Antithrombotic Therapy in Patients With Mechanical and Biological Prosthetic Heart Valves

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Abbreviation: INR = international normalized ratio

In the present consensus report, we continue to address literature that may permit a more refined assessment of the optimal level of the international normalized ratio (INR) for patients with modern mechanical prosthetic heart valves. We address whether treatment with low doses of aspirin or other antithrombotic drugs, in combination with oral anticoagulants, may be beneficial. Investigations of low levels of warfarin are also assessed. Investigations included in the present report are generally limited to those that report antithrombotic prophylaxis in terms of the INR. Some investigations that relied on an estimation of the INR were also included, and these studies are identified.

Most of the published investigations lack data that would permit a firm conclusion about the optimal antithrombotic regimen for specific patients. Patients rarely were stratified according to additional risk factors associated with the type and location of prosthetic valves. Most results of antithrombotic prophylaxis are from nonrandomized case series without controls. The safety and efficacy of a given range of INR are usually reported on the basis of an intention-to-treat analysis rather than on the basis of the intensity of anticoagulation actually achieved. In some important investigations, less than half of the INRs were in the target range. These limitations weaken the basis on which therapeutic recommendations can be made. They also indicate a need for further research in this area. Prospective studies that address both the risk factors among patients with each type and location of prosthetic valve and the level of anticoagulation actually achieved are needed before controversy regarding prophylaxis can be resolved.

Mechanical Prosthetic Valves

St. Jude Medical Bileaflet Mechanical Valve

Experience with St. Jude Medical bileaflet mechanical valves is shown in Table 1.3–6 Lack of prophylaxis gave unacceptable results.7 Horstkotte et al,3 in a study of patients with St. Jude Medical valves in the aortic position, showed that less intense anticoagulation, at an estimated INR of 1.8 to 2.8, in comparison to an estimated INR of 2.5 to 3.5, resulted in only a mild increase in the rate of thromboemboli (3.9%/yr vs 2.8%/yr) but a prominent reduction in the rate of major bleeding (0.4%/yr vs 1.2%/yr). Loss of atrial contraction had a pronounced effect on thromboembolic rates.8 Among patients, 86% of whom had St. Jude Medical valves, 96% of which were in the aortic position, thromboemboli were not more frequent at an INR of 2.0 to 3.0 than at an INR of 3.0 to 4.5, providing they were in sinus rhythm with a normal-sized left atrium.6

A case series by Cannegieter and associates,9 which included bileaflet valves in the aortic, mitral, or both positions, showed the fewest adverse effects, at an INR of 2.0 to 2.9.

A retrospective case series by Arom and associates,10 of patients age ≥70 years with St. Jude Medical aortic valves, showed a frequency of thromboemboli of 0.7%/yr, at an INR of 1.8 to 2.5. The INR was measured only during the later years of the investigation. The prevalence of atrial fibrillation was not stated.

Based on an analysis of published data, David et al concluded that there was no clinically important difference in the rate of systemic embolism among patients with the St. Jude Medical bileaflet valve and those with the CarboMedics bileaflet valve.

Tilting Disk Valves

In the aortic position, a low level of the INR (2.0 to 3.0) gave good results in a case series of patients with Medtronic-Hall valves.11 Regarding the Björk-Shiley spherical disk valve and the Björk-Shiley Convexo Con cave valve, to our knowledge, there are no investigations that use an INR of 2.0 to 3.0. Therefore, whether a low level of INR can be used safely with such valves, particularly in the aortic position, is undetermined.

Tilting disk valves showed more thromboemboli when in the mitral position than in the aortic position (Table 2).12–16 Withholding prophylaxis, or the use of prophylaxis with antiplatelet agents alone in patients with the Björk-Shiley spherical disk valve, showed unsatisfactory results.17

Various Valves

Saour and associates,18 in a randomized trial among patients with various types of mechanical valves, did not show fewer thromboembolic events in patients treated with oral anticoagulants at an estimated INR of 7.4 to 10.8 than at an estimated INR of 1.9 to 3.6. More frequent minor bleeding, however, was shown at the higher INR, and a trend suggested more frequent major bleeding.

Pengo and associates,19 in a study of patients with various valves (estimated 74% tilting disk valves, 25% bileaflet valves, 1% ball valves) in the aortic, mitral, or both positions, reported a rate of thromboemboli of 1.8%/yr with an INR of 2.5 to 3.5 and a comparable rate of 2.1%/yr with an of INR 3.5 to 4.5.

An INR of 2.5 to 4.9 was optimal in a case series reported by Cannegieter et al.9 Most patients (77%) described by Cannegieter and associates had tilting disk valves. Some (3%) had caged ball or caged disk valves.9
The INR associated with the fewest adverse events was dependent on the number of valves, the location of the valve (mitral or aortic), and the type of valve (caged ball or disk, tilting disk, or bileaflet).

An analysis of results of several investigations of patients with various types of valves, based on estimates of the INR, suggests that an INR of 2.5 to 3.5 is satisfactory.\(^\text{20}\) The analysis demonstrated that a low thromboembolic rate with an acceptable hemorrhagic rate can be achieved at a minimum INR range of 2.5 to 3.0 and a maximum INR range of 2.5 to 3.6. Increasing the INR beyond 3.6 did not reduce the thromboembolic rates, but did increase the risk of hemorrhage.

### Valve Position and Number of Valves

The prevalence of thromboemboli is higher with tilting disk prosthetic valves in the mitral position than in the aortic position (Table 2). This is probably true with bileaflet mechanical valves as well, but data that used strict criteria for the measurement of the INR are sparse (Table 1). Cannegieter et al,\(^\text{9}\) in a case series, showed an incidence of thromboembolism of 0.5%/yr with prosthetic aortic valves, 0.9%/yr with prosthetic mitral valves, and 1.2%/yr with both aortic and mitral valves. Irrespective of the type of mechanical valve, if the valve was in the aortic position, an INR of 2.0 to 2.9 gave results comparable to an INR of 3.0 to 3.9.\(^\text{9}\)

Higher rates of thromboembolic complications with valves in the mitral position may be attributed to a higher incidence of atrial fibrillation, left atrial enlargement, and perhaps endocardial damage from rheumatic mitral valve disease.\(^\text{5,21}\) A low left ventricular ejection fraction, old age, and history of prior thromboembolism also are associated with thromboembolic complications.\(^\text{21}\)

### Table 1—Thromboemboli With St. Jude Medical Bileaflet Mechanical Valves in Patients Who Received Prophylaxis With Coumarin Derivatives*

<table>
<thead>
<tr>
<th>Valve</th>
<th>Patients, No.</th>
<th>INR</th>
<th>THROM, %/yr</th>
<th>TE, %/yr</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ao</td>
<td>188</td>
<td>2.0–3.0</td>
<td>0</td>
<td>1.9</td>
<td>Acar et al(^\text{a})</td>
</tr>
<tr>
<td>Ao</td>
<td>47</td>
<td>2.8–4.3</td>
<td>0</td>
<td>3.0</td>
<td>Vogt et al(^\text{a})</td>
</tr>
<tr>
<td>Ao</td>
<td>192</td>
<td>3.0–4.5</td>
<td>0</td>
<td>1.7</td>
<td>Acar et al(^\text{a})</td>
</tr>
<tr>
<td>Ao</td>
<td>3.0–4.5</td>
<td>1.9</td>
<td>Horstkotte et al(^\text{a})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ao</td>
<td>4.0–6.0</td>
<td>1.4</td>
<td>Horstkotte et al(^\text{a})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>1.8–2.8</td>
<td>6.5</td>
<td>Horstkotte et al(^\text{a})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>2.5–3.5</td>
<td>0.6</td>
<td>3.7</td>
<td>Fiore et al(^\text{a})</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>2.5–3.5</td>
<td>4.7</td>
<td>Horstkotte et al(^\text{a})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>32</td>
<td>2.8–4.3</td>
<td>0</td>
<td>2.2</td>
<td>Vogt et al(^\text{a})</td>
</tr>
<tr>
<td>M</td>
<td>3.0–4.5</td>
<td>2.9</td>
<td>Horstkotte et al(^\text{a})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>4.0–6.0</td>
<td>2.5</td>
<td>Horstkotte et al(^\text{a})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Ao = aortic; M = mitral; THROM = valve thrombosis; TE = thromboemboli.  
†INR was estimated.  
96% aortic valves, 86% St. Jude Medical valves.

### Elderly Patients

Cannegieter and associates\(^\text{9}\) showed that the risk of thromboembolism was small among patients < 50 years of age (0.1%/yr). The frequency increased among patients 50 to 69 years of age (0.8%/yr), and the incidence was highest among patients 70 years of age.

### Table 2—Thromboemboli in Patients With Tilting Disk Valves Treated With Oral Anticoagulants*

<table>
<thead>
<tr>
<th>Valve</th>
<th>INR</th>
<th>Patients, No.</th>
<th>Throm, %/yr</th>
<th>TE, %/yr</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Med Hall</td>
<td>2.0–3.0</td>
<td>210</td>
<td>0</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>Med Hall</td>
<td>3.0–4.5</td>
<td>117</td>
<td>0</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Med Hall</td>
<td>2.5–3.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Sorin Mono</td>
<td>2.5–4.0</td>
<td>3,229</td>
<td>0.003</td>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>BS Spherical</td>
<td>2.0–4.5</td>
<td>109</td>
<td>0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>BS Spherical</td>
<td>3.0–4.0</td>
<td>162</td>
<td>0.6</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>BS Conv Conc</td>
<td>3.0–4.0</td>
<td>120</td>
<td>0.3</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

*Throm = Valve Thrombosis; TE = thromboemboli; Med Hall = Medtronic Hall; Mono = Monostrut; BS Spherical = Bjork Shiley; Spherical = Spherical Disk; Conv Conc = Convexo Concave.

†INR 2.5–3.5 for mitral valves.

‡Estimated.

§Includes aortic and mitral valves.
among patients ≥ 70 years of age (1.1%/yr). Even so, among elderly patients (≥ 70 years of age), a retrospective case series suggested that a low level of oral anticoagulants was satisfactory with St. Jude Medical valves in the aortic position. Many of these patients were treated before the INR was in use, but in recent years, an INR of 1.8 to 2.5 resulted in a rate of thromboemboli of 0.7%/yr.

**Children**

Antithrombotic therapy in children with prosthetic heart valves is discussed in this supplement in an article entitled “Antithrombotic Therapy in Children” by Monagle et al (see page 344).

**Anticoagulants and Bleeding**

Data from several individual reports show varying frequencies of bleeding with increasing levels of the INR (Table 3). Cannegieter and associates showed that the incidence of hemorrhagic stroke increased once the INR rose to ≥ 4.0, and a sharp increase occurred at an INR of 5.0. Van der Meer and associates showed a sequentially increased rate of bleeding as the INR increased from 3.0 to 6.0. Among women, a sharp increased rate of bleeding occurred at an INR of 6.0 and higher. An observational study from a large anticoagulation clinic, where anticoagulants were used for a variety of indications in addition to prosthetic valves, showed that the risk of intracranial hemorrhage increased dramatically at an estimated INR of 4.0. The incidence of bleeding was higher among patients ≥ 70 years of age than in younger patients.

**Aspirin in Combination With Oral Anticoagulants**

Turpie and associates, in a randomized trial, showed that aspirin 100 mg/d, in combination with oral anticoagulants at an INR of 3.0 to 4.5, was associated with fewer major systemic thromboemboli or death from vascular causes than oral anticoagulants alone, 1.9%/yr vs 8.5%/yr (p < 0.001). The rate of major bleeding, 8.5%/yr with aspirin plus oral anticoagulants vs 6.6%/yr with oral anticoagulants alone, was not statistically significantly different.

Meschengieser and associates, in a randomized trial, showed that aspirin 100 mg/d, in combination with oral anticoagulants at an INR of 2.5 to 3.5, was as effective as oral anticoagulants at an INR of 3.5 to 4.5. The frequency of thromboemboli or valve thrombosis was 1.3%/yr with aspirin in combination with the lower-intensity anticoagulation, and 1.5%/yr with the more intense anticoagulation without aspirin. Major bleeding was comparable—1.1%/yr with aspirin in combination with the lower-intensity anticoagulation, and 2.3%/yr with the more intense anticoagulation alone.

Meta-analysis supports the observation that the rate of thromboemboli is diminished with aspirin. Among the investigations reviewed in this meta-analysis, however, major bleeding was increased.

With an INR of 2.0 to 3.0 or 2.5 to 3.5, the frequency of bleeding is no greater with aspirin 325 mg to 600 mg/d than with 100 mg/d (Table 4). With an INR of 3.0 to 4.5, the risk of major hemorrhage may be high, irrespective of the use of aspirin. Low doses of aspirin did not increase the risk of major bleeding, but high doses of aspirin (660 mg/d) with an INR of 3.0 to 4.5 caused the risk of bleeding to be unacceptable. The combination of oral anticoagulants and aspirin may be particularly useful in patients with prosthetic valves who have coronary artery disease or stroke.

**Dipyridamole in Combination With Oral Anticoagulants**

We are aware of only one study in which dipyridamole was used in combination with warfarin at a known INR. Dipyridamole 300 mg/d was used in combination with warfarin (INR, 2.0 to 2.5) in a case series that included St. Jude Medical aortic, mitral, and two valves. The frequency of thromboemboli was 1.5%/yr. There was no control arm of that investigation.

A meta-analysis of six trials performed between 1971 and 1982, in which the INR is unknown, showed a reduction of fatal and nonfatal thromboemboli with dipyridamole in combination with oral anticoagulants. Katicicoglu and associates used a fixed dose of warfarin, 2.5 mg/d, in combination with aspirin 100 mg/d and dipyridamole 225 mg/d. In patients with St. Jude Medical valves in the aortic position, they showed thromboemboli at a rate of 1.4%/yr and no valve thrombosis. Using somewhat more aspirin (250 mg/d), but otherwise the same regimen among patients with St. Jude Medical aortic valves, mitral, or two valves, Yamak and associates showed a rate of 0.3%/yr valve thrombosis and 0.8%/yr thromboemboli. Others used dipyridamole in combination with aspirin, but no warfarin, in patients with St. Jude Medical aortic valves. They observed 1.6 to 2.1%/yr valve thrombosis and 0.0 to 1.6%/yr thromboemboli.

<table>
<thead>
<tr>
<th>Patients, No.</th>
<th>INR</th>
<th>Major Hemorrhagic Events, %/yr</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>834</td>
<td>1.6–3.9</td>
<td>0.7*</td>
<td>Butchart et al</td>
</tr>
<tr>
<td>196</td>
<td>2.0–3.0</td>
<td>4.0</td>
<td>Acar et al</td>
</tr>
<tr>
<td>238</td>
<td>2.0–4.5</td>
<td>1.6</td>
<td>Bloomfield et al</td>
</tr>
<tr>
<td>104</td>
<td>2.5–3.5</td>
<td>1.2</td>
<td>Pengo et al</td>
</tr>
<tr>
<td>181</td>
<td>2.5–4.8</td>
<td>2.1</td>
<td>Gossinger et al</td>
</tr>
<tr>
<td>178</td>
<td>2.8–4.3</td>
<td>2.0</td>
<td>Vogt et al</td>
</tr>
<tr>
<td>188</td>
<td>3.0–4.5</td>
<td>5.6</td>
<td>Acar et al</td>
</tr>
<tr>
<td>351</td>
<td>3.0–4.5</td>
<td>0.4</td>
<td>Vallejo et al</td>
</tr>
<tr>
<td>184</td>
<td>3.0–4.5</td>
<td>6.6</td>
<td>Turpie et al</td>
</tr>
<tr>
<td>101</td>
<td>3.5–4.5</td>
<td>3.8</td>
<td>Pengo et al</td>
</tr>
<tr>
<td>245</td>
<td>3.5–4.5</td>
<td>2.3</td>
<td>Meschengieser et al</td>
</tr>
<tr>
<td></td>
<td>5.0–5.4</td>
<td>4.8</td>
<td>Cannegieter et al</td>
</tr>
<tr>
<td></td>
<td>&gt; 6.5</td>
<td>75.0</td>
<td>Cannegieter et al</td>
</tr>
</tbody>
</table>

*Includes moderate.
Table 4—Oral Anticoagulant Plus Aspirin and/or Dipyridamole in Patients With Aortic, Mitral, and Multiple Valves*

<table>
<thead>
<tr>
<th>INR</th>
<th>ASA, mg/d</th>
<th>DIP, mg/d</th>
<th>Valve</th>
<th>THROM, %/yr</th>
<th>TE, %/yr</th>
<th>MAJ HEM, %/yr</th>
<th>REF</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0–3.0</td>
<td>100</td>
<td>–</td>
<td>VAR</td>
<td>0</td>
<td>0.5</td>
<td>3.6</td>
<td>Altman et al 28</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>650</td>
<td>±</td>
<td>VAR</td>
<td>0</td>
<td>1.1</td>
<td>5.1</td>
<td>Altman et al 28</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>660</td>
<td>150</td>
<td>B, BS</td>
<td>0</td>
<td>1.9</td>
<td>3.8</td>
<td>Altman et al 28</td>
</tr>
<tr>
<td>2.5–3.5</td>
<td>100</td>
<td>–</td>
<td>VAR</td>
<td>0</td>
<td>2.8</td>
<td>5.1</td>
<td>Altman et al 28</td>
</tr>
<tr>
<td>2.5–3.5</td>
<td>100</td>
<td>–</td>
<td>VAR</td>
<td>0.2</td>
<td>1.1</td>
<td>1.1</td>
<td>Meschenmoser et al 2</td>
</tr>
<tr>
<td>2.5–3.5</td>
<td>325</td>
<td>–</td>
<td>VAR</td>
<td>0</td>
<td>2.0</td>
<td>3.4</td>
<td>Altman et al 28</td>
</tr>
<tr>
<td>3.0–4.5</td>
<td>100</td>
<td>–</td>
<td>VAR</td>
<td>0</td>
<td>1.9</td>
<td>8.5</td>
<td>Turpie et al 1</td>
</tr>
<tr>
<td>3.0–4.5</td>
<td>660</td>
<td>150</td>
<td>B, BS</td>
<td>0</td>
<td>4.9</td>
<td>24.7</td>
<td>Altman et al 27</td>
</tr>
</tbody>
</table>

*THROM = valve thrombosis; TE = thromboemboli; ASA = aspirin; DIP = dipyridamole; SJ = St. Jude; VAR = various; B = Bicer (tilting disk valve similar to Björk Shiley); BS = Björk Shiley; MAJ HEM = major hemorrhage.

Interruption of Anticoagulant Therapy, Major Surgery, Management of Patients Including Home Monitoring of INR, Management of Major Bleeding, Reversal of Anticoagulation With Vitamin K₁, and Management of Pregnancy

These subjects are discussed in an article entitled “Oral Anticoagulants: Mechanism of Action, Clinical Effectiveness and Optimal Therapeutic Range” by Hirsh et al, in this supplement (see page 8), in the article “Use of Antithrombotic Agents During Pregnancy” by Ginsberg, Greer, Hirsh (see page 122), and in the article by Ansell et al, “Managing Oral Anticoagulant Therapy” (see page 22).

Bioprosthetic Valves

First 3 Months After Insertion in the Mitral Position

The frequency of thromboemboli has been high in the first 3 months after bioprosthetic valve insertion among patients not receiving antithrombotic therapy, particularly among patients with bioprosthetic valves in the mitral position.36,37 Among patients with bioprosthetic valves in the mitral position, Ionescu et al37 reported thromboemboli during the first 3 months after operation in 4 of 68 patients (5.9%) who did not receive anticoagulants and in 0 of 182 patients (0%) who received anticoagulants.

Heras and associates36 showed that oral anticoagulants (estimated INR, 3.0 to 4.5) in patients with bioprosthetic valves in the mitral position decreased the frequency of thromboemboli. However, the frequency remained high during the first 10 postoperative days.36 This may have been due to delay in achieving therapeutic levels of the INR. It was suggested that the early administration of heparin might explain why some groups observed lower rates of thromboemboli in patients who received short-term oral anticoagulants.36

Among patients with bioprosthetic valves in the mitral position, thromboemboli during the first 3 months occurred in 2 of 40 patients (5.0%), with an INR of 2.5 to 4.0 and in 2 of 39 patients (5.1%), with an INR of 2.0 to 2.3.38 These patients also received heparin 5,000 U every 12 h. All of the patients with thromboemboli had atrial fibrillation.38 Fewer bleeding complications occurred in the group that received oral anticoagulants at the lower INR. Other studies have shown that thromboemboli during the first 3 months after operation occurred despite adequate anticoagulation in patients with atrial fibrillation.39 Those with atrial fibrillation, a history of prior thromboembolism, or thrombi in the left atrium had higher rates of thromboemboli than patients with atrial fibrillation alone.39

First 3 Months After Insertion in the Aortic Position

Among patients with bioprosthetic valves in the aortic position, who received subcutaneous heparin 22,500 IU/d and aspirin 100 mg/d for the first 14 to 22 days after operation, but did not receive oral anticoagulants, the frequency of thromboemboli during the first 6 months was 1 occurrence out of 57 subjects (1.8%).40 Among patients who received oral anticoagulants and heparin 5,000 U subcutaneously every 12 h, 0 of 109 patients with prosthetic valves in the aortic position had thromboemboli during the first 3 months.48 However, some showed no advantage of early anticoagulation among patients with bioprosthetic valves in the aortic position.41 With no anticoagulation, 5 of 76 patients (6.6%) suffered cerebral ischemic events during the first 3 months after valve insertion, vs 8 of 109 patients (7.3%) among those who received postoperative heparin followed by warfarin.41

Long-term Results

Patients with bioprosthetic valves, whether porcine or pericardial, have a long term-risk for thromboemboli of 0.2 to 2.6%/yr (Table 5).42–52 The risk of thromboembolic stroke in patients with bioprosthetic valves in the aortic position is higher in patients with atrial fibrillation than in patients in sinus rhythm.53 In addition to atrial fibrillation, a low ejection fraction, large left atrium, and history of thromboembolism may be considered as potential risk factors for late-occurring thromboemboli in patients with all types of prosthetic valves.21 The need for pacemaker cardiotimulation also appears to increase the risk of thromboemboli in patients with bioprosthetic valves.24

In a case series of 185 patients with bioprosthetic valves...
in the mitral or mitral-plus-aortic position who were in sinus rhythm and were treated long-term with aspirin 1 g daily or 500 mg every other day, no thromboemboli occurred in an average of 32 months.55 Also, no thromboemboli occurred in 31 patients, who had giant left atriums, who received aspirin.55 In a more recent case series in which 145 patients in sinus rhythm with porcine aortic valves received aspirin 75 mg/d, the rate of thromboemboli was 0.7%/yr.56

Thromboembolism in patients with bioprosthetic valves who are in atrial fibrillation presumably relates to both the bioprosthetic valve and the atrial fibrillation (see “Antithrombotic Therapy in Atrial Fibrillation,” page 194, by Albers et al) The occurrence of thromboembolism in mostly untreated patients with bioprosthetic valves and atrial fibrillation was reported to be as high as 16% at 36 months.57 Randomized trials in patients with atrial fibrillation who did not have prosthetic valves showed that long-term oral anticoagulants are effective, and they are more effective than aspirin (see article by Albers et al).

**SUMMARY**

1. Permanent therapy with oral anticoagulants offers the most consistent protection in patients with mechanical heart valves.
2. Antiplatelet agents alone do not consistently protect patients with mechanical prosthetic heart valves, including patients in sinus rhythm with St. Jude Medical valves in the aortic position.
3. Levels of oral anticoagulants that prolong the INR to 2.0 to 3.0 appear satisfactory for tilting disk valves and bileaflet prosthetic valves in the mitral position.
4. Levels of oral anticoagulants that prolong the INR to 2.5 to 3.5 are satisfactory for tilting disk valves and bileaflet prosthetic valves in the mitral position.
5. Experience in patients with caged ball valves who had prothrombin time ratios reported in terms of the INR is sparse, because few such valves have been inserted in recent years.9,18 The number of surviving patients with caged ball valves continues to decrease. It has been suggested that the most advantageous level of the INR in patients with caged ball or caged disk valves should be as high as 4.0 to 4.9.9 However, others have shown a high rate of major hemorrhage with an INR that is even somewhat lower, 3.0 – 4.5.1 The problem is self-limited, however, because few such valves are being inserted.
6. In patients with mechanical heart valves, aspirin, in addition to oral anticoagulants, has been shown to diminish the frequency of thromboembolism. The risk of bleeding is somewhat increased if the INR is 2.0 to 2.5 or 2.5 to 3.5. However, if the INR is 3.0 to 4.5, the risk of bleeding becomes excessive with aspirin. There are no investigations in which aspirin 80 mg/d in combination with oral anticoagulants was evaluated.
7. Data are insufficient to recommend dipyridamole over low doses of aspirin in combination with warfarin. Whether dipyridamole plus aspirin is more effective than aspirin alone when used with warfarin is undetermined.
8. Patients with bioprosthetic valves in the mitral position as well as patients with bioprosthetic valves in the aortic position may be at risk for thromboembolism during the first 3 months after operation.56
9. Among patients with bioprosthetic valves in the mitral position, oral anticoagulants at an INR of 2.0 to 2.3 were as effective as an INR of 2.5 to 4.0 and

### Table 5—Thromboemboli with Bioprosthetic Valves After the First 3 Months*

<table>
<thead>
<tr>
<th>Patient Years</th>
<th>THROM, %/yr</th>
<th>TE, %/yr</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Porcine aortic valve</td>
<td>3,361</td>
<td>0</td>
<td>1.5</td>
</tr>
<tr>
<td>2,689</td>
<td>0</td>
<td>1.9</td>
<td>David et al</td>
</tr>
<tr>
<td>1,673</td>
<td>0</td>
<td>2.3</td>
<td>Khan et al</td>
</tr>
<tr>
<td>Pericardial aortic valve</td>
<td>2,556</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>581</td>
<td>0</td>
<td>1.0</td>
<td>Nakajima et al</td>
</tr>
<tr>
<td>3,624</td>
<td>0</td>
<td>1.0</td>
<td>Neville et al</td>
</tr>
<tr>
<td>408</td>
<td>0</td>
<td>2.2</td>
<td>Borovicek et al</td>
</tr>
<tr>
<td>Porcine mitral valves</td>
<td>3,128</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>1,168</td>
<td>0.1</td>
<td>1.5</td>
<td>David et al</td>
</tr>
<tr>
<td>1,781</td>
<td>0</td>
<td>2.6</td>
<td>Khan et al</td>
</tr>
<tr>
<td>Pericardial mitral valve</td>
<td>969</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>Porcine aortic, mitral, or &gt; 1</td>
<td>10,405</td>
<td>0</td>
<td>1.7</td>
</tr>
<tr>
<td>17,471</td>
<td>0</td>
<td>2.4</td>
<td>Janieson et al</td>
</tr>
<tr>
<td>5,464</td>
<td>0</td>
<td>2.1</td>
<td>Janieson et al</td>
</tr>
<tr>
<td>Pericardial aortic, mitral, or &gt; 1</td>
<td>3,000</td>
<td>0.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

*THROM = valve thrombosis; TE = thromboemboli.
were associated with fewer bleeding complications during the first 3 months after operation.\textsuperscript{36} 10. Aspirin may reduce the long-term frequency of thromboembolism in patients with bioprosthetic valves.\textsuperscript{55,56}

**Recommendations**

The following recommendations, in many instances, are made on the basis of sparse or incomplete data. As new data become available, the consensus recommendations may change. Treatment should always be based on appraisal of the individual patient, and it may properly differ from these consensus recommendations. The recommendations made by this committee differ somewhat from the recommendations of the European Society of Cardiology.\textsuperscript{58} In general, we recommend lower levels of the INR.

**Mechanical Prosthetic Heart Valves**

1. We recommend that all patients with mechanical prosthetic heart valves receive oral anticoagulants (grade 1C recommendation).

2. We recommend that unfractionated heparin or low molecular weight heparin be used until the INR is at a therapeutic level for 2 consecutive days (grade 2C).

3. A target INR of 2.5 (range, 2.0 to 3.0) is recommended for patients with a St. Jude Medical bileaflet valve (grade 1A), CarboMedics bileaflet valve (grade 1C+) or Medtronic-Hall tilting disk mechanical valve (grade 1C+) in the aortic position, provided the left atrium is of normal size and the patient is in sinus rhythm.\textsuperscript{3,6,11,12}

4. Levels of oral anticoagulants that prolong the INR to a target of 3.0 (range, 2.5 to 3.5) are recommended for patients with tilting disk valves and bileaflet mechanical valves in the mitral position. (grade 1C+ recommendation)

5. Levels of oral anticoagulants that prolong the INR to a target of 3.0 (range, 2.5 to 3.5) are recommended for patients with bileaflet mechanical aortic valves, who have atrial fibrillation (grade 1C+ recommendation, based on extrapolation of results in patients with atrial fibrillation who do not have prosthetic heart valves, and based on investigations in patients with mechanical heart valves who do not have atrial fibrillation).

6. An alternative recommendation for patients with tilting disk valves, bileaflet mechanical valves in the mitral position, or bileaflet mechanical valves in the aortic position plus atrial fibrillation is a target INR of 2.5 (range, 2.0 to 3.0), in combination with aspirin 80 to 100 mg/d (grade 2C recommendation).

7. A target INR of 3.0 (range, 2.5 to 3.5) in combination with aspirin 80 to 100 mg/d is recommended for patients with caged ball or caged disk valves (grade 2A recommendation, based on results of one randomized trial with various types of valves, one fourth of which were caged ball valves).\textsuperscript{2}

8. In patients who have mechanical valves and additional risk factors, we recommend a target INR of 3.0 (range, 2.5 to 3.5), combined with low doses of aspirin (80 to 100 mg/d) (grade 1C+ recommendation based on extrapolation of data from investigations, one of which used a different level of the INR, and the patients may not have had additional risk factors\textsuperscript{1,2}).

9. In view of the advantageous effects of low-dose aspirin in combination with oral anticoagulants, the indications for dipyridamole require further evaluation.

10. For patients with mechanical prosthetic heart valves who suffer systemic embolism despite adequate therapy with oral anticoagulants, we recommend aspirin 80 to 100 mg/d, in addition to oral anticoagulants, and maintenance of the INR at target of 3.0 (range 2.5 to 3.5) (grade 1C+ recommendation based on extrapolation of data, in which aspirin 100 mg/d was used, sometimes with a higher INR, in patients who did not have emboli\textsuperscript{1,2}).

**Bioprosthetic Heart Valves**

1. We recommend that patients with bioprosthetic valves in the mitral position be treated for the first 3 months after valve insertion with oral anticoagulants (grade 1C+ recommendation). We also recommend that patients with bioprosthetic valves in the aortic position be treated for the first 3 months after valve insertion with oral anticoagulants, but the evidence is less compelling (grade 2C recommendation).

2. In view of the high risk of thromboembolism during the first 3 months after valve replacement, heparin (low molecular weight or unfractionated) might be used until the INR is at therapeutic levels for 2 consecutive days, but there is no evidence for this recommendation (grade 2C recommendation).

3. We recommend a target INR of 2.5 (range, 2.0 to 3.0) during the first 3 months after operation in patients with bioprosthetic valves in the mitral or aortic position (grade 1A recommendation based on an investigation that used an INR of 2.0 to 2.3).\textsuperscript{38}

4. We recommended that patients with bioprosthetic valves who have atrial fibrillation be treated with long-term oral anticoagulants, at a dose sufficient to prolong the INR to 2.0 to 3.0 (goal 2.5). This 1C+ recommendation is based on randomized trials of patients with atrial fibrillation who did not have prosthetic heart
valves (see article on atrial fibrillation). The need for anticoagulants is clear, based on these investigations. The dose of anticoagulants has not been established for patients with bioprosthetic valves and atrial fibrillation.

5. In patients with bioprosthetic valves who have evidence of a left atrial thrombus at surgery, the consensus is to treat with long-term oral anticoagulants with a dose sufficient to prolong the INR to a target of 2.5 (range, 2.0 to 3.0) (grade 1C). The duration is uncertain. This grade 1C recommendation is not based on published studies. Patients with bioprosthetic valves who have a permanent pacemaker are also at high risk for thromboemboli, but there is no evidence that oral anticoagulants are protective. We suggest that anticoagulants (target INR 2.5; range, 2.0 to 3.0) are optional in such patients (grade 2C recommendation).

6. It is recommended that patients with bioprosthetic valves who have a history of systemic embolism be treated with long-term oral anticoagulants. The INR and duration are uncertain. The consensus is to treat with oral anticoagulants 3 to 12 months, at doses sufficient to prolong the target INR to 2.5 (range, 2.0 to 3.0). This grade 2C recommendation is not based on published studies.

7. Among patients with bioprosthetic valves who are in sinus rhythm, we recommend long-term therapy with aspirin (80 mg/d as protection against thromboembolism (grade 2C)).

REFERENCES