Anticoagulation in Atrial Fibrillation: To Bridge or Not to Bridge?

Katie Galbreath, PharmD
Sanford Medical Center Fargo
October 13, 2015
• MW is a 63 year old male s/p right kidney biopsy receiving OAC therapy with warfarin for atrial fibrillation. Warfarin was held 5 days prior to procedure. PMH is significant for type 2 diabetes mellitus, coronary artery disease, and hypertension. No previous stroke or TIA. INR upon arrival back to the medical unit is 1.1.

• The MD orders enoxaparin 1mg/kg BID to start tomorrow AM, and warfarin to re-start this evening. What do you do?
  – Verify the enoxaparin order of 1mg/kg BID
  – Call the MD to suggest bridging with UFH instead of enoxaparin.
  – Call the MD to suggest not bridging in this patient
  – Call the MD to suggest prophylaxis enoxaparin dosing (40mg daily)
Objectives

1. Summarize current guidelines regarding anticoagulation and bridging anticoagulation in atrial fibrillation (AF)
2. Identify risks and benefits of bridging anticoagulation
3. Use recent literature data to guide bridging anticoagulation decision making
Abbreviations

- DVT: deep vein thrombosis
- INR: international normalized ratio
- LOE: level of evidence
- LMWH: low molecular weight heparin
- MHV: mechanical heart valve
- MI: myocardial infarction
- NOAC: novel oral anticoagulants
- NVAF: non-valvular atrial fibrillation
- OAC: oral anticoagulation
- PE: pulmonary embolism
- UFH: unfractionated heparin
- SC: subcutaneous
- TIA: transient ischemic attack
- VKA: vitamin K antagonist
What is Atrial Fibrillation?

- Hyperthyroidism
- Sleep apnea
- Valvular Disease
- Congestive Heart Failure
- Hypertension
- Surgery
- Electrolyte imbalances

Most common rhythm disturbance

Lifetime prevalence: 16%

Yearly incidence of new AF: 1.6%

Independent risk factor for stroke and thromboembolism

5-fold increased risk of stroke

Stroke Risk

• In patients with NVAF, the CHA\textsubscript{2}DS\textsubscript{2}-VASc score is recommended for assessment of stroke risk (Class I, LOE B)

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score</th>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Stoke/TIA</td>
<td></td>
<td>2</td>
</tr>
</tbody>
</table>
In patients with NVAF, the CHA$_2$DS$_2$-VASc score is recommended for assessment of stroke risk (Class I, LOE B)

<table>
<thead>
<tr>
<th>CHA$_2$DS$_2$-VASc Score</th>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C</strong> (CHF)</td>
<td>HF</td>
<td>1</td>
</tr>
<tr>
<td><strong>H</strong> (Hypertension)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong> (Age ≥ 75)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong> (Diabetes Mellitus)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong> (Stroke/TIA)</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td><strong>V</strong> (Vascular disease)</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong> (Age (65-74))</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>S</strong> (Sex category)</td>
<td>(female)</td>
<td>1</td>
</tr>
</tbody>
</table>
Stroke Risk

• In patients with NVAF, the CHA\textsubscript{2}DS\textsubscript{2}-VASc score is recommended for assessment of stroke risk (Class I, LOE B)

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2} Score</th>
<th>CHADS\textsubscript{2} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Stroke Risk

- In patients with NVAF, the CHA$_2$DS$_2$-VASc score is recommended for assessment of stroke risk (Class I, LOE B)

<table>
<thead>
<tr>
<th>Adjusted Stroke Rate (% per year)</th>
<th>CHA$_2$DS$_2$-VASc Score</th>
<th>CHA$_2$DS$_2$-VASc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>1</td>
<td>1.3</td>
<td>1.3</td>
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<tr>
<td>2</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
<td>3.2</td>
</tr>
<tr>
<td>4</td>
<td>4.0</td>
<td>4.0</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
<td>6.7</td>
</tr>
<tr>
<td>6</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>7</td>
<td>9.6</td>
<td>9.6</td>
</tr>
<tr>
<td>8</td>
<td>6.7</td>
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<tr>
<td>9</td>
<td>15.2</td>
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Stroke Risk

- In patients with NVAF, the CHA$_2$DS$_2$-VASc score is recommended for assessment of stroke risk (Class I, LOE B)

<table>
<thead>
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<th>CHADS$_2$ Score</th>
<th>CHADS$_2$ (%)</th>
<th>CHA$_2$DS$_2$-VASc Score</th>
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<tr>
<td></td>
<td></td>
<td>9</td>
<td>15.2</td>
</tr>
</tbody>
</table>

Guidelines for OAC in AF

- NVAF with prior stroke, TIA, or a CHA$_2$DS$_2$-VASc $\geq$ 2
  - OAC is recommended
    - Warfarin
      - INR 2.0 to 3.0
      - Class I, LOE A
    - Dabigatran (Pradaxa®)
      - Class I, LOE B
    - Rivaroxaban (Xarelto®)
      - Class I, LOE B
    - Apixaban (Eliquis®)
      - Class I, LOE B

- NVAF and a CHA$_2$DS$_2$-VASc of 1
  - No antithrombotic therapy, or treatment with OAC or ASA may be considered
    - Class IIb, LOE C

- NVAF and a CHA$_2$DS$_2$-VASc of 0
  - Reasonable to omit antithrombotic therapy
    - Class IIa, LOE B
Bridging anticoagulation:

- Giving a short-acting anticoagulant, consisting of SC LMWH or UFH for ~10 to 12 day period during interruption of VKA therapy when the INR is not within therapeutic range
- Minimize risk of thromboembolism

Bridging Considerations

- Mechanical valve status
- Assessment of thromboembolic risk (CHADS\textsubscript{2} score)
- Type of procedure
- Bleeding risk of the patient
- Risk vs. benefit
Bridging

• AF *with* MHV who require interruption of warfarin or new anticoagulants for procedures
  – Bridging therapy with UFH or LMWH is recommended
  – Decisions on bridging therapy should balance the risks of stroke and bleeding
  – Class I, LOE C
Bridging

- AF *without* MHV who require interruption of warfarin or new anticoagulants for procedures
  - Bridging therapy should balance the risks of stroke and bleeding and the duration of time a patient will not be anticoagulated
  - Class I, LOE C

Thromboembolism Risk Stratification

- **Low risk**
  - CHADS$_2$ score 0 to 2 (no prior stroke or TIA)
  - No bridging instead of bridging anticoagulation
    - Class II, LOE C

- **Moderate risk**
  - CHADS$_2$ score 3 or 4
  - Bridging or no bridging based on assessment of individual patient and surgery related factors

- **High Risk**
  - CHADS$_2$ score of 5 or 6, recent stroke or TIA, rheumatic valvular heart disease
  - Bridging anticoagulation instead of no bridging anticoagulation
    - Class II, LOE C
Procedural Bleeding Risk

High Risk Bleeding Procedures

- All cardiac and neurosurgeries
- Kidney/Liver biopsy
- Chest tube placement
- Joint replacement
- Hysterectomy
- Hickman and tunneled dialysis catheter placement

Low Risk Bleeding Procedures

- Endoscopy (+/- mucosal biopsy)
- Cataract surgery
- Bone marrow biopsy
- Dental extractions
- Dermatologic surgery
- Joint aspiration

# Bleeding Risk

## HAS-BLED

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H</strong>ypertension</td>
<td>1</td>
</tr>
<tr>
<td><strong>A</strong>bnormal renal/liver function</td>
<td>1 or 2</td>
</tr>
<tr>
<td><strong>S</strong>troke</td>
<td>1</td>
</tr>
<tr>
<td><strong>B</strong>leeding history/predisposition</td>
<td>1</td>
</tr>
<tr>
<td><strong>L</strong>abile INR’s (for patients on warfarin)</td>
<td>1</td>
</tr>
<tr>
<td><strong>E</strong>lderly (&gt;65 years of age)</td>
<td>1</td>
</tr>
<tr>
<td><strong>D</strong>rugs (concomitant aspirin or NSAIDS) or alcohol abuse</td>
<td>1 or 2</td>
</tr>
</tbody>
</table>

Max: 9 points

Bridging

- Use of any bridging anticoagulant is “off label”

Bridging: What Do We Know?

• Few, randomized controlled trials to guide decision making
  – LOE C: Recommendation that procedure/treatment is useful/effective
    • Weak recommendation
    • Only expert opinion, case studies, or standard of care

• Guidelines suggest utilizing patient and surgery specific information to guide decision making

• Benefit of bridging anticoagulation should outweigh risk of bleeding
Bridging: What Do We Know?

• Siegal et al 2012:
  – Meta-analysis evaluating safety and efficacy of periprocedural bridging anticoagulation
  – 34 studies included
  – Largest systematic review and meta analysis of the efficacy and safety of periprocedural bridging anticoagulation

• 44% of bridged patients had AF
Bridging: What Do We Know?

<table>
<thead>
<tr>
<th>Group</th>
<th>Thromboembolic events, %</th>
<th>Major bleeding, %</th>
<th>Overall bleeding, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bridged</td>
<td>0.9</td>
<td>4.2</td>
<td>13.1</td>
</tr>
<tr>
<td>Not bridged</td>
<td>0.6</td>
<td>0.9</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Use and Outcomes Associated with Bridging During Anticoagulation Interruptions in Patient’s with Atrial Fibrillation: Findings from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF).

Study Question:

- What are the outcomes among patients with AF requiring temporary interruption of OAC who received bridging anticoagulation versus those who did not receive bridging anticoagulation?
ORBIT-AF

• Methods
  – The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)
    • National, community-based registry of outpatients with AF
  – Prospective, observational

Steinberg et al. Circulation. 2014.
• Methods
  – Data collection from patient medical records
    • Baseline and every 6 months
  – Type of procedure and bridging anticoagulation used
  – Interruptions recorded for procedures only
## ORBIT-AF

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age &gt;18 years</td>
<td>• &lt;1 follow up visit</td>
</tr>
<tr>
<td>• Documented AF</td>
<td>• Not on baseline OAC</td>
</tr>
<tr>
<td></td>
<td>• Interruptions not relating to surgery or procedure</td>
</tr>
</tbody>
</table>

Steinberg et al. Circulation. 2014.
ORBIT-AF

• Outcomes*
  – Myocardial infarction
  – Stroke or systemic embolism
  – Major bleeding
  – Cause-specific hospitalization
  – Death

*Within 30 days following procedure for interruption

Steinberg et al. Circulation. 2014.
ORBIT-AF

- Interruptions:
  - Cardiac catheterization
  - Catheter ablation
  - Endoscopy (GI, bronchoscopic, genitourinary)
  - Cardiac surgery
  - Non-cardiac surgery (not further specified)
  - Device implantation
  - Dental procedures
  - Other (not further specified)
% of Temporary Interruptions with Bridging

Adapted from: Steinberg et al. Circulation. 2014.
Methods

10,132 Patients identified

9,642 Patients included

490 Excluded (<1 follow up visit)

2,270 Excluded (not on baseline OAC)

7,372 FINAL COHORT

Steinberg et al. Circulation. 2014.
Methods

7,372 FINAL COHORT

2,803 Reported interruptions

2,138 No bridging therapy

2,803

487 LMWH (74%)

97 UFH (15%)

7 Fondaparinux (1%)

665 Bridging therapy

76 Other (11%)

Steinberg et al. Circulation. 2014.
ORBIT-AF

• Bridging anticoagulation in ORBIT-AF:
  – Anticoagulant temporarily administered in place of chronic therapy, for the purpose of stroke prevention before, during, or after the periprocedural period

Steinberg et al. Circulation. 2014.
Methods

7,372
FINAL COHORT

2,803
Reported interruptions

2,138
No bridging therapy

665
Bridging therapy

487
LMWH (74%)

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Other (11%)

Steinberg et al. Circulation. 2014.
## ORBIT-AF

Baseline demographics, past medical history, and laboratory studies by incidence of temporary interruption

<table>
<thead>
<tr>
<th></th>
<th>No temporary interruption (5172)</th>
<th>No bridging (N=1608)</th>
<th>Bridging (N=592)</th>
<th>P value (no bridging vs. bridging)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>76 (68-82)</td>
<td>75 (68-81)</td>
<td>74 (67-80)</td>
<td>0.009</td>
</tr>
<tr>
<td><strong>CHADS2 scores, mean (SD)</strong></td>
<td>2.4 (1.3)</td>
<td>2.34 (1.21)</td>
<td>2.53 (1.31)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>CHA2DS2-VASc score, mean (SD)</strong></td>
<td>4.0 (1.7)</td>
<td>4.03 (1.62)</td>
<td>4.25 (1.74)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Adapted from: Steinberg et al. Circulation. 2014.
## ORBIT-AF

### Baseline demographics, past medical history, and laboratory studies by incidence of temporary interruption

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<th>Bridging (N=592)</th>
<th>P value (no bridging vs. bridging)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant valve disease</td>
<td>27</td>
<td>37</td>
<td>34</td>
<td>0.0006</td>
</tr>
<tr>
<td>• Moderate/severe mitral stenosis</td>
<td>1.7</td>
<td>1.1</td>
<td>2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>• Prior mechanical valve replacement</td>
<td>3.6</td>
<td>2.4</td>
<td>9.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Concomitant antiplatelet

<table>
<thead>
<tr>
<th>Antiplatelet</th>
<th>No temporary interruption (5172)</th>
<th>No bridging (N=1608)</th>
<th>Bridging (N=592)</th>
<th>P value (no bridging vs. bridging)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>36</td>
<td>36</td>
<td>38</td>
<td>0.4</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>4.5</td>
<td>4.2</td>
<td>6.98</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Adapted from: Steinberg et al. Circulation. 2014.
Categorical variables
- Frequencies/percentages
- Differences between 2 groups: Chi-square test

Continuous variables
- Mean/median
- Differences between 2 groups: Wilcoxon rank sum test
# ORBIT-AF: Results

Adjusted 30-day outcomes, by use of bridging anticoagulation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted, % (n)</th>
<th>Adjusted</th>
<th>Unadjusted, % (n)</th>
<th>Adjusted</th>
<th>P-value</th>
<th>Unadjusted, % (n)</th>
<th>Adjusted</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No bridging (N=1724)</td>
<td>Bridging (N=503)</td>
<td>P-value</td>
<td>Adjusted OR (95% CI), bridging vs no bridging</td>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td>2.5 (43)</td>
<td>4.3 (23)</td>
<td>0.02</td>
<td>1.62 (0.95-2.78)</td>
<td>0.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding events</td>
<td>1.3 (22)</td>
<td>5.0 (25)</td>
<td>&lt;0.0001</td>
<td>3.84 (2.07-7.14)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall composite*</td>
<td>6.3 (108)</td>
<td>13 (64)</td>
<td>&lt;0.0001</td>
<td>1.94 (1.38-2.71)</td>
<td>0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Composite of any MI, stroke, systemic embolism, or death within 30 days following date of procedure requiring interruption

Adapted from: Steinberg et al. Circulation. 2014.
## ORBIT-AF

### Limitations

<table>
<thead>
<tr>
<th>Observational study design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Why was decision made to interrupt OAC in some cases and not others?</td>
</tr>
<tr>
<td>Therapeutic vs. prophylactic dosing?</td>
</tr>
<tr>
<td>Reversal agents used?</td>
</tr>
<tr>
<td>No data on the timing of initiation and discontinuation of bridging agents</td>
</tr>
</tbody>
</table>
ORBIT-AF

• Significance
  – Results consistent with previous literature data on safety and efficacy of bridging anticoagulation in AF patients
  – Large, real-world population of outpatients
  – Room for improvement in types of procedures not requiring interruption of warfarin therapy
Conclusion

• Results suggest bridging anticoagulation in atrial fibrillation may be harmful

• Data show an increased risk of bleeding in patients receiving bridging anticoagulation, and no difference in thromboembolic events

• Additional data needed to identify best practices

Steinberg et al. Circulation. 2014.
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation (BRIDGE Trial)

• Study Question
  – Is bridging anticoagulation necessary during perioperative warfarin interruption for patients with atrial fibrillation or atrial flutter?

BRIDGE

• Methods
  – Randomized, double blind, placebo controlled
    • 108 sites
    • July 2009 through December 2014
  – Bridging anticoagulation vs. placebo
    • Warfarin stopped 5 days prior to procedure, and resumed within 24 hours after procedure
    • 100 IU dalteparin/kg or matching placebo SC BID from 3 days before procedure then 5-10 days after

## BRIDGE

### Inclusion
- ≥18 years old
- Chronic atrial fibrillation or atrial flutter
- Warfarin use ≥3 months
- INR 2-3
- Elective operation or invasive procedure
- At least 1 CHADS$_2$ risk factor

### Exclusion
- Mechanical heart valve
- Stroke, systemic embolism or TIA within previous 12 weeks
- Major bleeding within previous 6 weeks
- CrCl <30 ml/min
- Platelet count <100,000/mm$^3$
- Planned cardiac, intracranial, or intraspinal surgery

BRIDGE

• Study Outcomes
  – Primary
    • Arterial thromboembolism
      – Stroke, TIA, systemic embolism
    • Major bleeding
  – Secondary
    • Acute MI, DVT, PE and death
    • Minor bleeding

BRIDGE

• Statistical Analysis
  – Assumptions
    • Rate of arterial thromboembolism in bridging group: 1%
    • Rate of arterial thromboembolism in placebo group: 1%
  – Statistical tests
    • Arterial thromboembolism
      – Noninferiority analysis: one sided at 0.025 significance level
        » Barnard’s test: used to calculate 95% confidence interval for difference in event rate
    • Bleeding
      – Two sided test at 0.05 significance level
      – Fisher’s mid-P test to calculate p-values
  – 90% powered to detect primary endpoints

Results

6,585 Patient’s screened

1,884 Randomized

32 Discontinued study
- 23 withdrew consent
- 3 lost to follow up
- 2 withdrawn by principal investigator
- 4 other reasons
5 died

950 Placebo
913 Completed Study

934 Dalteparin
891 Completed study

39 Discontinued study
- 31 withdrew consent
- 3 lost to follow up
- 1 withdrawn by principal investigator
- 4 other reasons
4 died

<table>
<thead>
<tr>
<th></th>
<th>No Bridging (N = 950)</th>
<th>Bridging (N = 934)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yr</strong></td>
<td>71.8</td>
<td>71.6</td>
</tr>
<tr>
<td><strong>Male sex – no. (%)</strong></td>
<td>696 (73.3)</td>
<td>686 (73.4)</td>
</tr>
<tr>
<td><strong>CHF or LV dysfunction – no. (%)</strong></td>
<td>289 (30.4)</td>
<td>310 (33.2)</td>
</tr>
<tr>
<td><strong>Hypertension – no. (%)</strong></td>
<td>833 (87.7)</td>
<td>806 (86.3)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus – no. (%)</strong></td>
<td>390 (41.1)</td>
<td>382 (40.9)</td>
</tr>
<tr>
<td><strong>Stroke – no. (%)</strong></td>
<td>79 (8.3)</td>
<td>99 (10.6)</td>
</tr>
<tr>
<td><strong>TIA – no. (%)</strong></td>
<td>79 (8.0)</td>
<td>77 (8.2)</td>
</tr>
</tbody>
</table>

## Baseline Characteristics

<table>
<thead>
<tr>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; score</th>
<th>No Bridging (N = 950)</th>
<th>Bridging (N = 934)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mean</td>
<td>2.3</td>
<td>2.4</td>
</tr>
<tr>
<td>• Distribution – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>1</td>
<td>216 (22.7)</td>
<td>212 (22.7)</td>
</tr>
<tr>
<td>2</td>
<td>382 (40.2)</td>
<td>351 (37.6)</td>
</tr>
<tr>
<td>3</td>
<td>229 (24.1)</td>
<td>232 (24.8)</td>
</tr>
<tr>
<td>4</td>
<td>96 (10.1)</td>
<td>106 (11.3)</td>
</tr>
<tr>
<td>5</td>
<td>23 (2.4)</td>
<td>27 (2.9)</td>
</tr>
<tr>
<td>6</td>
<td>3 (0.3)</td>
<td>5 (0.5)</td>
</tr>
</tbody>
</table>

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Medication use – no. (%)</th>
<th>No Bridging (N = 950)</th>
<th>Bridging (N = 934)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>324 (34.1)</td>
<td>329 (35.2)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>30 (3.2)</td>
<td>21 (2.2)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>34 (3.6)</td>
<td>25 (2.7)</td>
</tr>
<tr>
<td>COX-2 inhibitor</td>
<td>8 (0.8)</td>
<td>13 (1.4)</td>
</tr>
</tbody>
</table>

## BRIDGE - Results

### Results – Primary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No Bridging (N = 918)</th>
<th>Bridging (N = 895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arterial thromboembolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.2)</td>
<td>3 (0.3)</td>
<td>0.01(^a), 0.73(^b)</td>
</tr>
<tr>
<td>TIA</td>
<td>2 (0.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Major Bleeding</strong></td>
<td>12 (1.3)</td>
<td>29 (3.2)</td>
<td>0.005(^b)</td>
</tr>
</tbody>
</table>

\(^a\): p value for noninferiority  
\(^b\): p value for superiority  

## BRIDGE - Results

### Results – Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>No Bridging (N = 918)</th>
<th>Bridging (N = 895)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 (0.5)</td>
<td>4 (0.4)</td>
<td>0.88(^b)</td>
</tr>
<tr>
<td>MI</td>
<td>7 (0.8)</td>
<td>14 (1.6)</td>
<td>0.1(^b)</td>
</tr>
<tr>
<td>DVT</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25(^b)</td>
</tr>
<tr>
<td>PE</td>
<td>0</td>
<td>1 (0.1)</td>
<td>0.25(^b)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>110 (12)</td>
<td>187 (20.9)</td>
<td>&lt;0.001(^b)</td>
</tr>
</tbody>
</table>

\(^a\): p value for noninferiority  
\(^b\): p value for superiority

## BRIDGE

### Limitations

<table>
<thead>
<tr>
<th>Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average CHADS&lt;sub&gt;s&lt;/sub&gt; score of 2.3</td>
</tr>
<tr>
<td>Major surgeries not addressed</td>
</tr>
<tr>
<td>Overall rate of thromboembolism lower than expected</td>
</tr>
<tr>
<td>Observed rate of bleeding modest</td>
</tr>
<tr>
<td>Diminished relevance?</td>
</tr>
</tbody>
</table>
BRIDGE - Conclusions

• Discontinuation of warfarin therapy without the use of bridging anticoagulation was noninferior to the use of bridging anticoagulation for the prevention of arterial thromboembolism.

• Bridging conferred a risk of major bleeding that was nearly triple the risk associated with no bridging.

• Results are consistent with those from nonrandomized comparisons of these strategies.
What about high risk patients?
A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism

PERIOP-2

Kovacs MJ. ClinicalTrials.gov. 2014.
## PERIOP-2

| Study design | • Phase III  
| • Prospective  
| • Randomized  
| • Placebo controlled  
| • Double blind |
| Intervention | • Bridging vs. no bridging in surgeries or procedures requiring warfarin interruption |
| Primary outcome | • Major thromboembolism |
| Patients | • Mechanical heart valve  
| • Atrial fibrillation |
| Results | • Expected March 2015 |

Kovacs MJ. ClinicalTrials.gov. 2014.
What About NOAC?

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban (Xarelto®)</th>
<th>Apixaban (Eliquis®)</th>
<th>Dabigatran (Pradaxa®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Onset</td>
<td>2 - 4 hours</td>
<td>3 - 4 hours</td>
<td>1 - 2 hours</td>
</tr>
<tr>
<td>Half Life</td>
<td>5 - 9 hours</td>
<td>12 hours</td>
<td>15 hours</td>
</tr>
</tbody>
</table>

- **Rapid onset of action**
  - Consider use of LMWH or UFH in patients unable to restart oral NOAC following surgery

- **No evidence to suggest use of these agents for bridging to warfarin**
  - Apixaban: May interact with INR. Discontinue apixaban and start a parenteral therapy if anticoagulation until INR is therapeutic is needed
MW is a 63 year old male s/p right kidney biopsy receiving OAC therapy with warfarin for atrial fibrillation. Warfarin was held 4 days prior to procedure. PMH is significant for type 2 diabetes mellitus, coronary artery disease, and hypertension. No previous stroke or TIA. INR upon arrival back to the medical unit is 1.1.

- CHADS$_2$ score = 2 (low risk thromboembolism)

- The MD orders enoxaparin 1mg/kg BID to start tomorrow AM, and warfarin to re-start this evening. What do you do?
  - Verify the enoxaparin order of 1mg/kg BID
  - Call the MD to suggest bridging with UFH instead of enoxaparin.
  - Call the MD to suggest not bridging in this patient
  - Call the MD to suggest prophylaxis enoxaparin dosing (40mg daily)
Conclusion

• Guidelines on the use of bridging OAC are based largely on observational data, and lack specific recommendations.

• The ORBIT-AF and BRIDGE trials conclude that patients receiving bridging anticoagulation are at a higher risk of bleeding than those that did not receive bridging anticoagulation.

• In patients with atrial fibrillation without a MHV considered low risk or moderate risk for thromboembolism, bridging anticoagulation should not be used.
References

- Lane DA, Lip GH. Use of the CHA$_2$DS$_2$-VAS$_c$ and HAS-BLED score to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation* 2012; 126: 860-865.
Questions?
Anticoagulation in Atrial Fibrillation: To Bridge or Not to Bridge?

Katie Galbreath, PharmD
Sanford Medical Center Fargo
October 13, 2015