Optimal thromboprophylaxis following bioprosthetic aortic valve replacement: still a matter of debate?

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INTRODUCTION

Aortic valve replacement (AVR) remains the treatment of choice for aortic valve disease and is one of the most commonly performed cardiac operations worldwide. The options available in replacing the diseased valve include a bioprosthetic or mechanical conduit; and this choice is dependent on a multitude of factors. One advantage of bioprostheses is that they are a less thrombogenic substitute than mechanical valves, and the need for anticoagulation is obviated. Their drawbacks include a lower durability than mechanical prostheses with a resultant increase in the risk of reoperations in the future [1].

Despite the overall lower thrombogenic state of bioprostheses, there remains an increased risk of thromboembolic events in the first 3 months following surgery [2, 3]. This has mainly been attributed to the time required for endothelialization of the sewing ring that could prevent the clot formation [4]. Early anticoagulation with vitamin K antagonists, mainly warfarin, has been proposed; this practice has to be weighed against the increased risk of bleeding complications associated with warfarin, which range from 1.5 to 2.4% per annum [5]. However, studies examining standard antplatelet therapy with aspirin have shown equivalent thrombotic outcomes, with the potential added benefit of reduced bleeding complications. The conflicting results in the literature are reflected in the development of the practice guidelines: the American College of Cardiologists (ACC)/American Heart Association (AHA) [6], the European Society of Cardiology (ESC) [7] and the American College of Chest Physicians (ACCP) [8] advocate anticoagulation therapy during the first 3 months following bioprosthetic AVR. However, the update of the ACC/AHA guidelines in 2006, which was also endorsed by the Society of Thoracic Surgeons, as well as the Guideline Committee of the European Association for Cardio-Thoracic Surgery (EACTS) recommend aspirin alone in the absence of other thromboembolic risk factors.

Until the next EACTS formal review (planned for September 2013), and in view of the controversy and a variable interpretation of the available data by the different working groups, an up-to-date critical review of the literature, including the most recent studies, could assist the decision-making in this very important clinical matter.

Summary

Optimal thromboprophylaxis following bioprosthetic aortic valve replacement (AVR) remains controversial. The main objective, which is the effective prevention of central nervous or peripheral embolic events, especially in the early postoperative period, will have to be weighed against the haemorrhagic risk that is associated with the utilization of different antithrombotic regimes. Most governing bodies in cardiovascular medicine have issued recommendations on thromboprophylaxis after the surgical implantation of aortic bioprostheses. However, the level of evidence to support these recommendations remains low, largely due to the inherent limitations of conducting appropriately randomized and adequately powered clinical research in this area. It is apparent from the recent surveys and large registries that there is a great variability in antithrombotic practice at an institutional or individual-clinician level reflecting this controversy and the lack of robust evidence. While organizational, financial or conceptual limitations could hinder the conduct and availability of conclusive research on optimal thromboprophylaxis after aortic bioprosthesis, it is imperative that all evidence is presented in a systematic way in order to assist the decision-making for the modern clinician. In this review, we provide an outline of the current recommendations for thromboprophylaxis, followed by a comprehensive and analytical presentation of all comparative studies examining anticoagulation vs. antplatelet therapy after bioprosthetic AVR.

Keywords: Aortic valve replacement • Bioprosthetic • Thromboprophylaxis • Aspirin • Warfarin

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METHODS

A literature search was performed on PubMed (National Library of Medicine), Medline, CINAHL, Scopus and Cochrane Central Registered of Controlled Trials (CENTRAL), for the period between January 1992 and January 2012. The search was limited to ‘English language’ and ‘Human’. The search terms were as follows: warfarin/or anticoagulants/or anticoagulation/or aspirin AND bioprosthesis/or bioprostheses/or tissue/or bioprosthetic AND aortic valve/or valve replacement/or heart valve prosthesis (‘aortic valve’ [MeSH Terms] OR ‘aortic’ [All Fields] AND ‘valve’ [All Fields]) OR ‘aortic valve’ [All Fields] AND (‘aspirin’ [MeSH Terms] OR ‘aspirin’ [All Fields]) AND (warfarin’ [MeSH Terms] OR ‘warfarin’ [All Fields]) AND (‘bioprosthesis’ [MeSH Terms] OR ‘bioprostheses’ [MeSH Terms] OR ‘bioprosthetic’ [All Fields]). Review articles were excluded.

RESULTS

Current guidelines

Both the ACC/AHA and ACCP recommend anticoagulation for patients following bioprosthetic AVR for 3 months (with a target International Normalised Ratio (INR) of 2.5–3.5 and 2.0–3.0, respectively) [6, 8]. Beyond this period, and in the absence of other thromboembolic risk factors (atrial fibrillation (AF), history of previous thromboembolism, poor left ventricular function and hypercoagulability states), the guidelines indicate that warfarin may be discontinued and low-dose aspirin (75–100 mg/day) commenced lifelong. Those with additional risk factors should continue warfarin therapy indefinitely.

Much of the above-mentioned detail is reiterated in the guidelines provided by the ESC [7]. Those with additional thromboembolic risk factors should be put on long-term warfarin treatment. Everyone else must ideally be anticoagulated for the first 3 months. If this is not adhered to, the alternative is aspirin (75–100 mg/day) combined with close monitoring in the follow-up period. Conversely, the British Committee for Standards in Haematology [9] do not support anticoagulation following bioprosthetic AVR. An audit by Vaughan and Waterworth [10] has showed that only 17% of cardiothoracic surgeons in the UK adhered to the ESC guidelines. This is in line with the more recent ACTION registry survey, showing that in 33% of the centres which responded, thromboprophylaxis was achieved through aspirin alone [11]. The decision not to routinely anticoagulate the patients is further strengthened by the revised ACC/AHA guidelines, which suggest that aspirin (75–100 mg/day) alone may be adequate for the patients undergoing bioprosthetic AVR (Class I recommendation) [12]. Finally, following the comprehensive assessment of all available evidence by the Audit and Guidelines Committee of EACTS, antiplatelet therapy alone was recommended for the standard thromboprophylaxis following AVR in the patients with no other indications for anticoagulation (e.g. permanent AF) [13].

Aspirin vs. warfarin for the first 3 months: the debate

The initial evidence in support of early anticoagulation emerged from the results of a single-centre, retrospective study by Heras et al. [2], which influenced much of the development of the current guidelines. It examined the patients undergoing mechanical AVR or bioprosthetic AVR at three time intervals up to 90 days following surgery. The study concluded that warfarin therapy for the first 10 days eliminated the risk of thromboembolic complications when compared with aspirin alone. Among those without therapy, the incidence of thromboembolism was estimated to be as high as 41% [2]. This paper became influential among those in the surgical community in favour of anticoagulation and encouraged further research, but the conclusions should be treated with caution as they examined mainly first-generation bioprosthetic valves that are more thrombogenic than those currently utilized.

Orszulak et al. [3] have examined 561 patients undergoing bioprosthetic AVR with a Carpentier-Edwards (CE) porcine valve over a 10-year period. The study focused on the early and late survival as well as the major neurological events. In total, 38% of these patients underwent concomitant coronary artery bypass grafting (CABG) and a smaller number of patients underwent other associated aortic/cardiac procedures. Twenty-seven patients suffered the major neurological events with 10 patients affected within the first 2 weeks. These results mirrored other subsequent studies where the highest incidence of strokes occurred within the first few months postoperatively, which decreased with time. Nevertheless, the authors recommend anticoagulation for the first 3 months for only a specific high-risk subgroup such as those with preoperative AF, low left ventricular function, NYHA Class IV and those having a paced rhythm. Further studies including the ones by Babin-Ebell et al. [14] and Moinuddeen et al. [15] showed no significant advantage in early warfarin use compared with aspirin following bioprosthetic AVR.

Mistiaen et al. [16] conducted a retrospective study examining 25 factors that influence postoperative thromboembolism in 500 patients undergoing AVR bioprosthesis with a CE Perimount valve over a 15-year period. It was demonstrated that the history of stroke (risk ratio, 4.8) and warfarin use (risk ratio, 3.0) were significant predictors of thromboembolism whereas carotid stenosis and AF were not. However, there was a non-significant trend in the use of postoperative warfarin in a certain high-risk subset of patients (i.e. preoperative AF, preoperative cerebrovascular accident, decreased left ventricular function and prior AVR). This may somewhat explain these counter intuitive results.

In 2004, Gherli et al. [5] presented a prospective observational single-institution trial with 249 patients undergoing bioprosthetic AVR (between 2001 and 2002) examining warfarin vs. aspirin therapy only (100 mg/day). Warfarin was associated with a higher incidence of complications compared with the aspirin group (stroke, major bleeding and mortality) although this lacked a statistical significance. The limitation of this study was that it was not randomized and the decision to anticoagulate was based on the surgeon’s preference. Thus, it concluded that there is no evidence for warfarin being superior to aspirin in this cohort of patients and, therefore, there may be no advantage in the early anticoagulation.

A much larger scale retrospective study by Sundt et al. [17] also concluded that anticoagulation conferred no benefit in preventing the thromboembolism. Anticoagulant treatment with warfarin was administered in 624 vs. 527 patients who did not receive anticoagulation (although 78% of this group received aspirin therapy). The results did not identify significant differences in thromboembolic or bleeding complications between
The two groups. Whilst this was a large study, there were a number of shortcomings, including the lack of randomization, concomitant CABG surgery in a large proportion of patients and the lack of standardization of aspirin therapy (including dose, duration, etc.).

The Spanish TRAC trial published in 2005 was the first randomized controlled trial in the field that examined triflusal (antiplatelet similar to aspirin) vs. acenocoumarol (anticoagulant) in 191 patients undergoing bioprosthetic AVR [18]. Although the incidence of thromboembolic events was higher in the triflusal group (6.3 vs. 3.2%), this was not statistically significant. There was a significantly higher rate of bleeding in the acenocoumarol group (10 vs. 3.1%). This could have been the result of suboptimal anticoagulation management since 25% of patients had an INR of >5 with a mean duration over the recommended range of 11 days [18]. Overall, this study could not justify the routine use of anticoagulation in patients without risk factors, mainly due to the increased incidence of bleeding complications.

The only other randomized controlled trial comparing anticoagulation with antiplatelet therapy came from Colli et al. (WoA Epic Trial) [19]. A total of 75 patients undergoing surgery with one type of bioprosthetic valve (Epic™ valve, St. Jude Medical, Minneapolis, MN, USA) were randomized to postoperative warfarin or aspirin 100 mg. There was only one cerebral ischaemic event noted in each group during the first 3 months, with one patient in the aspirin group developing a thromboembolic event after 3 months. The gastrointestinal bleeding rates were 2.9% (the aspirin group) vs. 8.8% (the warfarin group). However, this difference was not found to be statistically significant. Six patients (8%) were excluded from the final analysis as they developed de novo AF requiring warfarin. The authors acknowledge that this study was designed as a pilot trial as the sample size was not adequate to demonstrate the statistical differences between the two groups.

Jamieson et al. [20] retrospectively studied 1372 patients who underwent bioprosthetic AVR in three affiliated institutions over a 6-year period. The patients who underwent concomitant CABG were also included. There were three main groups: the antiplatelet group, the anticoagulation group and those who did not receive thromboprophylaxis. The incidence of thromboembolic events in the first 90 days was 2.2, 3.9 and 3.6%, respectively, and was not found to be statistically significant. In contrast to most other studies, multivariate analysis revealed that the independent predictors for thromboembolic events were preoperative stroke (odds ratio (OR) 4.45, 95% confidence interval (CI) 1.17–16.87) and concomitant CABG (OR 3.19, 95% CI 1.16–8.76) [20]. Therefore, the authors recommended only anticoagulation in the patients with these risk factors.

Taking a different perspective, Brueck et al. [21] in a retrospective, observational, two-institutional study examined the aspirin vs. no aspirin use. They did not identify significant differences in the bleeding events, cerebrovascular accidents or mortality between the two groups. Once again, due to the non-randomized nature of the study, patients with coronary artery disease were more likely to be administered aspirin, introducing a significant selection bias in addition to the known limitation of small numbers for identification of differences in the thromboembolic outcomes with consistently low incidence.

A prospective, cohort, non-randomized trial by di Marco et al. [22] did not reveal any significant differences in thromboembolic complications between the antiplatelet group (n = 0/125) and the anticoagulation group (n = 3/125). The major bleeding events were the same for both groups at 1.6%. Interestingly, late deaths were significantly higher in the warfarin group at 12% vs. 0.8% for the aspirin group. Five of the warfarin group deaths were attributed to neoplasia while another two related to strokes. The authors conclude that aspirin is just as effective as warfarin in protecting against the neurological events following implantation of a bioprosthetic AVR.

More recently, ELBardissi et al. [4] have presented an observational study of a high-dose aspirin (325 mg/day) vs. warfarin in 861 patients who underwent bioprosthetic AVR over a 7-year period. Patients who underwent concomitant procedures were excluded. The thromboembolic complication rates for both groups were similar at 5% although the gastrointestinal bleeding rates were not significantly higher in the warfarin group (4.6% vs. 2.8%). The design characteristics and main findings of all comparative studies published in the last 10 years are shown in Table 1.

### DISCUSSION

**Current evidence and methodological aspects**

The most current evidence does not appear to support anticoagulation therapy following bioprosthetic AVR. A multitude of limitations in this research area exist, which hinder the ability to reach definite conclusions. All but two studies reviewed were conducted retrospectively. Sample sizes were insufficient, especially when attempting to identify thromboembolic events, the incidence of which is likely to be low, thereby lacking power. There is also a large variation in the methods of detecting the thromboembolic events, including questionnaires, clinical assessment and imaging; no standardized criteria have been used, and in particular very few attempts to address the issue of microemboli and subclinical events have been made. The follow-up periods again vary hugely, as does the actual dose of aspirin administered, and very little is mentioned with regards to whether patients on warfarin were maintained within their target INR of 2–3. Multicentre, randomized, controlled trials with large numbers of patients (>5400) [23] are needed to focus on neurological and adverse bleeding events in three groups of patients (those taking aspirin, warfarin or neither). However, multiple factors hinder their feasibility. There is an increasing number of patients undergoing AVR and concurrent coronary revascularization who require aspirin anyway, limiting their eligibility for randomization. The surgeons’ individual preference and comfort with current practice makes it sometimes difficult for them to participate without hesitation, or eliminate selection prior to randomization. Logistical considerations, including the design, ethics and research governance arrangements, can be rather challenging for multicentre trials. Finally, the economic burden on organizations and healthcare institutions may not be justified by the effect size and the potential benefit of the intervention, making the funding of such studies unlikely, especially in the current economic climate. These considerations also reflect our group experience, which is based on the results of feasibility phase of a multicentre trial [23].

**Additional considerations**

**Second- and third-generation bioprosthetic valves.** The bioprosthetic valves currently in use hold very different
Comparative studies examining antithrombotic prophylaxis following bioprosthetic AVR

<table>
<thead>
<tr>
<th>Author, date</th>
<th>Design</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Number of patients</th>
<th>Thromboembolic complications</th>
<th>GI bleeding complications</th>
<th>Mortality</th>
<th>Follow up period</th>
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</thead>
<tbody>
<tr>
<td>Elbardissi et al. [31]</td>
<td>Retrospective, observational study</td>
<td>All patients undergoing bioprosthetic AVR (Dec 2001 - Oct 2008)</td>
<td>- Concomitant operations (n = 138, 12%) - Anticoagulation pre-op (n = 4, 0.4%) - Post-op AF requiring anticoagulation (n = 128, 11%)</td>
<td>Included: n = 861</td>
<td>Excluded: n = 270</td>
<td>ASA group: n = 39 (5%) Warfarin group: n = 6 (3%)</td>
<td>ASA group: n = 20 (2.8%) Warfarin group: n = 6 (4.6%)</td>
<td>P = 0.29</td>
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<tr>
<td>di Marco et al. [22]</td>
<td>Prospective, cohort study (non-randomized)</td>
<td>All patients undergoing bioprosthetic AVR (Jan 2002 - Sep 2005)</td>
<td>- Chronic anticoagulation therapy - Concomitant mitral or tricuspid valve replacement</td>
<td>Included: n = 250</td>
<td>Excluded: NA</td>
<td>ASA group: n = 0 (0%)</td>
<td>ASA group: n = 2 (1.6%)</td>
<td>NA</td>
</tr>
<tr>
<td>Brueck et al. [21]</td>
<td>Retrospective, observational</td>
<td>All patients undergoing bioprosthetic AVR (Jan 2001 - Dec 2003)</td>
<td>- Concomitant CABG or double valve replacement - AF - Coagulopathy - Concomitant mitral valve disease - Previous chronic anticoagulation therapy - Vascular disease requiring treatment</td>
<td>Included: n = 288</td>
<td>No ASA group: n = 123 No ASA group: n = 156</td>
<td>ASA group: n = 1 (0.8%)</td>
<td>No ASA group: n = 0</td>
<td>ASA group: n = 0 (0%)</td>
</tr>
<tr>
<td>Jamieson et al. [20]</td>
<td>Retrospective, observational</td>
<td>All patients undergoing bioprosthetic AVR (1994-2000)</td>
<td>NA</td>
<td>Included: n = 1372</td>
<td>ASA group: n = 912 (66.5%) Warfarin group: n = 154 (11.2%) No ASA/warfarin: n = 306 (22.6%)</td>
<td>ASA group: n = 20 (2.2%) Warfarin group: n = 6 (3.9%) No ASA/warfarin: n = 11 (3.6%)</td>
<td>P = 0.264</td>
<td>NA</td>
</tr>
<tr>
<td>Colli et al. [19]</td>
<td>Randomized controlled trial</td>
<td>All patients &gt;18 years old; in SR; undergoing bioprosthetic AVR (Feb 2003 - Nov 2004)</td>
<td>Previously implanted prosthetic valve - Concomitant CABG or double valve replacement - AF - Coagulopathy - Concomitant mitral valve disease - Previous chronic anticoagulation therapy - Vascular disease requiring treatment</td>
<td>Included: n = 69</td>
<td>Excluded: n = 6</td>
<td>ASA group: n = 35 (50.7%) Warfarin group: n = 34 (49.3%)</td>
<td>ASA group: n = 1 (2.9%)</td>
<td>Warfarin group: n = 3 (4.5%)</td>
</tr>
<tr>
<td>Aramendi et al. [18]</td>
<td>Randomized controlled trial</td>
<td>Patients &gt;18 years of age undergoing aortic or mitral valve bioprosthesis (May 2000 - Jan 2003)</td>
<td>- Allergy - Chronic anticoagulation - GI/cerebral bleed - Pregnancy - Active endocarditis - Aortic dissection - Cerebral ischaemia/GI bleed - Chronic anticoagulation</td>
<td>Included: n = 191</td>
<td>Excluded: n = 9</td>
<td>Trifusial group: n = 6 (6.3%) Phenindione group: n = 3 (3.2%)</td>
<td>P = 0.5</td>
<td>Trifusial group: n = 3 (3.1%)</td>
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<tr>
<td>Sundt et al. [17]</td>
<td>Retrospective, observational</td>
<td>All patients undergoing bioprosthetic AVR with or without CABG (1993-2000)</td>
<td>- Concomitant procedures</td>
<td>Total: n = 1151</td>
<td>ASA group: n = 410 (35.7%) No ASA/warfarin group: n = 117 (10.1%) Warfarin group: n = 624 (54.2%)</td>
<td>Warfarin negative group: 1.9% Warfarin positive group: 2.4%</td>
<td>Warfarin negative group: 0.8%</td>
<td>Warfarin positive group: 1.1%</td>
</tr>
<tr>
<td>Gherli et al. [10]</td>
<td>Prospective, observational</td>
<td>All patients in SR undergoing bioprosthetic AVR (Jan 2001 - Dec 2002)</td>
<td>- Cerebral ischaemia - Coagulopathy - Peripheral vascular disease-concomitant mitral valve-double valve replacement - Chronic anticoagulation therapy - Allergies to ASA/warfarin-AF at any time</td>
<td>Included: n = 249</td>
<td>Excluded: n = 26</td>
<td>Warfarin negative group: 3 (2.1%)</td>
<td>Warfarin positive group: 4 (3.7%)</td>
<td>Warfarin negative group: 0.47 (0.8%)</td>
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ASA: acetylsalicylic acid (aspirin); AVR: aortic valve replacement; CABG: coronary artery bypass grafting; SR: sinus rhythm; IABP: intra-aortic balloon pump; GI: gastrointestinal; HTN: hypertension; Post-op: postoperative; Pre-op: preoperative
properties than those that were initially utilized at the time when much of the relevant research was performed. The current bioprosthetic valves used are xenografts, porcine or bovine pericardial in composition, which can be stented or stentless; and their main advantage over mechanical valves has always been freedom from anticoagulation. The disadvantages include the reduced durability in contrast to mechanical valves, resulting in an increased risk of reoperation. However, advances in the technology have now rendered bioprosthetic valves even less thrombogenic, with a reduced susceptibility to structural failure [1]. Furthermore, the studies reviewed are difficult to compare, due to the inter-study variability of the type of valve used. Consequently, the interpretation of the evidence should be made with caution. It has already been mentioned that it is not uncommon for cardiac surgeons to opt for no anticoagulation after bioprosthetic AVR. One factor in such a decision may be due to the characteristics of modern valves, despite the lack of evidence scrutinizing the anticoagulation/antiplatelet therapy and the incidence of thromboembolic events.

**Shortcomings of current anticoagulation therapies.**

Warfarin therapy has always been associated with a significant morbidity risk with repercussions upon daily life, and commencing patients on such treatment regardless of absolute indication requires careful consideration of the potential risks vs. intended benefits. One feature is now the ease with which patients can manage their own dosing. The development of finger prick INR home testing devices has made warfarin therapy more accessible and safer, given patients greater control over treatment, and reduced the disruption upon lifestyle that previously existed. It could be argued that such modifications have rendered modern day warfarin therapy less problematic. However, excess anticoagulation due to warfarin’s narrow therapeutic window may be the cause for the increased adverse bleeding events [22].

Warfarin may be the oldest and best-known orally administered anticoagulant, but it no longer remains the sole contender. Pharmacological advances have already displayed promising new alternatives that will undoubtedly filter through and influence the postoperative bioprosthetic AVR anticoagulation. Dabigatran, which is a direct thrombin inhibitor, is a new oral anticoagulant that has been shown in early studies to be just as efficacious as warfarin in preventing thromboembolic events in the patients with AF. It has the added advantage of not requiring regular blood test monitoring and possibly just a once-daily dosing. Compared with warfarin, dabigatran has been shown to have a 35% reduced relative risk of stroke ($P < 0.001$), similar rates of major bleeding and 59% reduced relative risk of catastrophic intracranial bleeding ($P < 0.001$) [24, 25].

One other new oral anticoagulant receiving just as much attention is rivaroxaban. A factor Xa inhibitor, it again removes the need for blood test monitoring and has more predictable pharmacokinetics than warfarin. Positive results have again been demonstrated and the drug has recently been licensed for use in the USA for stroke prevention and thromboembolic prophylaxis in patients with AF.

**CONCLUSIONS**

The current guidelines informing the antithrombotic practice following bioprosthetic AVR remain contradictory. This is, to a great extent, a reflection of the quality of available data deriving from studies with multiple limitations and conflicting results. The approach endorsed by EACTS favours the routine use of aspirin after tissue AVR, unless risk factors for thromboembolism (e.g. AF, previous pulmonary embolism), mandate anticoagulation with warfarin. These recommendations are possibly more in line with the recent evidence suggesting the equivalent efficacy between warfarin and aspirin, with the added benefit of less bleeding complications for aspirin use. However, generation of evidence is still hindered by the quality of data available, while the design and conduct of randomized controlled studies to yield conclusive results remain rather challenging. On this basis, and until more definitive data come to light, the regular critical assessment of the available literature will remain an important driver for decision-making and good clinical practice in thromboprophylaxis following bioprosthetic AVR.

**Conflict of interest:** none declared.

**REFERENCES**


