How to Manage Patients Who Need a Procedure
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Mayo Clinic Rochester

Learning objectives:
Oral Direct Factor Inhibitors
To appreciate:
1. The nature of the problem
2. The published bleeding and thromboembolic event rates
3. Our general approach to peri-procedural AC management

Nature of the Problem
• 6,000,000 patients on chronic anticoagulants in U.S. today
• ~ 10% annually require an invasive procedure.

Bridging Therapy
Heparin substitution during warfarin interruption

Warfarin Bridging Metaanalysis
• 34 studies, 1 RCT.
• 2004 forward
• Event Rates:
  • Thromboembolism 0.9%. Major bleeding 4%.
  • "Bridging" Heparin
    • Increased major bleeding 3.6 fold.
    • No obvious impact on thromboembolism rates.
Oral Direct Factor Inhibitors

Fibrinogen → Fibrin

Thrombin → Dabigatran

Prothrombin → Va → Xa

Apixaban → Va → Xa

Rivaroxaban → Xa

Dabigatran → X

FDA Approved Indications

• Dabigatran
  - Atrial Fibrillation

• Rivaroxaban
  - Atrial Fibrillation
  - Venous thrombosis

• Apixaban
  - Atrial Fibrillation

No FDA approval for **mechanical heart valves**!

Uptake of Novel Anticoagulants

Direct Factor Inhibitor Uptake

• ~ 2,000,000 patients in US.
  - Dabigatran $827 million (2013)
  - Rivaroxaban $847 million (2013)
  - Apixaban $615 million (2016)

• 200,000 patients will require peri-procedural management of a direct factor inhibitor in 2014.

Interpreting the “Peri-procedure” Literature

Acknowledge:

• Anticipated annual bleeding and thrombosis rates **without** a procedure

Bayer, Johnson & Johnson, Pfizer 2013
Anticipated Annual Event Rates
Apart from a Procedure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke/Emboli</th>
<th>Major Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>1.1%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1.7%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Apixaban</td>
<td>1.3%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>


Interpreting the “Peri-procedure”
Literature

Acknowledge:
• Annual bleeding and thrombosis rates without a procedure
• Procedure-specific bleeding and thrombosis rates without a chronic anticoagulation.

Surgical Bypass Grafting

<table>
<thead>
<tr>
<th>Complications within 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
</tbody>
</table>

Ann Vasc Surg. 2010 Apr 1

Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Complications within 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
</tbody>
</table>

Diagnostic Endoscopy

Including biopsy
| Bleeding | <1.0% |

Polypectomy

Including biopsy
| Bleeding | 1.0 – 5.0% |
Interpreting the “Peri-procedure” Literature

**Acknowledge:**

- Annual bleeding and thrombosis rates without a procedure
- Procedure-specific bleeding and thrombosis rates without a chronic anticoagulation.
- Event rates must be interpreted in the context of duration of follow up.

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis (04)</td>
<td>215</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Pengo (09)</td>
<td>190</td>
<td>1 month</td>
</tr>
<tr>
<td>Kovacs (04)</td>
<td>112</td>
<td>3 months</td>
</tr>
<tr>
<td>Hammerstringl (07)</td>
<td>116</td>
<td>1 month</td>
</tr>
<tr>
<td>Daniels (2007)</td>
<td>556</td>
<td>3 months</td>
</tr>
</tbody>
</table>

**Time Frame varies by Study**

ISTH Guideline: Reporting Standards

- Risk stratification
- Procedure description
- Major event definition
- Time-frame for events

“Harmonized reporting would facilitate across-study comparisons, enable meta-analysis, allow robust assessments of benefits and risks of different peri-procedural antithrombotic strategies.”

**Bleeding Definitions**

**Major bleeding**

- Hemoglobin drop ≥ 2 g/dL
- Transfusion ≥ 2 units pRBCs
- Intraocular, intracerebral, or retroperitoneal bleed
- Fatal

**Non-major clinically relevant**

- Medical intervention required
- Unscheduled physician contact
- Drug discontinuation
- Pain or impairment of daily activities

**ROCKET AF Trial: Temporary Anticoagulant Interruption**

- 4,692 Patients
  - 7555 interruptions
  - 40% underwent an invasive procedure
  - Median interruption: 5 days
  - Majority stopped ≥ 3 days prior to procedure.
  - Bridging therapy used in 9% (left to investigator discretion)

**What are the published peri-procedural event rates for patients taking a oral direct factor inhibitor?**

Circulation. February 19, 2014;
Rivaroxaban Interruption: Procedure Type

~ 18% would be considered “major procedures”

Rivaroxaban Interruption: Bridging

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bridging therapy</th>
<th>Yes (n=431)</th>
<th>No (n=4251)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHADS2 Score, MN %</td>
<td></td>
<td>3.52</td>
<td>3.40</td>
<td>0.0094</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>0</td>
<td>&lt;0.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>9.5</td>
<td>16.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>47.1</td>
<td>42.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>27.1</td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>13.9</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2.3</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>History of stroke/TIA/TE</td>
<td></td>
<td>52.4</td>
<td>50.0</td>
<td>0.34</td>
</tr>
</tbody>
</table>

No Difference by Treatment Allocation (Outcomes for Surgical/Invasive Procedures)

<table>
<thead>
<tr>
<th>Event Rates @ 30 days</th>
<th>Rivaroxaban (n=968)</th>
<th>Warfarin (n=1162)</th>
<th>HR (CI) for Riva vs. Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TE</td>
<td>0.27%</td>
<td>0.42%</td>
<td>0.65 (0.2, 2.13)</td>
</tr>
<tr>
<td>Death</td>
<td>0.07%</td>
<td>0.16%</td>
<td>0.44 (0.05, 4.25)</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0.90%</td>
<td>0.97%</td>
<td>1.02 (0.95, 2.06)</td>
</tr>
</tbody>
</table>

No Difference by Bridging Strategy

<table>
<thead>
<tr>
<th>Event Rates @ 30 days</th>
<th>Bridging (n=483)</th>
<th>No Bridging (n=7072)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TE</td>
<td>0.17%</td>
<td>0.32%</td>
</tr>
<tr>
<td>Death</td>
<td>0.33%</td>
<td>0.17%</td>
</tr>
<tr>
<td>Major Bleed</td>
<td>0.91%</td>
<td>0.88%</td>
</tr>
</tbody>
</table>

Rivaroxaban Interruption: Bottom Line

For NVAF Patients from ROCKET-AF Trial undergoing temporary AC interruption:
- Event rates are very low with no clear difference compared to warfarin
- Context of primarily “minor procedures”
- No clear benefit to “bridging LMWH”

Periprocedural Bleeding and Thrombotic Events (RE-LY Trial)

4591 patients
- Dabigatran 2005 - 08: stop 24 hrs prior
- 2008 - 09: stop 24 hrs for minor
- Restart once hemostasis assured
- Management left to local provider

Circulation 2012;126:343-48
Periprocedural Bleeding and Thrombotic Events with Dabigatran vs. Warfarin (RE-LY Trial)

- Procedures:
  - PM/defib insertion (10.3%)
  - Dental procedures (10%)
  - Diagnostic (10%)
  - Cataract (8.6%)
  - Colonoscopy (8.6%)
  - Joint replacement (6.2%)

~18% of procedures would be considered “major”

Circulation 2012;126:343-48

Non-Valvular Atrial Fibrillation

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Clot</th>
<th>Bleed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Douketis (2004)</td>
<td>346</td>
<td>1.2%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Pengo (2009)</td>
<td>653</td>
<td>0.2%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Kovacev (2004)</td>
<td>112</td>
<td>2.7%</td>
<td>6.3%</td>
</tr>
<tr>
<td>Dunn (2007)</td>
<td>76</td>
<td>2.3%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Wysokinski (2008)</td>
<td>345</td>
<td>1.1%</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Total 1532 | 0.9% | 2.0%
RE-LY 1546 | 1.5% | 5.1%

> 50% of procedures would be considered “major”

Urgent Surgery and Risk for Events

<table>
<thead>
<tr>
<th>D150%</th>
<th>Warfarin%</th>
<th>D150% vs Warfarin%</th>
<th>P</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21.6/24.11</td>
<td>1.14/1.07/1.10</td>
<td>0.31</td>
<td>5 – 6 fold higher</td>
</tr>
<tr>
<td></td>
<td>3.8/3.14</td>
<td>2.02/1.95</td>
<td>0.33</td>
<td>4 fold higher</td>
</tr>
</tbody>
</table>

Dabigatran Interruption: Bottom Line

For NVAF Patients from RE-LY Trial undergoing temporary AC interruption:
- Thromboembolic event rates are low and similar to warfarin
- Major bleeding rates are high
- Context of primarily “minor procedures”
- Event rates are greatly increased with urgent/emergent surgery

What is the structured approach to peri-procedural anticoagulant management for patients taking direct factor inhibitors?
Management Decisions

Does procedure require anticoagulant discontinuation?

With Warfarin: Many Don’t

- Dental
  - Extraction
  - Endodontics (root canal)
- Dermatology
  - Skin cancer excision
- Gastroenterology
  - Endoscopy ± mucosal bx
  - Diagnostic ERCP
  - Cold-snare small polyp
- Gynecology
  - Diagnostic colposcopy
  - D&C
  - IUD insertion
- Interventional radiology
  - Thorac/paracentesis
  - Non-tunneled catheters
  - IVC filter placement
- Ophthalmology
  - Cataract surgery
  - Intraocular injections
- Pulmonary
  - Bronchoscopy ± BAL
  - Endobronchial FNA
- Urology
  - Cystoscopy without biopsy


Uninterrupted Anticoagulants during Atrial Fibrillation Ablation

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (n=157)</th>
<th>Warfarin (n=157)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>1.9%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>7.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>TIA</td>
<td>0.6%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Lakkireddy et al. Heart Rhythm Society 2013

Management Decisions

Does procedure require anticoagulant discontinuation?

No

Yes

Mayo Approach:
Until we have more experience, we suggest discontinuation of direct factor inhibitors prior to most invasive procedures.

Peri-procedural Risk of Major Bleeding

- “Low risk” < 2%
- “High risk” ≥ 2%
- Within 2 days of procedure

J Thromb Haemost 2012;10:682
Surgical Procedures at High Risk for Bleeding
- Open Heart Surgery
- Abdominal Vascular Surgery
- Neurosurgery
- Major Cancer Surgery
- Urologic Procedures
- Neuraxial anesthesia


Black Box Warnings: Neuraxial Anesthesia
- Dabigatran
- Rivaroxaban
- Apixaban

Neuraxial Anesthesia or spinal/epidural catheters*

<table>
<thead>
<tr>
<th>Catheter Retrieval</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stop Prior</td>
<td></td>
<td>≥ 18 hrs</td>
<td>≥ 24 hrs</td>
</tr>
<tr>
<td>Restart Post</td>
<td>“Exact timing not known”</td>
<td>≥ 6 hrs</td>
<td>≥ 5 hrs</td>
</tr>
</tbody>
</table>

*Catheter puncture, delay restarting for > 24 hours

Patient Specific Predictors of Peri-Procedural Bleeding

- Bleeding history
- Mitral MHV
- Active Cancer
- Platelet count <150,000/mm3

“Bleed-MAP”


Provider Specific Predictors of Peri-procedural Bleeding

- Premature re-initiation of heparin therapy within 24 hours after the procedure

HR 1.9; 95%CI 1.1–3.4

HAS-BLED predicts bleeding during bridging of chronic anticoagulation (BORDER Registry)

- 1000 procedures
  - Cardiac catheterization (n=533)
  - PM implantation (n=128)
  - Surgery (n=194)
  - Other (n=145)

- Independent predictors of bleeding events
  - Mechanical heart valves
  - HAS Bled Score ≥ 3
    - HR 11.8 (95% CI 5.6 – 24.9%; p<0.0001)

Management Decisions

Does procedure require anticoagulant discontinuation?

- Yes
  - Assess overall bleeding risk
    - Low
    - High

Determine Timing of DFI Discontinuation

Direct Factor Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Thrombin</td>
<td>Factor Xa</td>
<td>Factor Xa</td>
</tr>
<tr>
<td>T1/2 (hrs)</td>
<td>12-17</td>
<td>7-11</td>
<td>7-11</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>Enteric</td>
<td></td>
<td>Enteric</td>
</tr>
</tbody>
</table>

Dabigatran: Pre-procedural Discontinuation

<table>
<thead>
<tr>
<th>Cr Cl (mL/min/1.73m²)</th>
<th>T1/2 (hrs)</th>
<th>Minor Procedure</th>
<th>Major Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>15</td>
<td>24 hrs</td>
<td>≥ 48 hrs</td>
</tr>
<tr>
<td>30 - 50</td>
<td>18</td>
<td>≥ 48 hrs</td>
<td>≥ 96 hrs</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>27</td>
<td>≥ 48 hrs</td>
<td>≥ 96 hrs</td>
</tr>
</tbody>
</table>

*Both Cockcroft–Gault and MDRD tend to over estimate creatinine clearance!*

Peak and Trough Plasma Concentration of Dabigatran

<table>
<thead>
<tr>
<th>Dose</th>
<th>Cmax (ng/ml)</th>
<th>Ctrough (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg bid</td>
<td>184 (64 – 443)</td>
<td>90 (31 – 225)</td>
</tr>
</tbody>
</table>

Van Ryn Thromb Haemost 2010;103:1116
Mayo Prescriber Guidelines: “Dabigatran”

**Very Conservative**
- Peri-procedural (NVAF) thromboembolism rate ~1%.
- Rapid onset (1 hr) yet long half-life (15 hrs).
- No antidote.

Pre-procedural Recommendations (Dabigatran)

1. Define the surgical date.
2. Define the creatinine clearance:
   - If ≥ 50, stop 5 days prior.
   - If < 50, stop 7 days prior.
3. If “high” bleeding risk, check pre-operative thrombin time or aPTT to ensure complete elimination.

Pre-procedural Dabigatran Assessment

![Graphs showing Dabigatran Plasma Concentration](Thromb-Haemost-2010-103-1116)

Rivaroxaban: Pre-procedural Discontinuation

<table>
<thead>
<tr>
<th>Cr Cl</th>
<th>T½ (hrs)</th>
<th>Minor Procedure</th>
<th>Major Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>8</td>
<td>24 hrs</td>
<td>≥ 48 hrs</td>
</tr>
<tr>
<td>30 - 49</td>
<td>9</td>
<td>≥ 24 hrs</td>
<td>≥ 48 hrs</td>
</tr>
<tr>
<td>15 - 29</td>
<td>&gt; 9-10</td>
<td>≥ 36 hrs</td>
<td>≥ 48 hrs</td>
</tr>
</tbody>
</table>

Apixaban: Pre-procedural Discontinuation

<table>
<thead>
<tr>
<th>Cr Cl</th>
<th>T½ (hrs)</th>
<th>Minor Procedure</th>
<th>Major Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50</td>
<td>7.5</td>
<td>24 hrs</td>
<td>≥ 48 hrs</td>
</tr>
<tr>
<td>30 - 49</td>
<td>17.5</td>
<td>≥ 24 hrs</td>
<td>≥ 48 hrs</td>
</tr>
<tr>
<td>15 - 29</td>
<td>&gt; 17.5</td>
<td>≥ 36 hrs</td>
<td>≥ 48 hrs</td>
</tr>
</tbody>
</table>

Mayo Prescriber Guidelines (Rivaroxaban and Apixaban)

1. Define the surgical date.
2. Define the creatinine clearance:
   - If ≥ 50, stop 3 days prior.
   - If 30-49, stop 5 days prior.
   - If 15-30, stop 7 days prior.
   - If < 15, postpone surgery and reassess.
3. For high bleeding risk procedures, assess preoperative Anti-Xa and Prothrombin Time.
Mayo Prescriber Guidelines: Post-procedure Management

1. Deep vein thrombosis prophylaxis.
2. Delay DFI re-initiation ≥48 hours to ensure complete hemostasis.
3. If high risk of bleeding, consider warfarin for one month.
   - Slow onset (≥5 days for full effect)
   - Reversible with plasma and vitamin K.

What about bridging LMWH therapy? Isn’t there an increased thrombosis risk with DFI interruption?

Black Box Warnings: Drug Termination

- Dabigatran
- Rivaroxaban
- Apixaban

End of Study Transition resulted in more Thrombotic Events in Rivaroxaban vs Warfarin treated Participants

J Am Coll Cardiol. 2013;61:651

Permanent DFI Termination: Bottom Line

- Thromboembolic event rates will increase consistent with natural history of NVAF.
- Alternative anticoagulants must be considered.
- Temporary interruption for an invasive procedure does not require bridging therapy with LMW heparin or other anticoagulant.