Anticoagulation: Valvular Heart Disease and Periprocedural Bridging Considerations

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Disclosures

- Presenter has nothing to disclose
Objectives

- Review current anticoagulation recommendations for patients with valvular heart disease (VHD) including prosthetic heart valves

- Present direct oral anticoagulant (DOAC) data for use in VHD

- Define current periprocedural bridging therapy recommendations for anticoagulants
Anticoagulation: Valvular Heart Disease
# Guideline Recommendations - Native Valve Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>2014</th>
<th>2017 Update</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VKA indicated for patients with MS and</strong></td>
<td>VKA indicated for patients with MS and <strong>• AF</strong></td>
<td><strong>•</strong> Rheumatic MS and <strong>• AF</strong></td>
</tr>
<tr>
<td><strong>• Prior embolic event</strong></td>
<td><strong>•</strong> Prior embolic event</td>
<td><strong>•</strong> Prior embolic event</td>
</tr>
<tr>
<td><strong>• LA thrombus</strong></td>
<td><strong>• LA thrombus</strong></td>
<td><strong>• LA thrombus</strong></td>
</tr>
<tr>
<td></td>
<td><strong>COR</strong></td>
<td><strong>LOE</strong></td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td><strong>2017 Update</strong></td>
<td><strong>I</strong></td>
<td><strong>B-NR</strong></td>
</tr>
<tr>
<td><strong>VKA indicated for patients with rheumatic MS and AF</strong></td>
<td><strong>I</strong></td>
<td><strong>B-NR</strong></td>
</tr>
<tr>
<td><strong>Oral anticoagulant indicated in AF with CHA₂DS₂-VASc ≥2 and native AV or TV disease or MR</strong></td>
<td><strong>I</strong></td>
<td><strong>C-LD</strong></td>
</tr>
<tr>
<td><strong>DOAC as alternative to VKA in AF with CHA₂DS₂-VASc ≥2 and native AV or TV disease or MR</strong></td>
<td><strong>IIa</strong></td>
<td><strong>C-LD</strong></td>
</tr>
</tbody>
</table>

Nishimura RA et al. J Am Coll Cardiol 2014;63:e57-185
Nishimura RA et al. J Am Coll Cardiol 2017;70:252-89
Nishimura RA et al. J Am Coll Cardiol 2014;63:e57-185

Prosthetic Valve

Mechanical valve

MVR

VKA INR goal 3.0
ASA 75 mg–100 mg QD Long-term (I)

If VKA therapy interrupted for noncardiac procedures, minimize time with subtherapeutic INR

Bridging anticoagulation with UFH or SC LMWH (I)

AVR With risk factors

VKA INR goal 3.0
ASA 75 mg–100 mg QD Long-term (I)

If VKA therapy interrupted for noncardiac procedures, minimize time with subtherapeutic INR

No bridging additional anticoagulation needed (I)

On-X Valve VKA INR goal 1.5-2 after 3 mo (IIb)

Bioprosthetic valve

MVR

VKA INR goal 2.5
First 3-6 mo in low bleed risk patients (IIa)

AVR No risk factors

VKA INR goal 2.5
ASA 75 mg–100 mg QD Long-term (I)

No bridging additional anticoagulation needed (I)

ASA 75 mg–100 mg PO QD Long-term (IIa)

AVR

TAVR

VKA INR goal 2.5
First 3 mo in low bleed risk patients (IIb)

Clopidogrel 75 mg QD
ASA 75 mg–100 mg QD First 6 mo (IIb)
DOAC Use in Valvular Heart Disease

**Direct thrombin inhibitor:**
- Dabigatran (Pradaxa®)

**Factor Xa inhibitors:**
- Apixaban (Eliquis®)
- Betrixaban (Bevyxxa®)
- Edoxaban (Savaysa®)
- Rivaroxaban (Xarelto®)
RE-ALIGN Trial

- Mechanical valves (AV, MV, or both)
- Dabigatran 150mg/220mg/300mg twice daily (n=168) vs. warfarin (n=84)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dabigatran</th>
<th>Warfarin</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, stroke SE, or MI</td>
<td>13 (8%)</td>
<td>2 (2%)</td>
<td>3.37 (0.76-14.95)</td>
<td>0.11</td>
</tr>
<tr>
<td>Asymptomatic valve thrombosis</td>
<td>5 (3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any bleeding</td>
<td>45 (27%)</td>
<td>10 (12%)</td>
<td>2.45 (1.23-4.86)</td>
<td>0.01</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7 (4%)</td>
<td>2 (2%)</td>
<td>1.76 (0.37-8.46)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

# VHD in DOAC Clinical Trials

<table>
<thead>
<tr>
<th>Condition</th>
<th>RE-LY (n=18,113)</th>
<th>ROCKET-AF (n=14,171)</th>
<th>ARISTOTLE (n=18,197)</th>
<th>ENGAGE-AF (n=21,105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any VHD</td>
<td>3950 (21.8%)</td>
<td>2003 (14.1%)</td>
<td>4808 (26.4%)</td>
<td>2824 (13.4%)</td>
</tr>
<tr>
<td>MR</td>
<td>3101 (17.1%)</td>
<td>1756 (12.4%)</td>
<td>3526 (19.4%)</td>
<td>2250 (10.7%)</td>
</tr>
<tr>
<td>MS</td>
<td>193 (1.1%)</td>
<td>**</td>
<td>131 (0.7%)</td>
<td>**</td>
</tr>
<tr>
<td>AR</td>
<td>817 (4.5%)</td>
<td>486 (3.4%)</td>
<td>887 (4.9%)</td>
<td>369 (1.7%)</td>
</tr>
<tr>
<td>AS</td>
<td>471 (2.6%)</td>
<td>215 (1.5%)</td>
<td>384 (2.1%)</td>
<td>165 (0.8%)</td>
</tr>
<tr>
<td>TR</td>
<td>1179 (6.5%)</td>
<td>**</td>
<td>2124 (11.7%)</td>
<td>**</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>**</td>
<td>106 (5.3%)</td>
<td>251 (1.4%)</td>
<td>325 (1.5%)</td>
</tr>
</tbody>
</table>
VHD in DOAC Clinical Trials

<table>
<thead>
<tr>
<th>Major Bleeding</th>
<th>NOAC Event Rate/Year (n)</th>
<th>Warfarin Event Rate/Year (n)</th>
<th>Hazard Ratio 95% CI</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran 150 mg, VHD</td>
<td>4.21 (113)</td>
<td>5.12 (132)</td>
<td>0.82 [0.64, 1.06]</td>
<td>0.25</td>
</tr>
<tr>
<td>Dabigatran 150 mg, No VHD</td>
<td>3.06 (286)</td>
<td>3.14 (298)</td>
<td>0.98 [0.83, 1.15]</td>
<td></td>
</tr>
<tr>
<td>Dabigatran 110 mg, VHD</td>
<td>3.77 (96)</td>
<td>5.12 (132)</td>
<td>0.73 [0.56, 0.95]</td>
<td>0.38</td>
</tr>
<tr>
<td>Dabigatran 110 mg, No VHD</td>
<td>2.63 (246)</td>
<td>3.14 (289)</td>
<td>0.84 [0.71, 0.99]</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apixaban 5mg, VHD</td>
<td>2.49 (99)</td>
<td>3.14 (119)</td>
<td>0.79 [0.61, 1.04]</td>
<td>0.23</td>
</tr>
<tr>
<td>Apixaban 5mg, No VHD</td>
<td>2.01 (228)</td>
<td>3.07 (343)</td>
<td>0.65 [0.55, 0.77]</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban 20 mg, VHD</td>
<td>6.14 (88)</td>
<td>4.2 (68)</td>
<td>1.56 [1.14, 2.14]</td>
<td>0.01</td>
</tr>
<tr>
<td>Rivaroxaban 20 mg, No VHD</td>
<td>3.22 (307)</td>
<td>3.33 (318)</td>
<td>0.98 [0.84, 1.15]</td>
<td></td>
</tr>
</tbody>
</table>
DOACs in VHD

• Rivaroxaban
  – Bioprosthetic SAVR (ASA vs rivaroxaban for 6 mos)
  – RIVER: warfarin vs rivaroxaban in AF patients with bio MV
  – GALILEO: DAPT vs ASA/rivaroxaban after TAVR

• Apixaban
  – ATLANTIS: apixaban vs standard care after TAVR

• Edoxaban
  – ENVISAGE-TAVI AF: edoxaban vs VKA in AF patients after TAVR
  – ENAVLE: edoxaban vs VKA for 3 mos after MV repair or bioprosthetic MV or AV replacement

• Dabigatran
  – DECISIVE: dabigatran vs standard care for silent CVA in mod-severe valve disease

www.clinicaltrials.gov Accessed 9/12/17
Anticoagulation: Periprocedural Bridging
Risk Assessment

Lower Bleeding Risk:
• Dental extraction
• Diagnostic endoscopy
• Thoracentesis, paracentesis

Higher Bleeding Risk:
• Cardiac surgery
• Neurosurgery
• Vascular surgery

Lower Clotting Risk:
• AV replacement
• Atrial fib without prior stroke
• DVT/PE >3 months

Higher Clotting Risk:
• Mechanical MV
• Multiple mechanical valves
• Atrial fib with prior stroke
• DVT/PE ≤ 3 months

## Is OAC Interruption Necessary?

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
<th>Annual Bleeding Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>Score</td>
</tr>
<tr>
<td>Abnormal liver/renal function</td>
<td>1 each</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1-2</td>
</tr>
<tr>
<td>Bleeding history</td>
<td>1</td>
<td>≥3</td>
</tr>
<tr>
<td>Labile INR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Elderly (&gt;65y)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Drugs: NSAIDs/antiplatelet, EtOH</td>
<td>1 each</td>
<td></td>
</tr>
</tbody>
</table>

Doherty JU et al. JACC 2017;69:871-98
Uninterrupted Anticoagulation

- Cardiac catheterization
  - Right heart procedures
  - Radial access
  - Diagnostic

- Electrophysiology procedures
  - CIEDs
    - BRUISE-CONTROL: warfarin (3.5%) vs. bridge (16%)
    - BRUISE-CONTROL 2: uninterrupted DOAC
  - Ablation

Periprocedural anticoagulation strategies in patients undergoing ablation

Figure 2. Kaplan–Meier Plot of Time to First Adjudicated Major Bleeding Event (Ablation Set).

Major bleeding events were defined according to the International Society on Thrombosis and Hemostasis. The hazard ratio was calculated with a Cox proportional-hazards model, with a Wald confidence interval. The inset shows the same data on an expanded y axis.
Nishimura RA et al. J Am Coll Cardiol 2014;63:e57-185

Prosthetic Valve

Mechanical valve

- MVR
- AVV R With risk factors
- AVV R No risk factors

Bioprosthetic valve

- MVR
- AVV R
- TAVR

VKA INR goal 2.5
First 3-6 mo in low bleed risk patients (IIa)

On-X Valve
VKA INR goal 1.5-2 after 3 mo (IIb)

VKA INR goal 2.5
ASA 75 mg–100 mg PO QD Long-term (IIa)

Clopidogrel 75 mg QD ASA 75 mg–100 mg QD First 6 mo (IIb)

VKA INR goal 2.5
First 3 mo in low bleed risk patients (IIb)

VKA INR goal 2.0
ASA 75 mg–100 mg QD Long-term

VKA INR goal 3.0
ASA 75 mg–100 mg QD Long-term (I)

If VKA therapy interrupted for noncardiac procedures, minimize time with subtherapeutic INR

If VKA therapy interrupted for noncardiac procedures, minimize time with subtherapeutic INR

Bridging anticoagulation with UFH or SC LMWH (I)

No bridging additional anticoagulation needed (I)
## DOAC Holding Times

<table>
<thead>
<tr>
<th>DOAC</th>
<th>CrCl (mL/min)</th>
<th>Procedure Bleed Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
<td>Non-Low</td>
</tr>
<tr>
<td>Dabigatran</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>≥ 24 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>50-79</td>
<td>≥ 36 h</td>
<td>≥ 72 h</td>
</tr>
<tr>
<td>30-49</td>
<td>≥ 48 h</td>
<td>≥ 96 h</td>
</tr>
<tr>
<td>15-29</td>
<td>≥ 72 h</td>
<td>≥ 120 h</td>
</tr>
<tr>
<td>&lt;15</td>
<td>≥ 96 h (no data)</td>
<td>No data- check dTT?</td>
</tr>
<tr>
<td>Factor Xa Inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30</td>
<td>≥ 24 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>15-30</td>
<td>≥ 36 h</td>
<td>≥ 72 h (no data)- check anti-Xa level?</td>
</tr>
<tr>
<td>&lt;15</td>
<td>≥ 48 h (no data)</td>
<td></td>
</tr>
</tbody>
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Bridging Agent

• Unfractionated Heparin (UFH)
  – Inpatient setting
  – Renal insufficiency
  – Stop 4-6 h prior

• Low Molecular Weight Heparin (LMWH)
  – Self injection
  – Stop ≥ 24 h prior
  – Reduced hospital LOS

• Alternative agent for HIT history
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