Update in Perioperative Anticoagulation and Antiplatelet management

Grand Rounds
October 31, 2014
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Steve Komfeld, MD
Bruce McLellan, MD

Nothing to disclose
Objectives

- Describe the updates in perioperative anticoagulation
- Update the perioperative anticoagulation guidelines for elective surgery
- Define the novel anticoagulants and perioperative management
- Outline perioperative management of antiplatelet therapy in patients with stents

Anticoagulation Task Force

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The Challenge

• >6 million U.S. patients on anticoagulation for thromboembolism prevention
• 10% of patients on anticoagulants undergo surgery annually
• Increase in number of patients on dual antiplatelet therapy (DAPT)
• Goal of minimizing bleeding while preventing thromboembolic events
• Data limited, no universal protocol

Clinical outcomes

• Stroke: 20% fatal or permanent neurological deficit > 50% of cases
• Valve thrombosis: 10-20% mortality with emergency valve replacement
• Pulmonary embolism or DVT: 5-10% recurrent VTE are fatal
• Stent thrombosis: MI mortality rate >50%
• Bleeding: 9-13% major bleeding events are fatal but permanent disability rare
What is bridging?

“The administration of a short-acting anticoagulant, consisting of LMWH or IV UFH for an ~10- to 12-day period during interruption of VKA therapy when the international normalized ratio (INR) is not within a therapeutic range.”

Case 1

A 65 year old male with a mechanical mitral valve is on warfarin and plans to undergo Mohs surgery for melanoma. He has no history of stroke, congestive heart failure, or atrial fibrillation. How do you manage his warfarin perioperatively?
A. Stop warfarin 5 days prior to surgery, no bridging therapy, resume warfarin postoperatively on the day of surgery.

B. Stop warfarin 5 days prior to surgery, bridge with LMWH pre and postoperatively.

C. Stop warfarin 5 days prior to surgery, bridge with LMWH preoperatively only and resume warfarin postoperatively on the day of surgery

D. Continue warfarin without interruption

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**Step 1: Determine if anticoagulation can be continued without interruption**

Low Bleeding Risk Procedure, Continuation of Anticoagulants is recommended

<table>
<thead>
<tr>
<th>Ophthalmic</th>
<th>Dental</th>
<th>Dermatologic</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cataract surgery</td>
<td>Restorations Uncomplicated extractions Endodontics Prosthetics Periodontal therapy Dental hygiene</td>
<td>Mohs surgery Simple excisions</td>
<td>Diagnostic esophagastroduodenoscopy Colonoscopy without biopsy Diagnostic endoscopic retrograde cholangiopancreatography Biliary stent without sphincterotomy Endoscopic ultrasonography without biopsy Push enteroscopy</td>
</tr>
</tbody>
</table>
Case 2

72 year old female with a history of stroke 2 years ago, atrial fibrillation and hypertension plans to undergo right total knee arthroplasty. She is taking warfarin. How do you manage her anticoagulation perioperatively?
A. Stop warfarin 5 days prior to surgery, no bridging therapy, resume warfarin postoperatively on the day of surgery.
B. Stop warfarin 5 days prior to surgery, bridge with LMWH pre and postoperatively.
C. Stop warfarin 5 days prior to surgery, bridge with LMWH preoperatively only and resume warfarin postoperatively on the day of surgery
D. Continue warfarin without interruption

Atrial Fibrillation and Stroke risk

<table>
<thead>
<tr>
<th>Risk</th>
<th>points</th>
<th>Chads 2</th>
<th>Stroke rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>C: CHF</td>
<td>1</td>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>H: Hypertension</td>
<td>1</td>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>A: Age &gt;75</td>
<td>1</td>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>D: Diabetes</td>
<td>1</td>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>S: Stroke or TIA</td>
<td>2</td>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>Total points</td>
<td>6</td>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>
Systematic approach

1. What is the bleeding risk?
2. Can anticoagulation be continued?
3. What is the thromboembolic risk if anticoagulation is stopped?
4. If temporary cessation of anticoagulation is necessary, how should this be conducted?

<table>
<thead>
<tr>
<th></th>
<th>HIGH Thrombotic Risk: Bridging Required</th>
<th>LOW Thrombotic Risk: Bridging Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical Heart Valve</td>
<td>• All mitral valve prosthesis</td>
<td>• Bi-leaflet aortic valve prosthesis</td>
</tr>
<tr>
<td></td>
<td>• Older mechanical aortic valve</td>
<td></td>
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<tr>
<td></td>
<td>prosthesis</td>
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<tr>
<td></td>
<td>• Recent (&lt; 6 months) stroke/TIA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Bi-leaflet aortic valve prosthesis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>with &gt; 1 stroke risk factors(^1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Two or more mechanical valves</td>
<td></td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>• CHADS2(^*) Score 4-6</td>
<td>• CHADS2 Score 0-3 with no prior stroke/TIA</td>
</tr>
<tr>
<td></td>
<td>• Prior stroke or TIA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rheumatic mitral valvular heart</td>
<td></td>
</tr>
<tr>
<td></td>
<td>disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cardiac thrombus</td>
<td></td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td>• Recent VTE (within 6 months)(^1,2)</td>
<td>• Single unprovoked VTE &gt; 6</td>
</tr>
<tr>
<td></td>
<td>• Prior VTE and &gt; 1 other risk factor(^3)</td>
<td>months ago and no other risk factors(^4)</td>
</tr>
<tr>
<td></td>
<td>• Recurrent VTE(^*)</td>
<td></td>
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</tbody>
</table>
Venous Thromboembolism

- Risk of recurrent VTE:
  - 1 month: 50%
  - 2 months: 8-10%
  - 3 months: 5%
- Delay elective surgery if VTE <3 months
- Provoked VTE > 6 months ago and no other risk factors – consider stopping warfarin
The plan

A. Low bleeding risk procedure- continue anticoagulation

B. Moderate/High bleeding risk – determine the risk of thromboembolism (TE)
   1. Low TE risk – hold anticoagulation, no bridging
   2. High TE risk – bridging therapy recommended

How to bridge

• Check INR 7 days prior to surgery
• Last dose of warfarin 6 days prior to procedure
• 36 hrs after last warfarin dose, initiate enoxaparin 1 mg/kg SQ Q12hrs
• Last dose LMWH 1mg/kg SQ 24 hours prior to procedure
• Check INR in the morning on the day of surgery
Bleeding Risk

- No uniform definition
- Low bleeding risk: easily detected and controllable
- Major bleeding: difficult to detect or control, fatal, requiring further surgery, drop hemoglobin >2g/L, requiring transfusion
- Moderate to High bleeding risk:>1.5-2%

Procedural bleeding risk

- Bridging increases major bleeding 3X
- High bleeding risk procedures
  - Intracranial, intraspinal
  - Intraocular
  - Neuroaxial anesthesia
  - Retroperitoneal, intrathoracic, pericardial
Weighing the risk

<table>
<thead>
<tr>
<th></th>
<th>Bridging</th>
<th>No bridging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>0.4%</td>
<td>0.6%</td>
</tr>
<tr>
<td>(arterial or venous)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall bleeding</td>
<td>13.6%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>3.2%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Procedure</th>
<th>Low Bleeding Risk Procedure</th>
<th>Moderate Bleeding Risk Procedure</th>
<th>High Bleeding Risk Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental extraction</td>
<td>Endoscopy with bx</td>
<td>Neurosurgery (intracranial, spinal cont)</td>
<td></td>
</tr>
<tr>
<td>Skin Bx/Mohs</td>
<td></td>
<td>High risk urological</td>
<td></td>
</tr>
<tr>
<td>Cataracts</td>
<td></td>
<td>Other closed space procedures (post chamber eye)</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy, no bx</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low risk of thrombosis</th>
<th>Bileaflet Aortic Valve, no risk factors*</th>
<th>Atrial fibrillation with CHADS2** ≤ 3 and no prior stroke VTE &gt; 6 months, no risk factors***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue full dose</td>
<td>Resume warfarin 12-24 hours post procedure at usual dose (No bridging therapy) once hemostasis achieved</td>
<td></td>
</tr>
<tr>
<td>anticoagulation</td>
<td>Resume warfarin 3-7 days post procedure at usual dose (No bridging therapy)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elevated risk thrombosis</th>
<th>Mechanical mitral valve</th>
<th>Older mechanical aortic valve</th>
<th>Atrial fibrillation with CHADS2** 4-6 or prior stroke or TIA</th>
<th>Bileaflet aortic valve, with risk factors*</th>
<th>Recent VTE &lt;6 months VTE&gt;6 months and risk factors***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continue full dose</td>
<td>Resume full dose LMWH 24 hours post procedure (Can consider prophylactic dose LMWH for 1-3 days before initiating full dose) Resume warfarin 24 hours post procedure at usual dose Stop LMWH when INR ≥ 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anticoagulation</td>
<td>Consider starting prophylactic dose LMWH post-op when hemostasis achieved and increase to full dose at surgeon’s discretion (goal 48-72hrs postop) Resume Warfarin at usual dose once hemostasis achieved If utilized, stop LMWH when INR ≥ 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Team approach

• Communication is the key!
• Address well in advance of the elective procedure
• Involve the patient in the decision
• Individualized approach
• When possible, postpone the procedure until risk of discontinuing anticoagulant is low
Still more questions….

- More studies needed to determine safety and need for perioperative bridging
- Delay postoperative full dose bridging in high bleeding risk procedures
- Is bridging with prophylactic or intermediate dose LMWH a possibility?
- Are novel anticoagulants the answer?

DOAC in the Perioperative Setting

- TSOAC
  - Target Specific Oral Anticoagulant
- ODI
  - Oral Direct Inhibitor
- NOAC
  - Novel or New(er) Oral Anticoagulant
- DOAC
  - Direct Oral Anticoagulant
Mechanism of Action

- **Coumadin**
  - Inhibits coagulation factor synthesis
- **LMWH**
  - Indirect inhibitor by binding to Antithrombin
- **Direct Oral Anticoagulant (DOAC)**
  - Direct inhibition of activated enzymes
    - Ten-ase complex
    - Prothombin-ase which generates IIa (thrombin)

DOAC – Two Types

- **Direct Thrombin Inhibitors**
  - Parenteral – bivalirudin, argatroban
  - Oral – Dabigatran (Pradaxa)
- **Direct Factor Xa inhibitors**
  - Parenteral – none
  - Oral – Rivaroxaban (Xarelto)
    - Apixaban (Eliquis)
- Consider them as one group
DOAC – Onset of Action

- LMWH: 2 hours
- Coumadin: 2-3 days
- Dabigatran: 2-4 hours
- Rivaroxaban: 2-4 hours
- Apixaban: 1-3 hours
  – DOAC: work fast like LMWH but oral

DOAC - Monitoring

- LMWH: no routine monitoring – Xa level
- Coumadin: PT (INR)
- Dabigatran: PTT (marker of use)
- Rivaroxaban: PT (marker of use)
- Apixaban: Xa (marker of use)
  – DOAC: like LMWH no need to monitor
  – Lab results do not correlate with anticoag effect
DOAC – Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>T ½ - hrs</th>
<th>Renal</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMWH</td>
<td>4</td>
<td></td>
<td>qd - BID</td>
</tr>
<tr>
<td>Coumadin</td>
<td>36</td>
<td></td>
<td>qd</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>12</td>
<td>80%</td>
<td>BID</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>8</td>
<td>60%</td>
<td>qd</td>
</tr>
<tr>
<td>Apixaban</td>
<td>12</td>
<td>25%</td>
<td>BID</td>
</tr>
</tbody>
</table>

DOAC - Reversal

- LMWH: Protamine
- Coumadin: Vit K, FFP, PCC-4
  - Vit K requires 24-36 hours for factor synthesis (not reversal)
- Dabigatran: PCC-4
- Rivaroxaban: PCC-4
- Apixaban: PCC-4
  - Correction of coag tests may not correlate with reversal of the anticoagulant effect
DOAC in the Perioperative Setting

• Patients on Coumadin are in a Anti-coag clinic
• Patients on DOAC are not
  – Who will be in charge of management in the Perioperative setting?

DOAC in the Perioperative Setting
Low Bleeding Risk Procedure

• Patients on Coumadin – consider continuing Coumadin during low bleeding risk surgical procedures
• Patients on DOAC – early data suggests holding for 24 hours (1-2 doses) before low bleeding risk surgical procedure
• Patients on DOAC – resume drug 24 hours after procedure
  – Assuming hemostasis
DOAC in the Perioperative Setting
Mod/High Bleeding Risk Procedure

• Pre-op thrombosis risk always less than Post-op risk
• Conservative approach is to hold DOAC for 2 days before procedure
  – Consider CrCl for Dabigatran & Rivaroxaban
  – May hold for up to 4-6 days
• Resume 48 to 72 hours after procedure
  – Similar to lovenox in routine bridging

DOAC in the Perioperative Setting

• Use of DOAC as an alternative to LMWH to bridge patients on Coumadin
• Not FDA approved
• Could save a few dollars
• Perhaps Rivaroxaban
• Not standard of care
A few Take Home Points

• Not all patients require interruption in anticoagulation (low risk bleeding procedure)
  – Coumadin >> DOAC

• Not all patients who interrupt anticoagulation require bridging (low thrombotic risk patient)
  – Coumadin & DOAC (DOAC patients never bridge)

• Renal function matter
  – DOAC >> Coumadin

• Opportunity to rethink need for long term anticoag

• Lots of help available
  – Pre-op Clinic, Hematology

2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery

Developed in Collaboration With the American College of Surgeons, American Society of Anesthesiologists, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, and Society of Cardiovascular Anesthesiologists

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Newer Data on Duration of DAPT

**RESET**: 3 mos DAPT (ZES) vs 12 mos DAPT (ZES, EES, SES) for stable, ACS, STEMI pts: no difference in clinical outcomes or stent thrombosis.

**PRODIGY**: 6 mos equaled 24 month clopidogrel for DE & BM stents in D, MI, CVA, but had less bleeding.

**EXCELLENT**: 6 vs 12 mos DAPT after implant of 1\textsuperscript{st} & 2\textsuperscript{nd} generation stents showed no difference in TVF (CD, MI, IDTTR) or clinical events at 12 mos., except in diabetic pts.

**OPTIMIZE**: 3 mo noninferior to 12 mo clopidogrel NACCE in stable or low risk ACS pts receiving zotarolimus stents; no increase in late Stent Thrombosis
### Applying Classification of Recommendations and Levels of Evidence

#### Antiplatelet Agents

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients undergoing urgent noncardiac surgery during the first 4 to 6 weeks after BMS or DES implantation, DAPT should be continued unless the relative risk of bleeding outweighs the benefit of the prevention of stent thrombosis.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In patients who have received coronary stents and must undergo surgical procedures that mandate the discontinuation of P2Y(<em>{12}) platelet receptor–inhibitor therapy, it is recommended that aspirin be continued if possible and the P2Y(</em>{12}) platelet receptor–inhibitor be restarted as soon as possible after surgery.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Management of the perioperative antiplatelet therapy should be determined by a consensus of the surgeon, anesthesiologist, cardiologist, and patient, who should weigh the relative risk of bleeding versus prevention of stent thrombosis.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

* Clopidogrel (Plavix), prasugrel (Effient), ticagrelor (Brilinta)
### Antiplatelet Agents (cont’d)

In patients undergoing nonemergency/nonurgent noncardiac surgery who have not had previous coronary stenting, it may be reasonable to continue aspirin when the risk of potential increased cardiac events outweighs the risk of increased bleeding.

Initiation or continuation of aspirin is not beneficial in patients undergoing elective noncardiac noncarotid surgery who have not had previous coronary stenting, unless the risk of ischemic events outweighs the risk of surgical bleeding.

<table>
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<tr>
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<tr>
<td>Initiation or continuation of aspirin is not beneficial in patients undergoing elective noncardiac noncarotid surgery who have not had previous coronary stenting, unless the risk of ischemic events outweighs the risk of surgical bleeding.</td>
<td>III: No Benefit</td>
<td>C</td>
</tr>
</tbody>
</table>

### Risk of stent thrombosis

- **High Risk**
  - First 4-6 weeks after BMS or DES implant

- **Medium Risk**
  - 6 weeks – 6 months for DES

- **Low Risk**
  - After 6-12 months for DES

BMS – Bare metal stent  DES – Drug eluting stent
Proposed Algorithm for Antiplatelet Management in Patients with PCI and Noncardiac Surgery

Colors correspond to the Classes of Recommendations in Table 1.

*Assuming patient is currently on DAPT.

ASA indicates aspirin; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention.
Patients with BMS within 6 weeks and DES within 1 year were excluded.

Only 23% of subjects had known CAD.

Study excluded patients undergoing carotid endarterectomy.

Therefore, this is a primary prevention study of low risk subjects.