Update on Oral Anticoagulation for Mechanical Heart Valves

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Update on Oral Anticoagulation for Mechanical Heart Valves
Douglas C. Anderson, Pharm.D., D.Ph.

I have no financial relationships to disclose.

AND

I will not discuss off label use and/or investigational use in my presentation.
Prosthetic Valves and Thrombogenicity

• Two types of prosthetic valves
  • Bioprosthetic
    • Less thrombogenic
    • Less durable
  • Mechanical
    • More durable
    • Much more thrombogenic
      • Thrombogenicity depends on
        • Valve type and materials
        • Placement

• Thromboembolic events include:
  • Valve thrombosis which may necessitate treatment with fibrinolytics or valve replacement
  • Systemic embolism
  • Stroke.
Risk of Thrombosis w/ Mechanical Valves

• Annual risk ranges 4-23% without prophylaxis

• With prophylaxis relative risk is reduced to 0.21 , or 1–2 per 100 patient years

• Risk is highest in the early post-surgical period (approx. 3 months) until the valve is fully endothelialized
Evolution of the Prosthetic Valve
Thromboembolic Event Rates of Different MVPs

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>Annual Anticoagulated TE Rate (% per year)</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caged-ball</td>
<td>2.5</td>
<td>Starr-Edwards valve</td>
</tr>
<tr>
<td>Tilting disk</td>
<td>0.7</td>
<td>Medtronic-Hall valve</td>
</tr>
<tr>
<td>Bileaflet</td>
<td>0.5</td>
<td>On-X valve</td>
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</table>

Starr-Edwards valve

Medtronic-Hall valve

On-X valve
Influence of Valve Position on Thrombogenicity

• Mitral position appears to be more thrombogenic than aortic position
  • Annual TE rate with St. Jude Medical bileaflet valves without antithrombotic prophylaxis:
    • Aortic position: 12%
    • Mitral position: 22%
  • 5-year TE event rate with Starr-Edwards valves:
    • Aortic 35%
    • Mitral 70%

• Tricuspid valves are rarely replaced; however, they are the highest risk valves when they are replaced

• Other factors such as multiple valve replacement and co-morbidities also influence thrombogenicity
# Other Risk Factors for Thrombosis and/or Total Morbidity/Mortality

<table>
<thead>
<tr>
<th>Co-morbid Condition</th>
<th>Effect(s) on Morbidity/Mortality</th>
</tr>
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</table>
| **Aortic + Mitral valve replacement**        | • TE rate 2.4x higher than AVR alone and 1.33x higher than MVR alone  
• Early mortality rate 3x higher than AVR alone and 1.4x higher than MVR alone |
| **Atrial fibrillation**                      | • TE rate 1.6x higher than patients with AVR in sinus rhythm, and long-term mortality rate 2.2x higher |
| **Poor LV function/heart failure**          | • Patients with NYHA IV heart failure were 10.7x more likely to die within 5 years of aortic valve replacement with MVP compared with NYHA I-II |
| **Left atrial enlargement**                  | • 3x higher incidence of systemic embolism in patients with left atrial dimension ≥ 4 cm compared with patients with left atrial dimension < 4 cm |
| **Age > 70 years**                           | • 1.9x higher incidence of stroke compared to patients < 70 years  
• Higher risk of perioperative mortality  
• Higher incidence of valve-related reoperation |
| **History of prior TE**                      | • Patients with history of pre-operative TE had 3.2x risk for TE and 5.4x risk for repeated TE after AVR |
Antithrombotic Prophylaxis
Initiation of Anticoagulation

• Briding Post-Valve Replacement
  • ACC/AHA: UFH or LMWH
  • American College of Chest Physicians (ACCP): prophylactic dose UFH, or prophylactic or therapeutic dose LMWH

• Choice of anticoagulant
  • Consider position, number of valves, types of valves
  • Target INR influenced by position(s) and number of valve replacements
### Summary of ACC/AHA and ACCP Recommendations

<table>
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<tr>
<th>Condition</th>
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<tr>
<td>Aortic valve replacement</td>
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<tr>
<td>VKA</td>
<td><strong>Preferred</strong> over antiplatelet agents</td>
<td><strong>Preferred</strong> over no VKA or antiplatelet agents alone</td>
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</table>
| Target INR                 | **2.5** (range 2.0–3.0) for bileaflet or current-generation single tilting disc and no risk factors  
|                            | **3.0** (range 2.5–3.5) if additional risk factors or older generation valves (e.g. caged-ball) | **2.5** (range 2.0-3.0) for all valves |
| Aspirin                    | 75-100 mg/day, added to VKA                  | 50-100 mg/day, added to VKA if low risk of bleeding |

*Chest.* 2012;141(2 suppl):e576S-e600S.  
*J Am Coll Cardiol.* 2014;63(22):e57-e185.  
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PROACT Trial

- AVR with On-X valve: Multicenter, prospective, randomized, unblinded, controlled

- N=375, 3.82 years

- Treatment Groups:
  - Treatment: first 3 months, warfarin target INR 2.0-3.0 + ASA INR target 1.5-2.0 + ASA 81 mg/day.
  - Control: Warfarin target INR 2.0-3.0 + ASA 81 mg/day

- Mean INR
  - Treatment: 1.89±0.49
  - Control: 2.50±0.63

*J Thorac Cardiovasc Surg. 2014;147(4):1202-1211.e2*
Kaplan-Meier life tables with 5-year event-free rates

Kaplan-Meier plot of major or minor bleeding

Log-rank p-value = 0.002

Kaplan-Meier plot of thromboembolism

Log-rank p-value = 0.128
PROACT Trial

Outcomes:

• No difference in thromboembolic events
• No difference in cerebrovascular events
• Treatment group with significantly less minor, major, and total bleeding
• Limitation: Only applies to On-X AVR prostheses

LOWERING-IT Trial

• AVR with: Sorin Bicarbon, St Jude Medical, Edwards Mira, Carbomedics
• Single-center, open-label, prospective, randomized, controlled
• N=396, duration 5.6 years
• Treatment Groups:
  • Treatment: INR 1.5–2.5
  • Control: INR 2.0–3.0
  • No ASA was added
• Mean INR:
  • Treatment: 1.94±0.21
  • Control: 2.61±0.25

## Outcome Events

<table>
<thead>
<tr>
<th></th>
<th>Low-INR (n=197)</th>
<th>Conventional-INR (n=199)</th>
<th>P</th>
<th>OR (CI$^{95%}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic events</td>
<td>1</td>
<td>3</td>
<td>0.62</td>
<td>0.33 (0.006-4.20)</td>
</tr>
<tr>
<td>Hemorrhagic events</td>
<td>6</td>
<td>16</td>
<td>0.04</td>
<td>0.36 (0.11-0.99)</td>
</tr>
</tbody>
</table>

**Outcomes:**
- Non-inferiority for thromboembolic events; paradoxically more TE and CVA in Conventional-INR group
- Significantly less minor, major, and total bleeding

Direct Oral Anticoagulants (DOACs) for MVP

What we want:

• Therapeutically non-inferior to warfarin (superiority would be nice)
• Bleeding and other adverse effects better than warfarin (or at least no worse)
• Easier to manage than warfarin
RE-ALIGN Trial

• **Design**: Open-label, prospective, randomized, multi-center, phase 2 trial

• **Study patients**: 252 patients with mechanical bi-leaflet in aortic, mitral, or both, and implantation ≤ 7 days, or > 3 months

• **Study groups**:
  - Dabigatran adjusted for CrCl:
    - < 70 mL/min: 150 mg BID
    - 70–109 mL/min: 220 mg BID
    - ≥ 110 mL/min: 300 mg BID
  - Warfarin INR
    - “Low risk” 2.0–3.0
    - “High risk” 2.5–3.5

• **Duration**: 12 weeks, terminated early by safety monitors

• **Results** (dabigatran vs warfarin, respectively):
  - Thromboembolic events: 9% versus 5%, p=0.24
  - Any bleeding: 27% versus 12%, p=0.01
  - Major bleeding: 4% versus 2%, p=0.48

DOACs for MVP

• Thromboembolic events: worse than warfarin
• Bleeding: worse than warfarin
• Not recommended at this time in both ACC/AHA and ACCP guidelines
• Do we need to monitor and adjust them for MVPs?
Systemic Embolism Despite Therapeutic INR

- If patient was not previously on ASA, then add ASA 50–100mg daily, and
- Titrate VKA to a higher INR range
- Example: If a patient with a prior TE event were having an aortic valve replaced with a bileaflet valve then the VKA should be adjusted to an INR of 2.5–3.5 and low dose ASA added

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<tr>
<th>Previous INR Target (range)</th>
<th>Post Systemic Embolism INR Target (range)</th>
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<tr>
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Bioprosthetic Valves

• Lower thrombogenicity

• Most patients will not need life-long anticoagulation with bioprosthetic replacement

• Lower risk of stroke and mortality if patients receive anticoagulation for up to 6 months.

• Anticoagulation may also reduce risk of thrombosis of bioprosthetic valves.

# Recommendations for Prophylactic Antithrombics for Bioprothetics Valve Replacements

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<tr>
<td>VKA</td>
<td>At least 3 months*</td>
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<td>2.5 (2.0-3.0)</td>
<td></td>
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<td>Aspirin</td>
<td>75-100 mg/day, preferred after first 3 months</td>
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<td>Aspirin</td>
<td>75-100 mg/day after first 3-6 months**</td>
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*As long as 6 months in patients at low risk of bleeding.
**Presence of AF, previous TE, hypercoagulable condition or other indication for VKA requires long-term VKA therapy.

Transcatheter Aortic Valve Replacements (TAVR)

- Limited data comparing antithrombotic strategies
- ACCP: ASA 50-100 mg/day + clopidogrel 75 mg/day for first 3 months, then long-term ASA
- ACC/AHA: ASA 75-100 mg/day + clopidogrel 75 mg/day for first 6 months, then lifelong ASA
- Consider other risk factors

*Chest.* 2012;141(2 suppl):e576S-e600S.
*J Am Coll Cardiol.* 2014;63(22):e57-e185.
Questions?