant effect
- Comparison group was placebo
- Just too weird -- very different from usual practice

So now what?

**Screening for MINS?:** US guidelines ambivalent; Canadian guideline endorses it.

**Statin & ASA:** Association between their use and lower mortality in patients with MINS or postop MI (retrospective study only)
Postoperative Atrial Fibrillation

70-y.o. woman with hypertension undergoes knee replacement. On POD #1, she develops new atrial fibrillation. She is started on metoprolol and converts spontaneously to sinus rhythm the next day. A recent TTE shows normal LV function with mild LAE. Her CHA$_2$DS$_2$VASc = 3.

Would you recommend long-term anticoagulation?
1. No
2. Yes
3. Tough call…I’ll ignore it and inform the PCP
My problem

Not my problem

Also not my problem

Hospitalist Mentality

Apologies to Demetri Martin
Incidence & Risk Factors

• New onset AF requiring treatment occurs after ~ 1% of major non-cardiac surgery
• Risk factors: male, white race, pre-existing cardiovascular disease or cardiac risk factors
• More common with thoracic, abdominal, vascular, intra-cranial, and head & neck operations
• Associated with prolonged hospitalization, increased mortality, readmission
Does postop AF (POAF) have similar risk for stroke as “regular” non-valvular AF (NVAF)?

California database: 12,874 patients with new POAF

<table>
<thead>
<tr>
<th></th>
<th>POAF</th>
<th>No POAF</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-yr Stroke Risk</td>
<td>1.47%</td>
<td>0.36%</td>
<td>2.0 [1.7-2.3]</td>
</tr>
</tbody>
</table>

- 1.47% risk is similar to NVAF with CHA$_2$DS$_2$VASc between 1-2
- Median CHA$_2$DS$_2$VASc in this study = 3. Expected stroke risk in NVAF would be 3.2% (twice higher)

Stroke Risk with Postop AF

Danish registry: 3830 patients with new onset POAF

- Adjusted HR for thromboembolism = 1.9 compared to surgical patients who did not develop POAF
- Matched by CHA$_2$DS$_2$VASc score to patients with new onset NVAF:

<table>
<thead>
<tr>
<th></th>
<th>POAF</th>
<th>NVAF</th>
<th>Adjusted HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism (TE) Risk (events per 1000 person-yrs)</td>
<td>32</td>
<td>30</td>
<td>0.95 (NS)</td>
</tr>
<tr>
<td>Hazard ratio for TE if anticoagulant prescribed</td>
<td>0.52</td>
<td>0.56</td>
<td>NS</td>
</tr>
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</table>

J Am Coll Cardiol 2018;72:2027–36
Stroke Risk Conclusions

Long-term stroke risk from POAF underappreciated:

- Patients with POAF have 2-fold (adjusted) risk of stroke compared to surgical patients who do not develop AF
- Stroke risk for POAF may be similar to patients with usual, non-surgical NVAF
- Anticoagulation may have similar benefit in POAF

What to do?

- Take POAF seriously; not unreasonable to offer AC, especially if higher CHA$_2$DS$_2$VASc score
- Limited by retrospective data, lack of consensus & guidelines
Perioperative Steroid Coverage

You perform a preoperative medical evaluation on a 60-y.o. woman with rheumatoid arthritis who suffered a peri-prosthetic hip fracture. She takes prednisone 10 mg daily, leflunomide (Arava), and a TNF-inhibitor.

She is hemodynamically stable & does not appear Cushingoid

What should you about glucocorticoid dosing?

1. Give “stress dose steroids”
2. Just give usually home prednisone
3. Perform ACTH-stimulation test
Adrenal Response to Surgical Stress

Circadian rhythm of cortisol level

Unstressed state: 20 mg / day
Day of surgery: 75-150 mg / day

Adapted from Lamberts et al. *NEJM*, 1997
Adrenal Crisis: Does it Happen?

Review of published cases of perioperative hypotension or death attributed to adrenal insufficiency in steroid-treated patients:

- Plasma cortisol level measured in only 6 cases
- Only 3 of these cases also fulfilled other criteria for adrenal insufficiency

Do Patients Really Need Stress-dose Steroids?

80 patients on chronic steroids underwent transplant nephrectomy (n = 52) or major arthroplasty (n = 28):

- All received their usual daily prednisone (average dose 10 mg)
- No additional steroid coverage
- No episodes of unexplained hypotension

Continue the current daily dose of glucocorticoids in adult patients...who are receiving glucocorticoids for their rheumatic condition and undergoing THA or TKA, rather than administering perioperative supra-physiologic glucocorticoid doses (so-called “stress dosing”).
But I want to Use Stress-dose Steroids

Assume HPA axis suppressed:
• Prednisone $\geq$ 20 mg daily for at least 3 weeks

Assume HPA axis normal:
• Prednisone < 5 mg every morning for any duration
• Prednisone < 10 mg every other day for any duration
• Prednisone at any dose for < 3 weeks

Unknown HPA axis status:
• Everyone else $\rightarrow$ consider ACTH-stimulation test
But I **Want** to Use Stress-dose Steroids

**Moderate Stress:**
- open chole, hemicolecotomy,
- major orthopedic surgery

**Severe Stress:**
- major cardiac surgery,
- organ transplantation

Hydrocortisone 50 mg IV x 1 preop &
25 mg IV q 8 hrs x 3 doses post-op

Hydrocortisone 100 mg IV x 1 preop &
50 mg IV q 8 hrs post-op;
Taper by 50% per day to baseline

Adapted from Salem et al. *Ann Surgery*, 1994 and
Coursin and Wood. *JAMA*, 2002
2017 ACR Guideline for Arthroplasty

DMARDs & Biologics in RA patients:

Continue nonbiologic DMARDs (methotrexate, leflunomide, hydroxychloroquine, and/or sulfasalazine) for patients undergoing elective THA or TKA.

Withhold biologic agents prior to surgery and plan the surgery at the end of the dosing cycle for that specific medication. Resume at least 14 days after surgery in absence of wound complications.

Arthritis Care & Research, 2017; 69(8):1111–1124
ACE-I & ARB: Hold or Continue?

Background:

- ACE-inhibitors & angiotensin receptor blockers (ACEI/ARBs) associated with hypotension and need for vasopressors during surgery.
- Individual studies mostly retrospective and too small to show effect on clinical outcomes.
- Guidelines vary on whether to hold or continue ACEI/ARBs on day of surgery.

USA: Continue
Canada: Hold
Europe: Continue for CHF, not HTN.
New Studies on Periop ACEI/ARB

Randomized trial:
- 291 elective noncardiac, nonvascular operations on patients taking ACEI chronically
- Final preop dose either given or held
- Excluded patients with decompensated HF, EF < 40%, ESRD, or SBP < 90 or > 160

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<tr>
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<th>Given</th>
<th>Held</th>
<th>NNH</th>
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<tbody>
<tr>
<td>Intraop SBP &lt;80 + pressor</td>
<td>64%</td>
<td>45%</td>
<td>6</td>
</tr>
<tr>
<td>Postop SBP &lt; 90</td>
<td>11%</td>
<td>22%</td>
<td>9</td>
</tr>
<tr>
<td>Postop SBP &gt; 180</td>
<td>12%</td>
<td>24%</td>
<td>9</td>
</tr>
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New Studies on Periop ACEI/ARB

Large cohort trial:
- 4802 noncardiac operations on patients taking ACEI/ARB
- Examined association between giving ACEI/ARB and hypotension & composite endpoint of death, stroke, MINS

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<thead>
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<th>Adjusted Rist if ACEI/ARB Held</th>
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<tr>
<td>Intraop hypotension requiring intervention</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Death, Stroke, MINS</td>
<td>0.82 (0.70-0.96)</td>
</tr>
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Roshanov et al. Anesthesiology 2017; 126:16-27
ACE-I & ARB: Hold or Continue?

Conclusions:

• Trade off between hypotension (especially intraoperative) and postoperative hypertension
• Difficult to demonstrate effect on hard endpoints
• Personal & UCSF practice: Hold on morning of surgery; restart when BP and renal function stable
You admit a 75-year-old woman for suspected acute cholangitis. She has atrial fibrillation and took her last dose of apixaban last night. Creatinine is normal. She is stable, but GI wants to perform ERCP as soon as possible.

When should she have the procedure?

1. Today
2. Tomorrow (hold apixaban 1 day)
3. Day after tomorrow (hold 2 days)
4. When DOAC level is undetectable
How to PAUSE a DOAC

Perioperative Anticoagulation Use for Surgery Evaluation

• International study of 3007 elective surgery patients taking apixaban, rivaroxaban or dabigatran for atrial fibrillation
• Interrupted & resumed DOAC using standardized protocol
• Considered surgical bleeding risk and (for dabigatran) CrCl
• No bridging was permitted
• Drug level and coagulation times checked but not used for clinical decision-making

### Dabigatran (CrCl ≥ 50), Apixaban, Rivaroxaban:

<table>
<thead>
<tr>
<th></th>
<th>Day - 3</th>
<th>Day - 2</th>
<th>Day - 1</th>
<th>OR</th>
<th>Day + 1</th>
<th>Day + 2</th>
<th>Day + 3</th>
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### Dabigatran with CrCl < 50:

<table>
<thead>
<tr>
<th></th>
<th>Day - 5</th>
<th>Day - 4</th>
<th>Day - 3</th>
<th>Day - 2</th>
<th>Day - 1</th>
<th>OR</th>
<th>Day + 1</th>
<th>Day + 2</th>
<th>Day + 3</th>
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</table>
PAUSE Trial Results

- Average CHADS2 = 2.1 (CHA$_2$DS$_2$VASc = 3.4)
- Patients having high bleeding risk surgery = 33%

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
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</thead>
<tbody>
<tr>
<td>Major Bleeding</td>
<td>0.9%</td>
<td>1.35%</td>
<td>1.85%</td>
</tr>
<tr>
<td>Arterial Thromboembolism</td>
<td>0.6%</td>
<td>0.16%</td>
<td>0.37%</td>
</tr>
</tbody>
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Take Home Points

1. Silent myocardial injury predicts mortality – unfortunately effective management remains uncertain
2. Take postoperative atrial fibrillation seriously and consider offering anticoagulation
3. Stress-dose steroids probably treats the provider more than the patient – consider just giving usual daily steroid dose
4. A standardized protocol for PAUSE-ing DOACs leads to low risk of thromboembolism and bleeding
5. Hold ACE-I and ARB on morning of surgery by default
Thank You

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