Perioperative Anticoagulation Management

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Surgery Half-Day
April 21, 2010
Objectives

1. To address the perioperative management of patients receiving warfarin and require an elective surgical procedure

2. To outline a clinical approach to assessing thromboembolic and bleeding risks

3. To discuss the use of bridging anticoagulation

4. To discuss the recommendations in light of the American College of Chest Physicians (ACCP) guidelines
Perioperative anticoagulation

- Perioperative management of anticoagulation is increasingly common
  - 2.5 million people in North America are on vitamin K antagonists (VKA) for atrial fibrillation or mechanical heart valves
  - 250,000 patients assessed annually for perioperative anticoagulation

- Assessment of risk of thromboembolic event when antithrombotic agent is discontinued vs. risk of bleeding when antithrombotic agent is given close to surgery or invasive procedure

1. Is interruption of antithrombotic therapy in the perioperative period needed?

- Increased risk of bleeding if VKA or aspirin is continued perioperatively in major surgical procedures

- Minor surgical procedures may not require interruption (e.g., dental extractions, removal of skin lesions, cataract and eye procedures)
General approach

2. If antithrombotic therapy is interrupted, is bridging anticoagulation needed?

- Bridging is “the administration of a short acting anticoagulant, such as SC LMWH or IV UFH, administered typically as a therapeutic-dose regimen for approximately 8-10 d during interruption of VKA when the INR is not within a therapeutic range”
- Not typically considered in pts on antiplatelets
- Based on an assessment of patient’s thrombotic risk

Indications for antithrombotic therapy

VKA
- Mechanical heart valve
- Atrial fibrillation
- Venous thromboembolism (VTE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)

Antiplatelet therapy
- Coronary artery disease
  - Primary prevention
  - Secondary prevention (post MI)
- Stroke
- Peripheral vascular disease
Reversing anticoagulation
Reversing warfarin: Passive reversal

• Passive vs. active reversal of warfarin
• Dependent on acuity of need to normalize INR and restore normal hemostasis

Passive reversal
• Utilized in patients undergoing elective procedures
• Warfarin has a half-life of 36-42 hours
• Holding warfarin for 5 days prior to procedure will result in normalization of INR in almost all patients
Passive reversal

- Prospective studies have evaluated warfarin interruption 5-6 days before surgery
  - \( N = 224 \) patients, warfarin stopped 5 days before surgery
  - \( 15/224 \) (7%) had INR > 1.5 on day before surgery, all corrected with low-dose oral vitamin K (1 mg)

Which patients may need > 5 days to normalize?

- Mechanical heart valves (target INR 2.5-3.5)
- Elderly patients
- Phenprocoumon (\( t_{1/2} \) 96-140 h; need 10 d)

ACCP recommendations

“In patients who require temporary interruption of a VKA before surgery or a procedure and require normalization of the INR for the surgery or procedure, we recommend stopping VKAs approximately 5 days before surgery over a shorter time interval to allow adequate time for the INR to normalize (Grade 1B)”
Reversing warfarin: Active reversal

Active reversal
• Considered if patients are actively bleeding, or INR is ‘too high’ for surgery

Options:
1) Vitamin K
2) Frozen plasma
3) Prothrombin complex concentrates (PCC)
What dose of vitamin K should be given?

- Typical doses are 1-10 mg
- Although larger doses are more likely to ensure normalization of INR, larger doses may make the patient relatively resistant to re-anticoagulation following the procedure
- Retrospective cohort study, n = 43 with INR 1.5-1.9 on day before surgery, given vitamin K 1 mg orally
  - 91% had INR < 1.4 on day or surgery and did not result in resistance to re-anticoagulation

Woods K et al. J Thromb Thrombolysis 2007;24:93
Vitamin K

What route should the vitamin K be given?

- Oral or IV
- Normalization of INR within 6 hours with IV, 24 hours with oral
- No role for SC vitamin K
Frozen plasma

How much plasma should be given?
- Plasma is frozen in units (250 ml)
- Dose 10-15 ml/kg³
- Small adult: 2-3 units
- Large adult: 4 units

- Administration of FP does not result in complete correction of INR
- Even if FP is given, administer vitamin K to prevent rebound of INR
PCC (Octaplex)

- Prothrombin complex concentrates (PCC)
  - Octaplex®, contains FII, VII, IX, X, Protein C & S, heparin

- Used for treatment of acute bleeding caused by treatment with vitamin K antagonist or when rapid correction of the deficiency is required for urgent surgical procedures

- Comes in vials of 500 IU (lyophilized powder with 20 ml diluent), maximum dose ~3000 IU
PCC (Octaplex)

- Dosing for target INR~1.5

<table>
<thead>
<tr>
<th>INR</th>
<th>Octaplex dose</th>
<th>70 kg patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>20 IU/kg</td>
<td>1400 IU ~ 3 vials (1500 IU)</td>
</tr>
<tr>
<td>3-6</td>
<td>30 IU/kg</td>
<td>2100 IU ~ 4 vials (2000 IU)</td>
</tr>
<tr>
<td>&gt;6</td>
<td>40 IU/kg</td>
<td>2800 IU ~ 5-6 vials (2500-3000 IU)</td>
</tr>
</tbody>
</table>

- Add 10 IU/kg for target INR<1.2

Hamilton Regional Laboratory Medicine Program guidelines, 2007
ACCP recommendations

• “In patients who require temporary interruption of a VKA before surgery or a procedure and whose INR is still elevated (i.e., ≥ 1.5) 1 to 2 days before surgery, we suggest administering low-dose (i.e., 1 to 2 mg) oral vitamin K to normalize the INR instead of not administering vitamin K (Grade 2C)”
In practice...

1) Check patient’s INR
2) Hold further doses of warfarin
3) Assess how quickly normal hemostasis needs to be achieved
   • Urgent: Octaplex and vitamin K (IV)
   • Non-urgent: vitamin K (IV or po)
4) Can re-measure INR – Octaplex reliably reverses INR within minutes of infusion; 6 hours after IV vitamin K or 12 hours after po vitamin K
5) Assess if further FP or vitamin K is required
Bridging anticoagulant therapy
Anticoagulant options for bridging therapy

- Bridging requires an anticoagulant that is short-acting

- Current available options include heparin, low molecular weight heparin (LMWH) and fondaparinux

- Most bridging studies have used therapeutic dose LMWH (~70%); prophylactic dose LMWH in ~20% and therapeutic dose UFH in ~10%
Assessment of thrombotic risk

- Stratify each indication for anticoagulation into:

  - Low risk
  - Moderate risk
  - High risk
Mechanical heart valves

- Caged ball
- Tilting disc
- Bileaflet

Older generation valves associated with higher TE risk
Thromboembolic risk with mechanical heart valves

- Difficult to estimate; much data rests with older valves which were likely more thrombogenic than modern valves

- Mathematical modelling of risk based on an annual risk of arterial thromboembolism (stroke, arterial embolism) in patients not receiving VKA of 17% = 0.046%/day

- Estimated risk of 0.4% for 8 days when patients are not receiving VKA

Thromboembolic risk in chronic atrial fibrillation

- Risks based on randomized placebo controlled trials that assessed aspirin and VKA in patients with atrial fibrillation

- Mathematical modelling of risk based on average annual risk of stroke of 5% = 0.013%/day

- Estimated risk of 0.1% for 8 days when patients are not receiving VKA

- Clinical prediction rules can help risk stratify patients

CHADS\textsubscript{2} score

Score **1 point** each for:
- Congestive heart failure
- Hypertension
- Age $>$ 75 years
- Diabetes

Score **2 points** given for:
- Prior stroke

Score
- **0-2**: Low risk
  - $<$5\% per year
- **3-4**: Moderate risk
  - 5-10\% per year
- **5-6**: High risk
  - $>$10\% per year

Gage BF et al. JAMA 2001;285:2864-70
Thromboembolic risk in patients with prior VTE

- Risks differ from mechanical heart valve and atrial fibrillation patients – risk based on recurrent VTE, not arterial TE

- Prophylactic dose anticoagulation does decrease risk of postoperative VTE; stronger rationale for using prophylactic LMWH or UFH in these patients

- Risk assessment based on risk of recurrence after starting anticoagulation and risk of recurrence after anticoagulants have stopped

## Low risk patients (<4%/yr)

<table>
<thead>
<tr>
<th>Mechanical heart valve</th>
<th>Atrial fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bileaflet aortic valve without atrial fibrillation or no other risk factors for stroke</td>
<td>• CHADS$_2$ score 0-2 (and no prior stroke or transient ischemic attack)</td>
<td>• Single VTE occurring &gt; 12 months ago and no other risk factors</td>
</tr>
</tbody>
</table>

*CHADS2 = Congestive heart failure, hypertension, age > 75, diabetes, stroke

## Moderate risk patients (4-10%/yr)

<table>
<thead>
<tr>
<th>Mechanical heart valve</th>
<th>Atrial fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bileaflet aortic valve and 1 risk factor (atrial fibrillation, prior stroke/TIA, HTN, DM, CHF, age &gt; 75 yrs)</td>
<td>• CHADS$_2$ score 3-4</td>
<td>• VTE occurring in past 3-12 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Nonsevere thrombophilic conditions*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Recurrent VTE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Active cancer (treated within 6 mo or palliative)</td>
</tr>
</tbody>
</table>

- Heterozygous factor V Leiden, heterozygous prothrombin mutation
# High risk patients (>10%/yr)

<table>
<thead>
<tr>
<th>Mechanical heart valve</th>
<th>Atrial fibrillation</th>
<th>VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral valve</td>
<td>CHADS₂ score 5-6</td>
<td></td>
</tr>
<tr>
<td>Older aortic valve</td>
<td>Stroke/TIA within 3 mo</td>
<td>VTE within 3 mo</td>
</tr>
<tr>
<td>- Caged ball</td>
<td>Rheumatic valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>- Tilting disc</td>
<td></td>
<td>Severe thrombophilic conditions*</td>
</tr>
<tr>
<td>Stroke/TIA within 6 mo</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- CHADS₂ score
- Stroke/TIA within 3 mo
- Rheumatic valvular heart disease
- VTE within 3 mo
- Severe thrombophilic conditions*

- Protein C/S deficiency, AT deficiency, antiphospholipid antibodies, multiple abnormalities
ACCP recommendations

“In patients with a mechanical heart valve or atrial fibrillation or VTE at high risk for thromboembolism, we recommend bridging anticoagulation with therapeutic dose SC LMWH or IV UFH over no bridging during temporary interruption of VKA therapy (Grade 1C); we suggest therapeutic-dose SC LMWH over IV UFH (Grade 2C)”
ACCP recommendations

• “In patients with a mechanical heart valve or atrial fibrillation or VTE at moderate risk for thromboembolism, we recommend bridging anticoagulation with therapeutic dose SC LMWH, therapeutic-dose IV UFH, or low dose SC LMWH over no bridging during temporary interruption of VKA therapy (Grade 2C); we suggest therapeutic-dose SC LMWH over other management options (Grade 2C)”
ACCP recommendations

• “In patients with a mechanical heart valve or atrial fibrillation or VTE at low risk for thromboembolism, we suggest low-dose SC LMWH or no bridging over bridging with therapeutic-dose SC LMWH or IV UFH (Grade 2C)”
Timing of the last dose prior to surgery

IV UFH
- Half life = 45 min
- Stopping 4 h before surgery = 5 elimination half-lives

SC LMWH
- Half-life = 4-5 h
- Last dose 20-25 h before surgery (the morning of the day before surgery) = 5 elimination half-lives
  - Prospective cohort, n=98 with enoxaparin 1 mg/kg bid found residual anticoagulant effect in all patients at the time of surgery; 34% had therapeutic range anti-Xa
  - Prospective study, n=73 with od or bid dosing found 30% of patients receiving therapeutic dose LMWH had residual anticoagulant effect at time of surgery

ACCP recommendations

• “In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH, we recommend administering the last dose of LMWH 24 h before surgery or a procedure over administering LMWH closer to surgery (Grade 1C); for the last preoperative dose of LMWH, we recommend administering approximately half the total daily dose instead of 100% of the total daily dose (Grade 1C). In patients who are receiving bridging anticoagulation with therapeutic dose IV UFH, we recommend stopping UFH approximately 4 h before surgery over stopping UFH closer to surgery (Grade 1C)”
Assessment of bleeding risk

- Stratify by surgery type:
  - Low risk
  - Moderate risk
  - High risk
Bleeding risk

- No validated way of quantifying bleeding risk

- Postoperative bleeding based on patient characteristics, type of surgery and postoperative hemostasis

1) Patient characteristics
   - Underlying bleeding diathesis
     - INR >1.5 (important only if INR >3)*
     - Platelets: 50,000-100,000
   - Use of concomitantly drugs affecting hemostasis
     - ASA, clopidogrel, ticlopidine, dipyridamole
     - NSAIDs, COX-2

*Torn & Rosendaal Br J Hematol 2003;123:676
Bleeding risk

2) Type of surgery

- Surgery types associated with high bleeding risk:
  - CABG or valve replacement
  - Intracranial or spinal surgery
  - Aortic aneurysm repair
  - Peripheral bypass/vascular surgery
  - Hip/knee replacement
  - Major reconstructive plastic surgery
  - Major cancer surgery
  - Prostate/bladder surgery
Factors to consider in assessing bleeding risk

- **Vascularity** of operative site
  - Hepatic tumour resection, parathyroid/thyroid resection, H&N surgery, vascular surgery (AAA repair, lower limb bypass)

- **Size** of operative field
  - Large field procedures: major orthopedic and plastic surgery

- **Use of sutures** or other hemostatic techniques
  - GI endoscopic procedures (polypectomy)
  - Vascular access procedures (pacemaker/defibrillator implantation, AV fistula or graft repair/declotting)
  - Skin grafts (facial)
Balancing thrombotic and bleeding risks: Pre-op

<table>
<thead>
<tr>
<th>Thrombotic risk</th>
<th>Bleeding risk</th>
<th>Need for bridging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>No / Maybe</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>Maybe</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>
Balancing thrombotic and bleeding risks: Post-op

Thrombotic risk | Bleeding risk | Need for bridging
--- | --- | ---
Low | Low | No
Moderate | Moderate |
High | High |
Balancing thrombotic and bleeding risks: Post-op

- Thrombotic risk
  - Low
  - Moderate
  - High

- Bleeding risk
  - Low
  - Moderate
  - High

- Need for bridging
  - Yes
What is the clinical impact of bleeding after surgery?

- Bleeding may have more serious consequences after surgery

- Bleeding usually occurs at the operative site
  - Need for emergency re-operation: associated CV risks
  - Increased postoperative complications, duration of hospitalization

- Bleeding may require transfusion of blood products
Bridging anticoagulation protocol
Bridging protocol: Before procedure

- Day -5 .................................. stop warfarin
- Day -3 ................................. start LMWH (or UFH)
  - High TE risk: enoxaparin 1 mg/kg sc BID
  - Low-moderate TE risk: enoxaparin 40 mg sc OD
    (alternative LMWHs: dalteparin, tinzaparin)
  - UFH in patients with CrCl < 30 mL/min
- Day -1 ............................... re-check INR (if possible)
  - If INR 1.6-1.9 ~1-2 mg oral vitamin K
  - If INR 1.3-1.5 +/-1 mg oral vitamin K
  (Need to provide vitamin K to patient in case INR elevated)
Bridging protocol: Day of procedure

- Assess wound hemostasis and risk for ongoing bleeding
- Decide when to resume bridging therapy
- Consider resuming warfarin on evening of procedure
  - Usual dose for that day
  - Double usual dose if pre-op vitamin K administered
Bridging protocol: Post - procedure

- Day 0 or +1 .................. resume warfarin
- Day +1 ........................ restart LMWH
  - Adequate hemostasis after low-moderate bleeding risk procedure
- Day +2 or +3 ................ re-start LMWH
  - If adequate hemostasis after high bleeding risk procedure

- May withhold LMWH altogether if
  - Hemostasis not secured
  - Selected high bleeding risk procedures
Re-initiating anticoagulation
Postoperative anticoagulation

Heparin/LMWH

- Therapeutic LMWH and IV UFH with bolus and infusion will result in detectable anticoagulant effect within 1 h, peak effect in 3-5 h

- In assessing bleeding risk associated with starting heparin/LMWH, consider how much time has passed since surgery, the dose of UFH/LMWH, and the type of surgery and the adequacy of hemostasis
Postoperative anticoagulation

Warfarin

- Takes 2-3 days (48 h) for anticoagulant effect to start, and 5-7 days for full antithrombotic effect

Prospective studies evaluating starting VKA:
- $N = 650$, resumed VKA at usual dose postop; mean duration to therapeutic INR = 5.1 days*
- $N = 224$, doubled usual dose for initial 2 days; mean duration to therapeutic INR = 4.6 days**

Follow-up post discharge

• Most patients have INR monitoring and warfarin dosing done through their family physician
  – Limited number may be followed through specialized anticoagulant clinics
• Many will have subtherapeutic INR at time of hospital discharge
• May need to contact the family physician and ensure appropriate follow up
ACCP recommendations

“In patients undergoing a minor surgical or other invasive procedure and who are receiving bridging anticoagulation with therapeutic dose LMWH, we recommend resuming this regimen approximately 24 h after (eg, the day after) the procedure when there is adequate hemostasis over a shorter (eg, < 12 h) time interval (Grade 1C)”
ACCP recommendations

• “In patients undergoing a major surgery or a high bleeding risk surgery/procedure and for whom postoperative therapeutic dose LMWH/UFH is planned, we recommend either delaying the initiation of therapeutic dose LMWH/UFH for 48-72 h after surgery when hemostasis is secured, administering low dose LMWH/UFH after surgery when hemostasis is secured, or completely avoiding LMWH or UFH after surgery over the administration of therapeutic dose LMWH/UFH in close proximity to surgery (Grade 1C)”
ACCP recommendations

• “In patients who have had temporary interruption of VKA before surgery or a procedure, we recommend resuming VKAs approximately 12 to 24 h (the evening of or the next morning) after surgery and when there is adequate hemostasis over resumption of VKAs closer to surgery (Grade 1C)"
Summary

1) Reversing anticoagulation (VKA) can be done using vitamin K, Octaplex or FP depending on the need for rapidity

2) Prevention of bleeding = prevention of VTE
   • Major bleeding will delay resumption of anticoagulant therapy
   • Associated risk of TE may be considerable

3) Prevention of VTE = prevention of bleeding
   • Aggressive prophylaxis against VTE will reduce incidence of VTE – which mandates therapeutic range anticoagulation (which carries a higher bleeding risk than prophylactic dose anticoagulation)
Summary

4) An approach to assessing thromboembolic and bleeding risks is important to minimize patient morbidity/mortality
   • > 4 million patients from North America and Europe take warfarin

5) Anticoagulant management extends beyond hospital discharge – requires communication with primary care physicians