Prevention of Thromboembolic Events After Bioprosthetic Aortic Valve Replacement

What Is the Optimal Antithrombotic Strategy?*

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Valvular heart disease affects more than 100 million people worldwide and is a growing problem because of the high incidence of rheumatic heart disease in developing countries and the increasing burden of degenerative valve disease in the aging world population (1). Replacement of the diseased valve by a mechanical or biological prosthesis remains the only definitive treatment for valvular heart disease and is performed in several hundred thousand patients each year (2). Because they are much more durable than bioprostheses, mechanical valve replacements are preferred in younger patients, but the disadvantage is that these mechanical replacements require lifelong treatment with a vitamin K antagonist, which necessitates lifestyle restrictions and routine coagulation monitoring. Consequently, older patients requiring valve replacement surgery usually elect to receive a bioprosthesis.

An important unresolved issue in patients undergoing bioprosthetic heart valve replacement concerns the optimal initial antithrombotic treatment. Although less thrombogenic than mechanical valves, bioprostheses appear to be moderately prothrombotic during the first 3 months after surgery, presumably because they have a smaller effective orifice area than native valves do, which creates a transvalvular flow gradient, and they are not yet fully endothelialized (3). Observational studies suggest that bioprosthetic valves have a 1% to 5% annual risk of thromboembolic complications, even with the routine use of early antithrombotic prophylaxis, but studies are small and contemporary data are lacking (4,5). Two pilot randomized controlled trials have compared anticoagulation with antiplatelet therapy in patients with bioprosthetic valves, but collectively they involved less than 300 patients and their results were inconclusive (6,7).

Uncertainty about the efficacy and safety of anticoagulants compared with antiplatelet drugs for prevention of thromboembolic events during the first 3 months after bioprosthetic heart valve replacement is reflected by contrasting recommendations of international guidelines (Table 1) and highly variable physician practices (8). The European Society of Cardiology guidelines recommend warfarin (international normalized ratio: 2.0 to 3.0), although they do not grade the strength of this recommendation or the quality of evidence on which it is based (9). The American College of Cardiology/American Heart Association strongly recommend aspirin and provide a weaker recommendation for warfarin. The exception is patients deemed to be at high risk for thromboembolic complications (atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and hypercoagulable condition) for whom they strongly recommend warfarin (10). The American College of Chest Physicians’ guidelines recommend aspirin over warfarin (except for patients with atrial fibrillation), but this is a weak recommendation based on low-quality evidence (11).

In this issue of the Journal, Brennan et al. (12) report rates of readmission for thromboembolic and bleeding events between the time of hospital discharge and 3 months of follow-up in 25,656 patients at least 65 years of age undergoing bioprosthetic aortic valve replacement who were discharged home on aspirin, warfarin, or the combination of aspirin and provide a weaker recommendation for warfarin. The investigators identified patients undergoing bioprosthetic aortic valve replacement using the Society of Thoracic Surgeons’ database, which contains data on patients undergoing cardiac surgery at 797 hospitals in the United States, and used propensity methods to adjust for confounding due to differences in baseline characteristics between patients who received an anticoagulant and those who were treated with antiplatelet therapy.

The major findings of the study of Brennan et al. (12) can be summarized as follows.

First, there was substantial variation in the choice of antithrombotic therapy during the first 3 months after surgery for a bioprosthetic aortic valve replacement. Warfarin was more commonly used in patients with concomitant atrial fibrillation, but less than 60% of patients who received warfarin had atrial fibrillation.
Second, the rate of thromboembolic events during the first 3 months was remarkably low, ranging from 0.6% in patients who received the combination of aspirin and warfarin to 1.0% in those who received either aspirin alone or warfarin alone. Although this excluded early in-hospital events, the low event rates in patients treated with aspirin alone are reassuring and suggest that the routine use of warfarin following bioprosthetic aortic valve replacement is unnecessary. The low event rates also indicate that any future randomized controlled trial comparing different antithrombotic strategies following bioprosthetic aortic valve replacement will require many thousands of patients.

Third, there was no advantage of warfarin over aspirin for the prevention of thromboembolic events (adjusted risk ratio [RR]: 0.95, 95% confidence interval [CI]: 0.61 to 1.47) but also no increase in bleeding (adjusted RR: 1.23, 95% CI: 0.85 to 1.79). This latter finding contradicts many studies demonstrating higher risks of bleeding with warfarin compared with aspirin and might be explained by exclusion of patients with a contraindication for warfarin because of post-operative anticoagulant complication or gastrointestinal complications in hospital.

Fourth, the combination of aspirin and warfarin compared with aspirin alone reduced death by 20% (adjusted RR: 0.80, 95% CI: 0.66 to 0.96) and thromboembolic events by 48% (adjusted RR: 0.52, 95% CI: 0.35 to 0.76), at the cost of a 2.8-fold increase in bleeding (adjusted RR: 2.80, 95% CI: 2.18 to 3.60). The mortality effect became evident only after propensity adjustment, and the investigators do not report whether the benefits of the combination of aspirin and warfarin over aspirin was driven by patients with atrial fibrillation. The reduction in mortality is unexpected because the absolute reduction in thromboembolic events (0.4%) was outweighed by a much greater absolute increase in bleeding events (1.8%) and both thromboembolic and bleeding events were associated with a similar (3% to 4%) case-fatality at 2 weeks. Thus, it appears that the effects of the combination of aspirin and warfarin compared with aspirin on risk of thromboembolism and bleeding cannot explain the 20% mortality reduction.

The main strengths of the study by Brennan et al. (12) are that it included large numbers of consecutive, unselected patients undergoing bioprosthetic aortic valve replacement who were followed during the period of highest risk for thromboembolic and bleeding events. The main limitations are that it did not count pre-discharge in-hospital thromboembolic and bleeding events or post-discharge out-of-hospital events that did not prompt readmission and cannot exclude the potential for confounding despite careful propensity adjustment.

What are the implications of these results for clinical practice? The data by Brennan et al. (12) suggest that for the majority of patients undergoing aortic bioprosthetic valve replacement, aspirin alone provides adequate protection against thromboembolic complications during the first 3 months after discharge from hospital. Warfarin alone does not appear to offer any benefits over aspirin in unselected patients, but the combination of warfarin and aspirin may reduce thromboembolic events and seems to be a reasonable option in patients who are at increased risk of thromboembolic events because they have atrial fibrillation. Despite the data suggesting a reduction in thromboembolic events with warfarin plus aspirin, we do not recommend the combination in all patients because the data are not of high quality; questions remain about the apparent reduction in mortality; and there is a large body of high-quality evidence that the combination increases bleeding. Our recommendation concerning the choice of antithrombotic therapy applies to patients at the time of discharge from hospital who do not have a contraindication to warfarin and should also take into account patient values and preferences concerning the balance between thromboembolic and bleeding risks.

What are the implications of these results for future iterations of antithrombotic guidelines? Although the data by Brennan are observational, we believe that they represent the highest quality evidence available for early antithrombotic management of patients undergoing bioprosthetic aortic valve replacement and thus should influence guideline recommendations. Based on the very low rates of thromboembolic events in this study, randomized trials to test different antithrombotic strategies in this population are unlikely ever to be performed and thus the study by Brennan et al. will likely remain the best guide for many years to come.

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<thead>
<tr>
<th>Bioprosthesis</th>
<th>ACC/AHA</th>
<th>ACCCP</th>
<th>ESC</th>
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<tbody>
<tr>
<td>AVR, low risk (sinus rhythm)</td>
<td>ASA 75–100 mg/day (Class I*)</td>
<td>ASA 50–100 mg/day over VKA (grade 2c‡)</td>
<td>VKA (target INR: 2.5)</td>
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<tr>
<td></td>
<td>Warfarin INR: 2.0–3.0 (Class I†)</td>
<td>VKA as per AF guidelines</td>
<td>No separate recommendation</td>
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<tr>
<td>AVR, high risk§</td>
<td>ASA 75–100 mg/day (Class I*)</td>
<td>Warfarin INR: 2.0–3.0 (Class I*)</td>
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*Class I: conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective. †Class Ila: weight of evidence/opinion is in favor of usefulness/efficacy. ‡Grade 2c: weak recommendation based on low quality of evidence. §AHA risk factors: atrial fibrillation, left ventricular dysfunction, previous thromboembolism, and hypercoagulable condition; ACCP risk factors: atrial fibrillation.

ACC = American College of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; AHA = American Heart Association; ASA = acetylsalicylic acid (aspirin); AVR = aortic valve replacement; ESC = European Society of Cardiology; INR = international normalized ratio; VKA = vitamin K antagonists.
REFERENCES


Key Words: anticoagulation strategies • aortic valve replacement • outcomes.