How to Manage Anticoagulant Therapy

After Valve Replacement

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Aortic Valve Prosthesis
Risk of Major Bleeding and Reoperation

Risk of Reoperation and Major Bleeding (%)

Patient Age at Implantation

Prosthetic Valve Thrombosis Mechanisms

Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886
Prosthetic Valve Thrombosis
Pathophysiological Factors

Potential mechanism of prosthetic valve thrombus by anatomical location

- **Right-sided heart valves**
  - Clotting pathway > platelet pathway
  - **Tricuspid Valve**
    - **Hemodynamic factors**
      - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
    - **Hemostatic factors**
      - Hypercoagulability
      - Tissue injury
    - **Surface factors**
      - Incomplete prosthesis endothelialization
      - Prosthesis malpositioning

- **Pulmonic Valve**
  - **Hemodynamic factors**
    - Slow venous blood flow (especially if concomitant pulmonary hypertension with low RV output).
  - **Hemostatic factors**
    - Hypercoagulability
  - **Surface factors**
    - Valve frame fracture

- **Left-sided heart valves**
  - Platelet pathway > clotting pathway
  - **Aortic Valve**
    - **Surface factors**
      - Incomplete prosthesis endothelialization
      - Prosthesis malpositioning
    - **Hemostatic factors**
      - Tissue injury
      - Prosthesis malpositioning
    - **Hemodynamic factors**
      - Local blood flow turbulences
      - Incomplete apposition
  - **Mitral Valve**
    - **Hemodynamic factors**
      - Relatively slow blood flow in case of AF, atrial dilation or low LV output
      - Local blood flow turbulences
      - Incomplete apposition
    - **Hemostatic factors**
      - Tissue injury
    - **Surface factors**
      - Incomplete prosthesis endothelialization
      - Prosthesis malpositioning
      - Leaflet injury

Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886
Prosthetic Valve Thrombosis Classification

Temporal Classification

- **ACUTE**
  - 0 to 3 days after TAVR
- **SUBACUTE**
  - 3 days to 3 months after TAVR
- **LATE**
  - 3 months to 1 year after TAVR
- **VERY LATE**
  - >1 year after TAVR

Diagnostic Certainty Classification

**Definite valve thrombosis**
- **Clinical criteria**
  - Regression of new-onset heart failure symptoms after initiation of anticoagulation therapy
- **CTA criteria**
  - Presence of reduced leaflet motion
  - Presence of hypoattenuated leaflet thickening
- **Echocardiographic criteria**
  - Direct visualization of valve thrombosis
  - Regression of elevated mean gradient (<10 mm Hg) after oral anticoagulation therapy
- **Pathological criteria**
  - Evidence of device thrombosis at autopsy or via examination of tissue retrieved during cardiac surgery

**Probable valve thrombosis**
- **Clinical criteria**
  - Acute- or subacute-onset heart failure symptoms (i.e., progressive dyspnea, peripheral edema, pulmonary rales, jugular turgor)
- **CTA criteria**
  - Reduced leaflet motion
  - No hypoattenuated leaflet thickening visible
- **Echocardiographic criteria**
  - Increase in mean gradient >10 mm Hg
  - No thrombus visible

**Possible valve thrombosis**
- **Clinical criteria**
  - Unexplained arterial thromboembolic event at any time after TAVR in patients without prior documented cardioembolic source without culprit epicardial or carotid atherosclerosis

Dangas GD et al. J Am Coll Cardiol 2016;137:2670-886
Mechanical Valve Replacement
Initiation of Anticoagulation

## Biological Valve Replacement
### Initial Anticoagulation Regimen

**Randomized Trial**
**Warfarin vs Aspirin**
**3 months postoperative**

<table>
<thead>
<tr>
<th>Total population</th>
<th>Warfarin (n = 167)</th>
<th>Aspirin (n = 161)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (n%)</td>
<td>2 (1.2%)</td>
<td>5 (3.1%)</td>
<td>0.267</td>
</tr>
<tr>
<td>DVT (n%)</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>TCI/Stroke (n%)</td>
<td>8 (4.8%)</td>
<td>6 (3.7%)</td>
<td>0.602</td>
</tr>
<tr>
<td>Other thromboembolic complication (n%)</td>
<td>1b (0.6%)</td>
<td>1a (0.6%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Total thromboembolic events (n%)</td>
<td>11 (6.6%)</td>
<td>12 (7.5%)</td>
<td>0.830</td>
</tr>
</tbody>
</table>

**Multivariate analysis of factors associated with major bleeding events.**

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.04 (0.94–1.14)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7.80 (0.96–63.08)</td>
</tr>
<tr>
<td>Gender</td>
<td>0.19 (0.02–1.57)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.67 (0.13–3.33)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2.14 (0.42–10.79)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5.18 (1.06–25.43)</td>
</tr>
</tbody>
</table>

Biological Valve Replacement
Initial Anticoagulation Regimen

STS Database
# Biological Valve Replacement

## Initial Anticoagulation Regimen

### Table 2: Outcomes at 3 Months With Anticoagulant Strategies in the Overall Population of Patients Receiving Aortic Valve Bioprostheses

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted 3-Month Incidence (%)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aspirin-Only (n = 12,457)</td>
<td>Warfarin-Only (n = 2,999)</td>
</tr>
<tr>
<td>Death</td>
<td>3.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Embolism</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.0</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Brennan JM et al. J Am Coll Cardiol 2012;60:971–7
Biological Valve Replacement

Thromboembolic Risk

Heras M et al. J Am Coll Cardiol 1995;25:1111–1119
Biological Valve Replacement
Thromboembolic Risk

Heras M et al. J Am Coll Cardiol 1995;25:1111–1119
## Valve Replacement Anticoagulation Regimen

### Table 2: Current recommendations for anti-thrombotic therapy following surgical prosthetic valve replacement

<table>
<thead>
<tr>
<th>Site</th>
<th>Mechanical prosthesis</th>
<th>Bioprosthesis</th>
<th>3 post-operative months</th>
<th>&gt;3 post-operative months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESC/EACTS guidelines(^{14})</td>
<td>Aortic</td>
<td>2.5</td>
<td>3.0 or 3.5(^{b})</td>
<td>Aspirin (IIa)</td>
</tr>
<tr>
<td></td>
<td>Mitral</td>
<td>3.0 or 3.5(^{b})</td>
<td>3.0 or 3.5(^{b})</td>
<td>VKA (IIb)</td>
</tr>
<tr>
<td>AHA/ACC guidelines(^{15})</td>
<td>Aortic</td>
<td>2.5</td>
<td>3.0</td>
<td>VKA</td>
</tr>
<tr>
<td></td>
<td>Mitral</td>
<td>3.0</td>
<td>3.0</td>
<td>VKA + aspirin</td>
</tr>
<tr>
<td>ACCP consensus(^{16})</td>
<td>Aortic</td>
<td>2.5</td>
<td>2.5</td>
<td>Aspirin</td>
</tr>
<tr>
<td></td>
<td>Mitral</td>
<td>3.0</td>
<td>3.0</td>
<td>VKA + aspirin</td>
</tr>
</tbody>
</table>

**Notes:**
- Risk factors include AF, previous thromboembolic event, left ventricular dysfunction, hypercoagulable state and for AHA/ACC Guidelines older generation prosthesis.
- According to whether prosthesis is at low or intermediate thrombogenicity (high-thrombogenicity prostheses are not represented here).
- Patients with concomitant atherosclerotic disease or with thromboembolism despite adequate INR.
Mechanical Valve Replacement
Bridging Anticoagulation

**Figure 1** Main bridging steps for an intervention requiring withdrawal of oral anticoagulation in a patient with a mechanical prosthesis. *Intravenous UFH may be favoured in patients at high thromboembolic risk. Timing should be individualized according to patient characteristics, actual INR, and the type of intervention.*
## Transaortic Valve Implantation

### Antithrombotic Therapy

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-term anti-thrombotic treatment</strong></td>
<td>Aspirin 81 mg/day indefinitely</td>
<td>Lifelong aspirin 75–100 mg daily (Class IIb; level of evidence: C)</td>
<td>Low-dose aspirin indefinitely</td>
<td>Low-dose aspirin indefinitely</td>
</tr>
<tr>
<td><strong>Post-procedural anti-thrombotic treatment</strong></td>
<td>Aspirin 81 mg/day + clopidogrel 75 mg/day for 3–6 months If warfarin indicated (AF), then no clopidogrel</td>
<td>Aspirin 75–100 mg/day + clopidogrel 75 mg/day for 6 months</td>
<td>ASA 80 mg/day + thienopyridine for 1–3 months If oral anticoagulant indicated (AF), avoid triple therapy unless definite indication exists</td>
<td>Low-dose aspirin + a thienopyridine early after TAVI In patients in AF, a combination of VKA and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding</td>
</tr>
</tbody>
</table>

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[^44]: Iung B, Rodes-Cabau J. Eur heart J 2014;35:2942-2949
Mechanical Valve Anticoagulation

Reason for Dabigatran Failure

Potential pharmacodynamic explanation for the failure of dabigatran to prevent clotting in patients with MHVs. By triggering the intrinsic pathway, MHVs induce the generation of thrombin (IIa) in concentrations that overwhelm those of dabigatran. By contrast, by reducing the levels of fIX, fX, and prothrombin, warfarin attenuates fXa and thrombin generation, thereby preventing clotting. f = factor; MHV = mechanical heart valve.

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# Bioprosthetic Valve Failure

## Valve Thrombosis vs Structural Failure

<table>
<thead>
<tr>
<th>Bioprosthetic Thrombosis</th>
<th>Bioprosthetic Degeneration</th>
</tr>
</thead>
</table>

Bioprosthetic Valve Failure

Valve Thrombosis vs Structural Failure

Bioprosthetic Valve Failure
Subclinical Valve Thrombosis

Reduced Leaflet Motion in 13 to 40% of pts

Antithrombotic Therapy after Valve Replacement

Gaps of Evidence

• Combination of aspirin with VKA in patients with a mechanical prosthesis
• Optimal timing, doses, and type of heparin to be used early after mechanical valve replacement
• Use of aspirin vs. VKA during the first three post-operative months following aortic valve replacement using a bioprosthesis
• Use of DOACs in patients with a bioprosthesis
• Anti-thrombotic therapy after TAVI in patients in sinus rhythm and in AF
Antithrombotic Therapy after Valve Replacement
Gaps of Evidence

Table 4  Major gaps in evidence in anti-thrombotic therapy after valve replacement

- Combination of aspirin with VKA in patients with a mechanical prosthesis and contemporary target INRs
- Optimal timing, doses, and type of heparin to be used early after mechanical valve replacement
- Use of aspirin vs. VKA during the first three post-operative months following aortic valve replacement using a bioprosthesis
- Use of DOACs in patients with a bioprosthesis
- Use of anti-Xa DOACs in patients with a mechanical prosthesis
- Anti-thrombotic therapy after TAVI in patients in sinus rhythm and in AF
# Valve Replacement Anticoagulation Regimen

<table>
<thead>
<tr>
<th></th>
<th>ACC/AHA</th>
<th>ACCP</th>
<th>ESC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical MHV replacement</strong></td>
<td>Anticoagulation with VKA (INR of 2.5 for AVR and no risk factors for TE; INR of 3.0 for AVR with risk factors for TE or MVR) plus aspirin 75-100 mg daily (Class I)</td>
<td>VKA (INR of 2.5 for AVR and 3.0 for MVR) indicated over no VKA for long-term management (Grade 1B)</td>
<td>Anticoagulation with VKA (target INR according to prosthesis thrombogenicity and patient-related risk factors [Table 1]; Class I) Aspirin ≤100 mg daily if concomitant atherosclerotic disease and/or TE despite adequate INR (Class IIa)</td>
</tr>
<tr>
<td><strong>Surgical BHV replacement</strong></td>
<td>Anticoagulation with VKA (INR of 2.5) plus aspirin 75-100 mg for the first 3 months followed by aspirin 75-100 mg daily alone (Class IIa/IIb)</td>
<td>Aspirin 50–100 mg indicated in the first 3 months (Grade 2C) Aspirin 50–100 mg is indicated over VKA and over no APT for the first 3 months after AVR in patients in sinus rhythm (Grade 2C) VKA (INR: 2.5) indicated over no VKA for the first 3 months after MVR (Grade 2C)</td>
<td>Anticoagulation with VKA for the first 3 months after MVR, MVRep, or TVR (Class IIa) Anticoagulation with VKA for the first 3 months after AVR (Class IIb) Aspirin ≤100 mg daily for the first 3 months after AVR (Class IIa)</td>
</tr>
<tr>
<td><strong>TAVR</strong></td>
<td>Clopidogrel 75 mg plus aspirin 75-100 mg for 6 months followed by aspirin 75–100 mg daily alone (Class IIb)</td>
<td>Aspirin 50–100 mg plus clopidogrel 75 mg/dl is indicated over VKA and over no APT for the first 3 months (Grade 2C)</td>
<td>No specific recommendations</td>
</tr>
</tbody>
</table>

**ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AHA = American Heart Association; APT = antiplatelet therapy; AVR = aortic valve replacement; BHV = bioprosthetic heart valve; ESC = European Society of Cardiology; INR = international normalized ratio; MHV = mechanical heart valve; MVR = mitral valve replacement; MVRep = mitral valve repair; TAVR = transcatheter aortic valve replacement; TE = thromboembolism; TVR = target vessel revascularization; VKA = vitamin K antagonist.**