Perioperative Management of Warfarin Interruption

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Faculty Disclosures

There are no actual or potential conflicts of interest associated with this presentation.

Learning Objectives

- Review recommendations for when to interrupt warfarin therapy
- Review guidelines for determining thromboembolic risk
- Review recommendations for bridging therapy implementation
- Review cases for appropriate method to manage warfarin interruption based on risk stratification
- Identify case-specific monitoring parameters for anticoagulation bridge therapy

What's the hype about interrupting warfarin therapy?

- Anticoagulation serves an important role in reducing the risk of thromboembolism or stroke
- A number of patients are at risk of developing arterial or venous thromboembolism if warfarin therapy needs to be withheld.
- Patients will eventually need to undergo some type of procedure.
- Perioperative management is a common clinical problem.

What do we do?

Ask the Audience

- Warfarin therapy must be interrupted for all surgical procedures?
  a. True
  b. False
  c. Not sure

What is bridging therapy?

- “In the absence of a universally accepted definition, we define bridging anticoagulation as the administration of a short-acting anticoagulant, for an ~10-12 day period during interruption of VKA therapy when the INR is not within a therapeutic range”.

Chest 2012; 141: e326S-e350S
Who is a candidate for bridging?
Ask yourself 3 questions…

- Does warfarin need to be withheld?
- What is the patient’s risk for clotting?
- What is the patient’s risk for bleeding?

Does warfarin need to be withheld?

- Continue warfarin:
  - Dental procedures (2C)
  - Cataract Removal (2C)
  - Endoscopy (diagnostic)
  - Joint injections*
    - Knees, wrist, hip
  - Minor dermatologic procedures (2C)
    - Consider procedures that do not pose increased bleeding risk while on warfarin

Discontinue warfarin:

- Orthopedic surgeries
  - TKR, THR
- Biopsy
  - Breast, Lung
- Neurosurgery
- Hernia Surgery
- Colonoscopy
  - Family history of cancer/polyps

Ask the Audience

- To assess the risk of clotting, we need to review?
  a. The patient’s warfarin indication
  b. The type of procedure
  c. Co-morbidities
  d. All of the above

What is the patients’ risk of clotting?

- Considerations
  - Underlying indication for warfarin therapy
  - Patient’s risk factors for thromboembolism
    - Morbid obesity, hypercoagulable state, immobility
  - Duration of anticoagulation cessation
    - MHV – TE risk 0.046%/day
    - A fib – TE risk 0.013%/day

- There are no validated risk stratification tools to determine the risk of perioperative thromboembolism.

- "Only limited data exist to aid clinicians in classifying which patients are sufficiently high risk for thromboembolism to warrant the risk and cost of full (therapeutic) doses of heparin products perioperatively".

- "Standardizing periprocedural anticoagulation management for VTE patients has not been adequately defined by either randomized, controlled trial data or observational cohorts".

- Now what?.........
Thrombosis Risk

- Chest guidelines
  - Evidence based practice guidelines which incorporate data from existing literature.
  - Atrial fibrillation
  - Mechanical Heart Valves
  - VTE

- Most common indications for long term anticoagulation

Risk Stratification for Perioperative TE

<table>
<thead>
<tr>
<th>Risk</th>
<th>Mechanical Heart Valve</th>
<th>Atrial Fibillation</th>
<th>Venous Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Any Mitral Valve Prosthesis. Caged-ball or tilting disk aortic valve prosthesis. Strokes/TIA within previous six months.</td>
<td>CHADS2: 3-4</td>
<td>VTE within past 3-12 months, recurrent VTE, Active cancer (within 6 months), Non-valvular thrombophilia (heterozygous Factor V Leiden mutation).</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Bileaflet aortic valve prosthesis and any of the following: a. prior stroke/TIA, HTN, DM, CHF, age &gt;75</td>
<td>CHADS2: 5-6, Stroke, or DM within 1 months, mycotic aortic heart disease.</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Bileaflet aortic valve prosthesis without war and no other risk factors for stroke</td>
<td>CHADS2: 0-2, No prior stroke or TIA</td>
<td></td>
</tr>
</tbody>
</table>

What is CHADS2 Scoring?

- Clinical prediction rule for estimating the risk of stroke in patients with nonrheumatic atrial fibrillation.
- Used to determine the degree of anticoagulation needed.

Ask the Audience

- Which is the correct description of CHADS2 scoring?
  a. CHF, hypertension, age >65, DM, prior history of stroke
  b. Cardiomyopathy, hypertension, age >75, DM, prior history of stroke
  c. CHF, hypertension, age > 75, DM, prior history of stroke
  d. CHF, hyperlipidemia, age >75, DM, prior history of stroke

CHADS2 Score

<table>
<thead>
<tr>
<th>CHADS2 Risk Criteria</th>
<th>Score</th>
<th>Total Score</th>
<th>Risk Level</th>
<th>Stroke Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>1</td>
<td>0-2</td>
<td>Low</td>
<td>1.9-4</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>1-3</td>
<td>Intermediate</td>
<td>5.9-8.5</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td></td>
<td>1</td>
<td>Intermediate</td>
<td>5.9-8.5</td>
</tr>
<tr>
<td>DM</td>
<td>1</td>
<td>1-5</td>
<td>High</td>
<td>12.5-18.2</td>
</tr>
<tr>
<td>Stroke/TIA</td>
<td>2</td>
<td>2-6</td>
<td>High</td>
<td>12.5-18.2</td>
</tr>
</tbody>
</table>

CHEST 2012
ACC/AHA/ESC 2006
Gage, BF
What about CHA²DS²VASc?

- Refinement of CHADS²
  - Additional common stroke risk factors
    - Female gender, vascular disease, age range 65-74
- Max score is 9
  - More patients classified as high risk?
  - Score >/= 2 may benefit from anticoagulation therapy
  - More patients require bridging for warfarin interruption?

Case #1 – GH

- GH is a 66 year old male on indefinite warfarin therapy for a h/o multiple DVT’s with an INR range of 2-3. PMH includes HTN, hyperlipidemia, diverticulitis. GH is scheduled for colon resection.
  1) What is GH’s TE risk level when warfarin is withheld?
  2) What perioperative plan should be implemented?

GH’s risk?

- Thromboembolic
  - Intermediate
  - h/o recurrent DVT’s

Risk Stratification for Perioperative TE

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<th>Venous Thromboembolism</th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td>Any Mitral Valve Prosthesis, Caged-ball or tilting disk aortic valve prosthesis, Stroke/ TIA within previous six months</td>
<td>CHADS₂: 5-6, Stroke or TIA within 3 months, Malignant vascular heart disease</td>
<td>VTE within 3-12 months, Severe thrombophilia (protein C, S or antithrombin deficiency), APA</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Bileaflet aortic valve prosthesis and any of the following: afib, prior stroke/TIA, HTN, DM, CHF, age &gt;75</td>
<td>CHADS₂: 3-4</td>
<td>VTE within 3-12 months, recurrent VTE, Active cancer (treated within 6 months), Non-severe thrombophilia (heterozygous Factor V Leiden mutation)</td>
</tr>
<tr>
<td>Low</td>
<td>Bileaflet aortic valve prosthesis without afib and no other risk factors for stroke</td>
<td>CHADS₂: 0-2</td>
<td>No prior stroke or TIA</td>
</tr>
</tbody>
</table>

Risk level has been determined….

Let’s review pre and post procedure/surgical plan
Pre Procedure Plan

- **Low TE Risk**
  - Hold warfarin 5 days prior to procedure (Grade 1C)
  - No Bridging (Grade 2C)
  - Check INR 1 day prior to procedure
  - If INR > 1.5, consider administering 1mg po Vitamin K

- **Intermediate TE Risk**
  - Bridging or no-bridging approach chosen is based on an assessment of individual patient and surgery related factors
  - No grade assigned
  - Consider patient/surgery related criteria

- **High TE Risk**
  - Bridging anticoagulation suggested instead of no bridging (Grade 2C)
  - Refers to therapeutic dose bridging regimen - most widely studied and used in clinical practice
Types of Bridging Strategies
- High dose (therapeutic dose)
  - similar to that used in acute TE
- Low dose (prophylactic dose)
  - doses used typically to prevent postop VTE or prophylaxis in hospitalized patients
- Intermediate dose
  - between high and low

NOACs for Bridging?
- Fast onset and offset
- No need for injection as the currently available NOACs for Afib and VTE are oral

The use of NOACs has not been adequately studied as a bridging agent and are not currently recommended at this time for bridging. Safety and Efficacy unknown for this purpose.

Implementing bridging
- What does the provider need to know before implementation of LMWH?
  - Allergies
  - Weight
  - Creatinine Clearance
  - Platelet count
  - INR

William W Backus Hospital Anticoagulation Clinic
- Bridging protocol
  - Intermediate/High Risk
    - hold warfarin 5 days prior to procedure
    - initiate enoxaparin 1.5mg/kg sc daily when INR is below the patients defined therapeutic range
    - Day prior to procedure, administer 0.75mg/kg

Post Procedure
- Anticipate bleeding risk (preop) and hemostasis (postop)
- Factors affecting the risk for surgery related bleeding:
  - How close to surgery is the anticoagulant administered?
  - What is the dose of anticoagulant?
  - What type of surgery and its bleeding risk?

Procedures associated with HIGH bleeding risk
- Major surgery - expected duration> 1 hr
- Bowel resection or any major abdominal procedure
- Kidney biopsy
- Radical Prostatectomy
- Neurosurgical
- Heart valve replacement
- Joint replacement

CHEST 2008, 305s
Bleeding and Bridging

- Various clinical data suggests major bleeding can occur up to 20% in cases of vascular surgery or major surgeries.
- “…consider consequences of thromboembolism or major bleed when developing a periprocedural anticoagulant management strategy”.

Bleeding and Bridging Continued

- PROSPECT Trial, Dunn et al.
  - Prospective, multicenter, cohort study.
  - 260 patients, 24 sites
  - Afib and DVT patients received bridging with full dose enoxaparin
  - “…bleeding risk varied markedly by the extensiveness of procedure: incidence of major bleeding - invasive procedures 0.7%, minor surgery 0%, major surgery 20%.”

The BRIDGE Study

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

- Randomized double blind placebo controlled
- Elective or scheduled procedures
- US & Canada, 108 sites
- Patients with atrial fibrillation, mean CHADS2 = 2.3
  - 38% had a CHADS2 score >/= 3
- Warfarin held x 5 days prior to procedure
- Randomized to LMWH (Dalteparin) vs placebo injection
  - Total of 1884 patients randomized, 950 placebo injection, 934 Dalteparin
  - Injection started 3 days before procedure until 24 hours prior to procedure
- Post procedure
  - Bridged with placebo or LMWH with warfarin
  - Patients followed for 30 days post procedure

BRIDGE Study Results

- Placebo vs LMWH
  - Risk of stroke - holding warfarin alone non-inferior to bridging
  - Incidence of arterial thromboembolism
    - of 108 interruptions bridged, 13% had a bleeding event: 3.7% major; 9.3% significant, non major
- Limitations
  - No prosthetic valve or VTE patients
  - % of group male - think CHA2DS2VASc
  - Less patients in the non-bridge group had a stroke
Bruise Control
Pacemaker or Defibrillator Surgery without Interruption of Anticoagulation

- Multicenter, single blind, RCT
- Randomly assign patients with annual TE risk $\geq 5\%$ to continue warfarin or bridge with heparin
- Primary outcome – clinically significant device pocket hematoma

Bruise Control Results

- 681 pts randomized
- 343 continue warfarin vs 338 bridge with IV heparin or full dose LMWH
- Primary outcome
  - 3.5\% in the continue warfarin arm developed pocket hematoma vs 16\% in the bridging arm
  - $P < 0.001$
- Continue warfarin arm reported increased satisfaction with AC therapy
  
Authors do not apply results to patients on NOACs

Post Procedure

For Warfarin
- Resume warfarin approximately 12-24 hours after surgery (evening of or next morning) and when adequate hemostasis achieved (Grade 2C)
- LMWH
  - As per risk selection for bleeding

Post Procedure

Low risk patient (William W Backus Hospital protocol)
- Resume warfarin the evening of the procedure at usual dosing
- Follow-up INR check ~ 1 week after resumption of warfarin

Post Procedure

Intermediate/High Risk

<table>
<thead>
<tr>
<th>Minor Surgery/Low Bleeding Risk</th>
<th>Moderate Bleeding Risk</th>
<th>High Bleeding Risk</th>
<th>Very High Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resume enoxaparin 1.5mg/kg/day 24 hrs post procedure</td>
<td>Resume enoxaparin 1.5mg/kg/day 48 hours after procedure</td>
<td>Enoxaparin 40mg daily starting 24 hours after procedure</td>
<td>No post-procedure enoxaparin</td>
</tr>
</tbody>
</table>

Resume warfarin day of procedure

Continue enoxaparin post procedure, if ordered, until INR within therapeutic range for two consecutive days

Monitoring in the bridging patient
- Intermediate/High Risk

| - Begin INR testing 3-5 days after restarting warfarin, then daily until INR therapeutic x 2 consecutive days |
| - Repeat platelet count 5-14 days after initiation of LMWH |
| - HIT - rare with use of enoxaparin ( \sim 3\% risk) |
| - DC enoxaparin if platelet count < 100,000/mm$^3$ or 50\% or more decrease of platelet count from baseline |
| - Bruising or bleeding |

CHEST 2008
**Ask the Audience**

- Routine monitoring of AntiXa levels is necessary for LMWH bridging patients?
  - a. True
  - b. False

**Monitoring continued**

- Anti Xa monitoring may be considered if...
  - Severe renal insufficiency
    - CrCl < 30mL/min or SCr > 2 g/dL
  - Extremes of body weight

Chest guidelines suggest against the routine use of Anti Xa levels to monitor the anticoagulant effect of LMWH during bridging (Grade 2 C)

**GH – Intermediate risk for TE/High bleeding risk surgery**

- Pre procedure
  - Hold warfarin 5 days prior to procedure
  - Initiate enoxaparin 1.5mg/kg sc daily when INR is below patients established INR range
  - Day before procedure initiate 0.75mg/kg sc x1

- Post Procedure
  - Restart warfarin night of procedure at usual dosing
  - Enoxaparin 40mg sc daily 24 hours after procedure
  - Continue enoxaparin bridge until INR therapeutic x 2 consecutive days
    or at discretion of treating MD; hemostasis should be assured

**GH’s Bridge Plan - PRE**

<table>
<thead>
<tr>
<th>Date</th>
<th>Warfarin dose</th>
<th>INR</th>
<th>Enoxaparin dose</th>
<th>Plt count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 5 pre</td>
<td>0</td>
<td></td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 4 pre</td>
<td>0</td>
<td>2</td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 3 pre</td>
<td>0</td>
<td>1.8</td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 2 pre</td>
<td>0</td>
<td></td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 1 pre</td>
<td>0</td>
<td></td>
<td>Goal &lt; 1.5</td>
<td>0.75mg/kg sc x1</td>
</tr>
<tr>
<td>Day 0 – Surgery</td>
<td>5mg</td>
<td></td>
<td>HOLD</td>
<td></td>
</tr>
</tbody>
</table>

**GH’s Bridge Plan - POST**

<table>
<thead>
<tr>
<th>Date</th>
<th>Warfarin dose</th>
<th>INR</th>
<th>Enoxaparin dose</th>
<th>Plt count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 post</td>
<td>5mg</td>
<td>1</td>
<td>40mg sc daily</td>
<td>ORDER</td>
</tr>
<tr>
<td>Day 2 post</td>
<td>5mg</td>
<td>1.4</td>
<td>40mg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 3 post</td>
<td>5mg</td>
<td>1.7</td>
<td>40mg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 4 post</td>
<td>5mg</td>
<td>2.1</td>
<td>40mg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 5 post</td>
<td>5mg</td>
<td></td>
<td>40mg sc daily</td>
<td></td>
</tr>
</tbody>
</table>

Continue post procedure bridge until INR therapeutic x 2 consecutive days.

**Case #2 MJ – Risk Selection**

- MJ is an 80 year old male on warfarin indefinitely for atrial fibrillation with an INR range of 2-3. PMH includes hypertension and overactive bladder.
- MJ is scheduled for colonoscopy and gastroenterologist wants warfarin held.
- What is his risk for clot? What plan should be implemented?
Ask the Audience

What is MJ's TE risk?
- a. low
- b. intermediate
- c. high

Case #1- MJ.....
- CHADS2 Score
  - HTN, Age >75
- Score = 2 = Low Risk

Case #3 - CC
- CC is a 84 year old male on warfarin indefinitely for the diagnosis of mechanical AVR, INR goal 2-3. PMH includes atrial fibrillation, hypertension, and CKD. CC is scheduled for Left Total Knee Replacement.
- How should CC’s warfarin therapy be managed for surgery - what is his TE risk?

Ask the Audience

CC's TE risk can be classified as
- a. low
- b. intermediate
- c. high

Evaluating Risk for Thromboembolism
CC’s Risk

- Thromboembolic
  - Intermediate
    - AVR + Afib + HTN + age > 75
- Bleeding Risk
  - Moderate selected (high per outline)

CC’s Bridge Plan - PRE

<table>
<thead>
<tr>
<th>Date</th>
<th>Warfarin dose</th>
<th>INR</th>
<th>Enoxaparin dose</th>
<th>Plt count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0 – Surgery</td>
<td>7.5mg</td>
<td></td>
<td>0.75mg/kg sc</td>
<td>HOLD</td>
</tr>
<tr>
<td>Day 1 pre procedure</td>
<td>0</td>
<td></td>
<td>Goal &lt; 1.5</td>
<td></td>
</tr>
<tr>
<td>Day 2 pre procedure</td>
<td>0</td>
<td>1.7</td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 3 pre procedure</td>
<td>0</td>
<td></td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 4 pre procedure</td>
<td>0</td>
<td></td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 5 pre procedure</td>
<td>0</td>
<td></td>
<td>1.5mg/kg sc daily</td>
<td></td>
</tr>
</tbody>
</table>

CC’s Bridge Plan - Post

<table>
<thead>
<tr>
<th>Date</th>
<th>Warfarin dose</th>
<th>INR</th>
<th>Enoxaparin dose</th>
<th>Plt count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 post procedure</td>
<td>5mg</td>
<td>1.5</td>
<td>Resume 1.5mg/kg sc daily</td>
<td>ORDER</td>
</tr>
<tr>
<td>Day 2 post procedure</td>
<td>7.5mg</td>
<td>1.8</td>
<td>2.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 3 post procedure</td>
<td>5mg</td>
<td>2</td>
<td>2.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 4 post procedure</td>
<td>7.5mg</td>
<td></td>
<td>2.5mg/kg sc daily</td>
<td></td>
</tr>
<tr>
<td>Day 5 post procedure</td>
<td>7.5mg</td>
<td></td>
<td>2.5mg/kg sc daily</td>
<td></td>
</tr>
</tbody>
</table>

Continue post procedure bridge until INR therapeutic x2 consecutive days

Summary of Perioperative Management for Warfarin Interrupted Patients

- Low TE risk patient
  - Hold warfarin 5 days prior to procedure
  - Resume warfarin night of procedure or when hemostasis assured

- Intermediate/High TE risk patient
  - Hold warfarin 5 days prior to procedure
  - Start LMWH when INR below defined range
  - Resume warfarin night of procedure or when hemostasis assured
  - Resume LMWH 24 hours after procedure or when hemostasis assured
  - Discontinue LMWH when INR in therapeutic range

LMWH

- Enoxaparin
  - Anti Xa and antithrombin effects
  - T1/2: 7 hours
  - Weight based dosing (ABW)
  - Thrombocytopenia risk < 3%
  - Risk major hemorrhage 4% or less
  - Dosing: 1.5mg/kg sc daily or 1mg/kg sc bid

- Dalteparin
  - Anti Xa and antithrombin effects
  - T1/2: 3-5 hours
  - Weight based dosing (ABW)
  - Thrombocytopenia risk < 1%
  - Risk major hemorrhage 0-4.6%
  - Dosing: 100 IU/kg sc bid 24 hr, Max 18,000 IU
  - Dosage based on TBW up to 190kg

Other Injectables

- Fondaparinux
  - Inhibitor of factor Xa
  - T1/2: 17-21 hours
  - Fixed dosing
  - Thrombocytopenia risk – 0.5% up to 3%
  - Risk of major hemorrhage < 3%; up to 5% in pts < 50kg
  - Body weight
    - < 50kg: 5mg
    - 50-100kg: 7.5mg
    - >100kg: 10mg
  - SC once daily dosing
Other considerations

- Who will perform injections?
- Does patient have RX coverage?
- Is patient homebound following surgery?
- Does patient understand instructions?
  - Provide written instructions

Down the pipeline

- PERIOP-2
  - Double blind randomized controlled trial of Post-Operative LMWH Bridging Therapy vs Placebo Bridging Patients Who Are at High Risk for Arterial TE

Summary

- Determine if warfarin needs to be withheld for procedure
- Determine risk for thromboembolism
- Determine bleeding risk
  - Pre and post procedure
  - Hemostasis achieved
- Implement monitoring parameters
- Patient education and teaching is important throughout entire perioperative period
- CHEST guidelines are just that...GUIDELINES
  - There is no one standardized bridging strategy to date

Thank you

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