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
Oral Direct Factor Inhibitors

- Apixaban
- Rivaroxaban
- (Edoxaban)
- Dabigatran

Thrombin

Factor Xa

VIIIa

Prothrombin

Fibrinogen

Fibrin

Direct Factor Inhibitors

<table>
<thead>
<tr>
<th>Factor Target</th>
<th>Thrombin</th>
<th>Xa</th>
<th>Xa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T½ (hrs)</strong></td>
<td>12-17</td>
<td>7-11</td>
<td>7-11</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Renal Hepatic</td>
<td>Renal Hepatic Enteric</td>
</tr>
</tbody>
</table>

Oral Direct Factor Inhibitors

Advantages:
- Few drug interactions
- No food interactions
- No monitoring
- No continuous dose adjustments

Increased Use of Novel Anticoagulants

Use of Antiocoagulants – Non atrial fibrillation

Use of Antiocoagulants – Atrial Fibrillation

Use of Novel Anticoagulants

Real World Experience: ORBIT AF

AF patients: New onset
50% started on a NoAC

AF patients: Chronic on warfarin
25% transitioned to a NoAC

Circ Cardiovasc Qual Outc. 2014; 7: A336
Direct Factor Inhibitor Use

~3 Million Patients in USA

Periprocedural Management: Novel Anticoagulants

- ~10% annually require an invasive procedure.
- 300,000 patients will require peri-procedural management of a direct factor inhibitor in 2014.

Bayer, Johnson & Johnson, Pfizer 2013

Bridging Therapy

Heparin substitution during warfarin interruption

<table>
<thead>
<tr>
<th>INR</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.0</td>
<td>2.0 (2.5)</td>
</tr>
<tr>
<td>2.0 (2.5)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Warfarin Stop | Warfarin Restart

Time

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.

Circulation. 2012;126:1630

Interpreting the “Peri-procedure” Literature

Acknowledge:

- Anticipated annual bleeding and thrombosis rates without a procedure
Anticipated Annual Event Rates

**Apart from a Procedure**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Stroke/Embolism</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><strong>Bleeding</strong></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><strong>Bleeding</strong></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.

Time Frame varies by Study

<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>Hammerstingl (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>

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?
Rivaroxaban Interruption: Procedure Type

~18% would be considered “major procedures”

Circulation. 2014;129:1850-9

Rivaroxaban Interruption: Bridging

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bridging therapy</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n=431)</td>
<td>No (n=4281)</td>
</tr>
<tr>
<td>CHADS2 Score, MN %</td>
<td>3.52</td>
<td>3.40</td>
</tr>
<tr>
<td>Percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>2</td>
<td>9.5</td>
<td>16.4</td>
</tr>
<tr>
<td>3</td>
<td>47.1</td>
<td>42.9</td>
</tr>
<tr>
<td>4</td>
<td>27.1</td>
<td>27.3</td>
</tr>
<tr>
<td>5</td>
<td>13.9</td>
<td>11.5</td>
</tr>
<tr>
<td>6</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
<td>History of stroke/TIA/TE</td>
<td>52.4</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Circulation. 2014;129:1850-9

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>0.99%</td>
<td>0.97%</td>
<td>1.02 (0.5, 2.06)</td>
</tr>
</tbody>
</table>

Circulation. 2014;129:1850-9

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>

Circulation. 2014;129:1850-9

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

<table>
<thead>
<tr>
<th>Dabigatran</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005 - 08: stop 24 hrs prior</td>
<td>Management left to local provider</td>
</tr>
<tr>
<td>2008 - 09: stop 24 hrs for minor stop 2-5 days for major</td>
<td></td>
</tr>
</tbody>
</table>

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 (9.3%)
  - Colonoscopy (8.6%)
  - Joint replacement (6.2%)

~ 18% of procedures would be considered “major”

Circulation 2012;126:343-48

Periprocedural Bleeding and Thrombotic Outcomes at 30 days

<table>
<thead>
<tr>
<th>30 day Outcomes</th>
<th>Dabigatran* (n=1546)</th>
<th>Warfarin (n=1558)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Bleed</td>
<td>5.1%</td>
<td>4.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Fatal Bleed</td>
<td>0.1%</td>
<td>0.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Bleed requiring reoperation</td>
<td>1.4%</td>
<td>1.0%</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>1.5%</td>
<td>1.2%</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Dabigatran 150 mg

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>Kovacs (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>3.5%</td>
</tr>
<tr>
<td>Wysokinski (2008)</td>
<td>345</td>
<td>1.1%</td>
<td>2.7%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1532</td>
<td>0.9%</td>
<td>2.0%</td>
</tr>
<tr>
<td><strong>RE-LY</strong></td>
<td>1546</td>
<td>1.5%</td>
<td>5.1%</td>
</tr>
</tbody>
</table>

> 50% of procedures would be considered “major”

Circulation 2012;126:343-48

Urgent Surgery and Risk for Events

<table>
<thead>
<tr>
<th>D50%</th>
<th>D50% vs Warfarin RR (95% CI, P Value)</th>
<th>P-inter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgent surgery</td>
<td>17.7 (95/153)</td>
<td>21.6 (27/128)</td>
</tr>
<tr>
<td>Elective surgery</td>
<td>3.8 (3/99)</td>
<td>3.3 (13/397)</td>
</tr>
<tr>
<td>Major surgery</td>
<td>6.5 (33/511)</td>
<td>7.8 (69/1026)</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>3.2 (10/329)</td>
<td>1.8 (61/3436)</td>
</tr>
<tr>
<td>Original dabigatran protocol</td>
<td>4.9 (68/1348)</td>
<td>4.6 (60/1378)</td>
</tr>
<tr>
<td>Amended dabigatran protocol</td>
<td>6.0 (12/229)</td>
<td>5.6 (12/222)</td>
</tr>
</tbody>
</table>

Major bleeding 5 – 6 fold higher
Stroke/TE 4 fold higher

Circulation 2012;126:343-48

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
  - Thoracentesis
  - 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.

Management Decisions

Does procedure require anticoagulant discontinuation?

Yes

Assess overall bleeding risk

- Procedure specific
- Patient specific
- Provider specific

Peri-procedural Risk of Major Bleeding

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

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

*If traumatic puncture, delay restarting for > 24 hours

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>Target</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>T½ (hrs)</td>
<td>12-17</td>
<td>7-11</td>
<td>7-11</td>
</tr>
<tr>
<td>Elimination</td>
<td>Renal</td>
<td>Renal Hepatic</td>
<td>Renal Hepatic</td>
</tr>
<tr>
<td>Cr Cl</td>
<td>Minor Procedure</td>
<td>Major Procedure</td>
<td></td>
</tr>
<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 overestimate creatinine clearance!

Thromb Haem. 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

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>

*Respective package inserts

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>

*Respective package inserts

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.
Anti Xa Activity (Heparin Levels) and Apixaban levels

Relationship between INR and Plasma Apixaban levels

Reagent dependent Variation of INR values

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.