Antithrombotic therapy following bioprosthetic aortic valve replacement

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Summary

The life expectancy of the general population is increasing. This has meant that more elderly patients are requiring aortic valve replacement (AVR). The choice of valve replacement and its durability are important. Bioprosthetic (tissue) heart valves were introduced into clinical use in the 1960s and were developed primarily to reduce the complications associated with thromboembolism (TE) and the need for lifelong oral anticoagulation, due to their low thrombogenicity compared to mechanical prostheses. This makes them suitable for use in elderly patients (aged > 65 years) and in others where the risks of anticoagulation are higher or anticoagulation is contraindicated. There is thought to be a higher risk of TE for up to 90 days following bioprosthetic AVR. Guidelines for the management of patients with valvular heart disease published by the American College of Cardiology (ACC)/American Heart Association (AHA), the American College of Chest Physicians (ACCP) and the European Society of Cardiology (ESC) all recommend the use of an anticoagulation regimen for the first 3 months following bioprosthetic AVR. However, there is division of opinion and practice, despite these recommendations, and more recent studies have not supported the evidence for these guidelines. In this article, we review the literature on the use of anticoagulation in the first 90 days following bioprosthetic AVR.

Keywords: Bioprosthesis; Anticoagulation; Aortic valve

1. Introduction

Aortic valve replacement (AVR) is the treatment of choice for aortic valve disease and is one of the most commonly performed cardiac operations [1]. The native valve is usually replaced with either a bioprosthetic or mechanical valve prosthesis. Bioprostheses were introduced in the 1960s as a less thrombogenic alternative to mechanical prostheses. They do, however, have less durability than mechanical prostheses [2,3] and suffer from structural deterioration that may require reoperation and therefore increased morbidity and mortality [4–9]. Pericardial valves were introduced in the 1970s to improve haemodynamics and decrease the rate of structural failure [10–15]. Stentless bioprostheses was introduced in 1992 with the aim to improve haemodynamic function and increase durability compared to stented tissue valves [16–19].

Mechanical prostheses are thrombogenic and there is good evidence for lifelong anticoagulation [20,21]. During the first 3 months following bioprosthetic AVR, there is thought to be a higher risk of thromboembolism (TE) [22]. This may be related to lack of endothelialisation of the bioprosthetic material. Many authorities, including guidelines, recommend anticoagulation during the early postoperative period. However, recently it has been suggested that there may be no benefit from early anticoagulation in the first 90 days after bioprosthetic AVR [23]. With an increasingly elderly population more patients are requiring AVR [24]. In this group, the complications associated with anticoagulation are increased. In this article, we have performed a systematic review of the literature and reviewed the current guidelines.

2. Review methodology

We have searched Medline, Embase, CINAHL and Cochrane databases (1966 to July 2006). We combined three MeSH terms: heart valve prosthesis or bioprosthesis or aortic valve and thromboembolism and anticoagulants. The search was limited to studies of humans and articles in English. For search completion, references of articles, which fulfilled the inclusion and exclusion criteria, were hand searched. Identified studies were independently assessed by two reviewers (EW and JN). Articles were included if they provided data on at least five patients aged over 18 years. Where articles included tissue aortic valve...
replacement as a subset of patients then this subset was included. Aortic mechanical valve, mitral and tricuspid valve replacement were all excluded. Abstracts were also excluded. The majority of the studies are retrospective case series. There are very few randomised studies. It has previously been established that the few randomised studies that do exist do not lend themselves to meta-analysis or systematic review due to various shortcomings [25]. In many cases, it was difficult to identify the effect of treatment in different study populations, due to the heterogeneity of the patient population, and difficulty in clarifying the effect of individual treatments, due to the use of combination therapy and presence of risk factors in some cases. This makes meta-analysis of the different studies difficult and potentially unreliable. To our knowledge, there is no systematic review of the literature in this subject. In this systematic review, we have summarised those studies supporting, and those providing evidence against anticoagulation. We have also reviewed data on the risk of thromboembolism and the factors, which have been associated with increased risk. This information is essential in planning any definitive trial of anticoagulation in this patient group.

3. Data extraction

The methodological quality of included articles was independently evaluated, by two reviewers (EW and JN) on a standardised form. The criteria for data extraction included demographic information (number of men/women, age—mean and range), methodological quality (prospective, consecutive), number of patients in the study, length of follow-up, treatment regime (aspirin, vitamin K antagonist or nil) and outcomes (death, stroke, TIA, thromboembolism). If it was not stated we assumed the study was retrospective or non-consecutive.

4. Results

Out of 1007 publications that were identified, 164 were duplicate articles and by applying the inclusion and exclusion criteria, only 28 studies fulfilled the criteria for data extraction. Two reviewers (EW and JN) independently reviewed these final 28 manuscripts. Only two studies were prospective randomised trials comparing an antiplatelet agent with vitamin K antagonists [26,27]. The age of the study populations ranged from 6 to 95 years. The results of the articles reviewed are summarised in Table 1. The data are not uniform due to the retrospective analysis of the majority of the papers, different anticoagulation and anti-thrombotic regimes. In many of the studies, the results of aortic and mitral valve replacements are combined. We have attempted to separate out the aortic valve patients and their respective anticoagulation and anti-thrombotic regimes. Some columns in the table are intentionally blank, since the data were simply not available. A significant number of manuscripts failed to specify the exact anticoagulation or anti-thrombotic regime employed (Table 2).

5. Evidence for early anticoagulation

Heras et al. [22] carried out a retrospective study to determine the rate of TE in 816 patients who underwent bioprosthetic AVR (n = 424), mitral valve replacement (MVR) (n = 326) or both (n = 66), at three time intervals following surgery (1–10, 11–90 and >90 days) and the effects of anti-thrombotic therapy (anti-coagulation with intravenous heparin followed by warfarin and antiplatelet therapy using aspirin or dipyridamole, alone or in combination). Anticoagulation was considered adequate when the INR was between 3.0 and 4.5. Within the AVR only group, 51 patients (12%) (2.2% per year) had one TE episode and 10 patients (2%) (4.6% per year) had two episodes. Ninety-six percent of the first TE episodes involved the cerebral circulation and 4% affected the peripheral arteries. Of the 51 patients, 8% were on warfarin, 25% on aspirin, 25% on dipyridamole and 41% were not on any anti-thrombotic therapy. The second TE episodes only affected the cerebral circulation. Of these 10 patients, 30% were on warfarin, 20% on aspirin, 40% on dipyridamole and 10% on no anti-thrombotic therapy. There was no coronary TE. The rate of TE episodes during the first 10 days following AVR only was extremely high (41% per year) in patients without anticoagulation and was significantly higher than the rate at 11–90 days (3.6% per year) and >90 days (1.9%/year) (p < 0.001). This figure of 41% is perhaps less striking after taking into account that it represents a linearised event rate for a whole year derived from just five thromboembolic events in the first 10 days in a total of 424 AVR patients. They concluded that anticoagulation was indicated in all patients as early as possible for 3 months and thereafter in patients with risk factors. The linearised rates of bleeding for patients who underwent AVR only were 6.2%/year with anticoagulation compared to 1.6%/year without anticoagulation. The risk factors found to be associated with bleeding were anticoagulation and increased age. They also found that aspirin and dipyridamole did not reduce the risk of TE.

Orszulak et al. [28] carried out a retrospective study (n = 561) of patients who underwent AVR, with the Carpentier–Edwards porcine bioprosthesis (n = 343) or with associated coronary artery bypass grafting (CABG), over a 12-year follow-up period. Five percent of patients had a major neurological event, of which 2% occurred between 2 and 14 days following surgery. None of the patients were on warfarin at the time of the event. From their results, they concluded that an interim period of anticoagulation following surgery would be of benefit in the prevention of TE episodes. They also showed that the risk of early postoperative neurological events was increased by preoperative low ejection fraction (p ≤ 0.003), older age (<73 years; p ≤ 0.02) and preoperative AF or paced rhythm (p ≤ 0.01).

A prospective, non-randomised study (n = 209), designed by Aramendi et al. [29], investigated the efficacy of ticlopidine (n = 137), an antiplatelet agent, for >3 months following surgery, compared to oral anticoagulation (n = 40) (maintaining INR 2.0–3.0), aspirin (n = 14) or no medication (n = 18) in patients undergoing heart valve repair or replacement with a bioprosthesis. One percent of patients (0.5% per patient-year) in the ticlopidine group and 10% of patients (3% per patient-year) in the oral anticoagulant group
<table>
<thead>
<tr>
<th>Study</th>
<th>n (AVR only unless stated)</th>
<th>Mean F/U (mo)</th>
<th>Incidence of TE (%/patient-year)</th>
<th>TE events (%)</th>
<th>% of patients on warfarin at time of TE event</th>
<th>Antithrombotic therapy</th>
<th>p-value</th>
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<tr>
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<td>105.6 1.8 45 Not specified</td>
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<tr>
<td>Banbury et al. [11] 1982—1985</td>
<td>292 Some concomitant procedures</td>
<td>105.6 5.7</td>
<td>105.6 1.8 45 Not specified</td>
<td>105.6 1.8 45 Not specified</td>
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<td>Neville et al. [12] 1984—1995</td>
<td>958</td>
<td>45</td>
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<tr>
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<td>121 Some concomitant procedures</td>
<td>105.6 57.7</td>
<td>105.6 1.8 45 Not specified</td>
<td>105.6 1.8 45 Not specified</td>
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<td>105.6 1.8 45 Not specified</td>
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<td>Poirier et al. [14] 1981—1996</td>
<td>812 Some concomitant procedures</td>
<td>57.7</td>
<td>105.6 1.8 45 Not specified</td>
<td>105.6 1.8 45 Not specified</td>
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<td>Dellgren et al. [15] 1984—1995</td>
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<td>60 1.4 60 1.4</td>
<td>60 1.4 60 1.4</td>
<td>60 1.4 60 1.4</td>
<td>60 1.4 60 1.4</td>
<td>60 1.4 60 1.4</td>
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<tr>
<td>Heras et al. [22] 1979—1982</td>
<td>816</td>
<td>103.2</td>
<td>103.2 112 24—22 events</td>
<td>112 24—22 events</td>
<td>112 24—22 events</td>
<td>112 24—22 events</td>
<td>112 24—22 events</td>
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<tr>
<td>Turpie et al. [34] 1987—1996</td>
<td>210</td>
<td>3</td>
<td>26 100</td>
<td>26 100</td>
<td>26 100</td>
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<td>Moinud-deen et al. [30] 1987—1996</td>
<td>185</td>
<td>53 2.9 warfarin</td>
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<th>Authors</th>
<th>Year(s)</th>
<th>N</th>
<th>Duration</th>
<th>Warfarin</th>
<th>Dose</th>
<th>Aspirin</th>
<th>Dose</th>
<th>Other Treatments</th>
<th>Notes</th>
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<td>12</td>
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<td>Aspirin/warfarin (3 mo) then aspirin</td>
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<td>500</td>
<td>50.4</td>
<td>1.8</td>
<td>48</td>
<td>Warfarin</td>
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<td>Butchart et al.</td>
<td>1979—1992</td>
<td>619</td>
<td>62</td>
<td>1.7</td>
<td>53</td>
<td>Warfarin/aspirin</td>
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<td>748</td>
<td>84</td>
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<td>Warfarin: 2.9%</td>
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<td>Mistiaen et al.</td>
<td>1998—2002</td>
<td>193</td>
<td>6</td>
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<td>Aspirin: 0.8% No Rx: 1.5%/pt-year</td>
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<td>Aramendi et al.</td>
<td>2000—2003</td>
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<td>Warfarin: 2.3%</td>
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<td>Eichinger et al.</td>
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<td>561</td>
<td>38.4</td>
<td>0.6</td>
<td>14</td>
<td>Warfarin</td>
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<td>David et al.</td>
<td>1982—1994</td>
<td>1051</td>
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<td>Not specified</td>
<td></td>
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<td>1975—1982</td>
<td>768</td>
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<td>0.5</td>
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<td>Freedom from TE at 12 years</td>
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<td>1989—1993</td>
<td>204</td>
<td>24</td>
<td>1.7</td>
<td>7</td>
<td>Freedom from TE at 12 years</td>
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<td>Louagie et al.</td>
<td>1977—1987</td>
<td>100</td>
<td>53.6</td>
<td>2.01</td>
<td>9 (7 isolated MVR)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

had a TE event. The difference in linearised incidence of TE between the ticlopidine and anticoagulant group was significantly different ($p < 0.01$). No TE episodes occurred in the other study groups. They showed that the risk of TE was highest in the first month following surgery and declined rapidly thereafter. They also found that ticlopidine significantly increased freedom from TE events compared to oral anticoagulant ($p = 0.002$) but had a similar incidence of bleeding-related episodes (0.75% per patient-year).

### 6. Evidence not supporting early anticoagulation

A prospective study comparing the effects of warfarin ($n = 108$) with low-dose (100 mg/day) aspirin ($n = 141$) on cerebral protection from TE in the early postoperative period following bioprosthetic AVR was carried out by Gherli et al. [27]. LMWH was started in all patients on the first postoperative day and warfarin and aspirin were started on day 2. LMWH was continued in the warfarin group until the INR was between 2.0 and 3.0. Anticoagulation with warfarin was continued for 3 months postoperatively and then converted to aspirin. The number of cerebral ischaemic events was not significantly different between the two groups, in either the early (24 h–3 months) or late (>3 months) periods, and no difference was found in the rate of bleeding events. However, the numbers of cerebral ischaemic events totalled four events from the antiplatelet group ($n = 141$) and eight events from the warfarinised group ($n = 108$). The authors concluded that there seemed to be no advantages in performing early anticoagulation therapy in these patients compared to a low dose antiplatelet regime.

There are several retrospective studies that suggest early anticoagulation is unnecessary. Moinuddeen et al. [30] carried out a retrospective study of two groups of patients who underwent biological AVR ($n = 185$), with or without concomitant CABG. One group underwent immediate postoperative anticoagulation with heparin and warfarin ($n = 109$), continued for 3 months only. The other group ($n = 76$) received no postoperative anticoagulation. They found that the number of cerebral ischaemic episodes, 20 from the antiocoagulated group versus 14 from the non-anticoagulated group, was not significantly different between the two groups during any of the time frames examined ($p > 0.10$). The authors conclude that routine early anticoagulation following bioprosthetic AVR was therefore unnecessary. The bleeding complication rate between the two groups was the same, so despite no improvement in outcome with the use of anticoagulants, there appeared to be no increased risk associated with their use. Once again the possibility of a multicentre, prospective, randomised trial is raised, in order to clarify this question.

In another retrospective study, Blair et al. [31] identified patients who had undergone valve replacement, aortic ($n = 378$) or mitral ($n = 370$), with the Carpentier—Edwards bioprosthesis and recorded the antithrombotic therapy they received (warfarin, aspirin or no treatment). Whilst the incidence of TE tended to be greatest in the first 90 days, the rates of TE did not differ between warfarin, aspirin or no therapy ($p = 0.07$). They concluded that treatment with aspirin alone following AVR was sufficient, if no other risk factors are present.

Goldsmith et al. [32] carried out a retrospective analysis of 145 patients who had undergone bioprosthetic AVR, had remained in sinus rhythm postoperatively and had only received oral low-dose aspirin (75 mg/day). Two percent of patients had TE events, all occurring >1 year following surgery and all transient in nature. They concluded that low-dose aspirin was associated with minimal bleeding complications and no increase in the incidence of TE events when started in patients in sinus rhythm following AVR with the Tissueum porcine bioprosthesis.

A more recent retrospective study by Sundt et al. [23] analysed the data from the first 90 days following bioprosthetic AVR ($n = 1151$), with ($n = 641$) or without ($n = 510$) associated CABG. Six hundred and twenty-four patients received anticoagulation with heparin and warfarin and 527 patients received no anticoagulation, 410 of which received antiplatelet therapy. There was no significant difference between gender distribution, incidence of hypertension, diabetes, prior CVA or renal insufficiency. Postoperative CVA occurred in 2.4% of patients receiving anticoagulation and 1.9% of patients not anticoagulated ($p = NS$). They concluded that early anticoagulation with warfarin after bioprosthetic AVR did not protect against neurological events.

### 7. Current guidelines

The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines [33] recommend that low-risk patients with biological prosthetic AVR receive antithrombotic therapy with aspirin (Class I) or warfarin with INR 2.0—3.0 (Class IIA) for the first 3 months. For bioprosthetic valves the recommendation is largely based on a retrospective study by Heras et al. [22], in which the rate of TE was extremely high (41% per year) during the first 10 days following bioprosthetic AVR without anticoagulation and was significantly higher than the rate at >90 days ($p < 0.001$). After 3 months the ACC/AHA suggests the tissue valve can be treated like native valve disease and warfarin discontinued, assuming no risk factors for TE (atrial fibrillation (AF), previous TE, left ventricular dysfunction or hypercoaguable state) are present. This is based on studies showing that there is an increased risk of bleeding complications associated with long-term anticoagulation that outweighs the risk of TE events [2,22,34]. For patients with risk factors mentioned above the use of lifelong warfarin, maintaining the international normalised ratio (INR) between 2.0 and 3.0 is recommended by the ACC/AHA.

### Table 2

Current recommendations; first 90 days following bioprosthetic AVR

<table>
<thead>
<tr>
<th>Organization</th>
<th>Warfarin</th>
<th>Target INR</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC/AHA</td>
<td>Yes</td>
<td>2.0—3.0</td>
<td>Class IIA</td>
</tr>
<tr>
<td>ACCP</td>
<td>Yes (or aspirin)</td>
<td>2.0—3.0</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>ESC</td>
<td>Yes</td>
<td>2.0—3.0</td>
<td>Consensus</td>
</tr>
</tbody>
</table>

Key: ACC/AHA, American College of Cardiology/American Heart Association. ACCP: American College of Chest Physicians. ESC: European Society of Cardiology.

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The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines [33] recommend that low-risk patients with biological prosthetic AVR receive antithrombotic therapy with aspirin (Class I) or warfarin with INR 2.0—3.0 (Class IIA) for the first 3 months. For bioprosthetic valves the recommendation is largely based on a retrospective study by Heras et al. [22], in which the rate of TE was extremely high (41% per year) during the first 10 days following bioprosthetic AVR without anticoagulation and was significantly higher than the rate at >90 days ($p < 0.001$). After 3 months the ACC/AHA suggests the tissue valve can be treated like native valve disease and warfarin discontinued, assuming no risk factors for TE (atrial fibrillation (AF), previous TE, left ventricular dysfunction or hypercoaguable state) are present. This is based on studies showing that there is an increased risk of bleeding complications associated with long-term anticoagulation that outweighs the risk of TE events [2,22,34]. For patients with risk factors mentioned above the use of lifelong warfarin, maintaining the international normalised ratio (INR) between 2.0 and 3.0 is recommended by the ACC/AHA.
After 3 months they advise that, unless risk factors are present, patients receive low-dose aspirin (80–100 mg/day). The American College of Chest Physicians (ACCP) guidelines [35] recommend either warfarin (INR 2.0–3.0) for the first 3 months following bioprosthetic AVR or low-dose aspirin (80–100 mg/day). These recommendations are graded as 1C. It is based on a retrospective study by Babin-Ebell et al. [36] and a randomised trial by Turpie et al. [34] who showed that low-dose anticoagulation was as effective as high dose at preventing TE events, with less haemorrhagic complications. They also cite Moinudddeen et al. [30], who showed that early anticoagulation following bioprosthetic AVR did not confer any advantage compared to no anticoagulation, and Gherli et al. [27] who concluded that there is no advantage from anticoagulation with warfarin, compared to treatment with low-dose aspirin, in the prevention of TE events. The ACCP advise lifelong treatment with aspirin (75–100 mg/day) for patients in sinus rhythm following bioprosthetic AVR. This is based on evidence from Armendi et al. [29] and Goldsmith et al. [32] showing a lower rate of late TE in patients treated with antiplatelet agents. For patients in AF, long-term treatment with warfarin is recommended. The European Society of Cardiology (ESC) recommendations for the management of patients after valve surgery [25] are similar to the guidelines of the ACC/AHA and ACCP. The ESC recommends lifelong treatment with warfarin for patients following bioprosthetic AVR who have other indications for anticoagulation (AF, heart failure and impaired left ventricular function). This is based on evidence used by the ACCP for antithrombotic therapy in native and valvular heart disease [35]. ESC advises warfarin therapy in the first 3 months in all patients with bioprosthesis as a consensus view. This is based on the notion that there is an absence in the literature of studies specifically addressing the question of the safety of omitting warfarin after AVR. Therefore, the risk-to-benefit ratio overall probably does favour the use of anticoagulants. Furthermore, they mention the widespread use of aspirin as an alternative, and cite the observational study by Gherli et al. [27] to support this. They advise that all patients with a bioprosthesis, who are not anticoagulated, be followed up closely to detect structural valve deterioration or the onset of AF, based on the randomised prospective trial by Oxenham et al. [3]. The Scottish Intercollegiate Guideline Network [37] also recommends warfarin for 3 months after aortic bioprosthesis (Grade C). The British Committee for Standards in Haematology (BCSH) published their Guidelines on Oral Anticoagulation in 1998 [38]. Although they do not recommend warfarin for aortic bioprostheses, they accept that many institutions do this.

Vaughan et al. [39] surveyed UK consultant practice in 2005 with regard to antithrombotic therapy after valve surgery. Interestingly, 53% of respondents did not follow AHA guidelines and never instituted warfarin therapy after tissue AVR. The response rate to this survey, however, was just over 50%. CTSNet editors performed a survey in 2004 looking at anticoagulation management for bioprosthetic AVR [40]. Whilst 79% of respondents were aware of the guidelines, 60% did not use warfarin and 63% respondents felt that warfarin was no longer the standard of care for tissue aortic valves.

8. Risk factors for TE following bioprosthetic AVR

Virchow [41] in his eponymous triad, first postulated the factors leading to thrombus formation. These factors are changes in the vessel wall, blood flow and constituents (coagulability) of the blood. Arterial thrombi form under conditions of high flow and are composed mainly of platelet aggregates held together by thin fibrin strands [42]. The factors that influence the risk of TE following bioprosthetic AVR include age, smoking, hypertension, diabetes, hyperlipidaemia, AF, previous TE, hypercoaguable state, left ventricular dysfunction and left atrial size [43]. The guidelines for reporting morbidity and mortality after cardiac valvular operations define TE events as non-haemorrhagic neurological deficits, for example an ischaemic stroke, and peripheral arterial emboli until proved otherwise [44].

Heras et al. [22] have shown that the TE risk was especially high during the first 10 days following surgery, high (mitral) to medium (aortic) risk at 11–90 days after operation and medium (mitral) to low (aortic) risk thereafter. The risk of TE was increased by lack of anticoagulation (p = 0.007), mitral valve location (p < 0.001), previous TE (p = 0.002) and increasing age (p = 0.014).

Several authors have reported age to be a significant risk factor for TE events following bioprosthetic AVR (p < 0.02) [28], whereas others [23,45] have shown TE to be independent of age.

Mistiaen et al. [45] found that preoperative CVA (p = 0.0016), the use of warfarin (p = 0.0028), preoperative endocarditis (p = 0.006) and hospital TE (the occurrence of a TE event in the first 30 days after the operation or in the same hospital period if this >30 days) (p = 0.016) were all significant risk factors for TE. They also showed that hypertension has a borderline effect (p = 0.063), but recommend tight control of blood pressure.

Butchart et al. [46] found that pre- and postoperative hypertension significantly increased the risk of TE. They also found that smoking, both prior and after surgery, and diabetes were also significant risk factors. These risk factors, however, are unlikely to be modified by the use of oral anticoagulants.

Orszulak et al. [28] showed that decreased ejection fraction (≤0.54) (p ≤ 0.003) and preoperative AF or a paced rhythm (p ≤ 0.01) contribute to increased risk of TE. They showed that the influence of preoperative AF was only significant in combined AVR and CABG (p ≤ 0.01) compared to AVR alone (p ≤ 0.45). Blair et al. [31] have also shown that preoperative AF was an independent risk factor for TE following bioprosthetic AVR (p = 0.004).

There are reports that preoperative endocarditis significantly decreases the 5-year event-free rate of TE after bioprosthetic valve replacement [45]. Butchart et al. [47] analysed clinical, echocardiographic, haematological, biochemical and microbiological parameters in an attempt to devise a scoring system to determine TE risks after valve replacement. However, the authors have not reported specific results for tissue versus mechanical valve replacement and, similarly, it is unclear as to which group received what type, if any, antithrombotic therapy. It is therefore difficult to establish possible predictors for TE in bioprosthetic AVR based on this study.
There is no increase in the risk of TE due to gender, specific valve pathology (aortic stenosis, regurgitation or mixed disease) or previous AV surgery [28,45].

9. Incidence of TE events

Arterial emboli, valve thrombus and bleeding are major complications following AVR. The incidence of TE following bioprosthetic AVR is between 0.9% and 2.2% per patient-year. The results of several studies with their antithrombotic regimes are summarised in Table 1.

10. Bleeding complications due to anticoagulation

Anticoagulant-related bleeding is a significant cause of postoperative morbidity and mortality with a rate of 0.75–2.4% per patient-year.

Turpie et al. [34] carried out a randomised trial (n = 210) of anticoagulation with warfarin, using standard (target INR 2.5–4.0) versus a less intensive regimen (target INR 2.0–2.25), in consecutive patients undergoing tissue valve replacement. The patients were followed up for 3 months postoperatively. Of these patients, 117 underwent AVR (n = 58 standard group, n = 59 less intensive regimen group). Two percent of patients had major embolic events at a mean of 22.7 days following surgery (1% in each treatment group). All episodes occurred in patients who underwent MVR and were in AF. Ten percent of patients (5% in each treatment group) had minor embolic events, including TIA's. Haemorrhagic complications occurred in 10% of patients (n = 15 standard group, n = 6 less intensive group). The results indicated that a less intensive anticoagulation regimen was as effective as the standard regimen in preventing major embolism, and was associated with fewer major and minor haemorrhagic episodes.

A prospective randomised trial of 193 patients comparing the use of trifusal (n = 97), an antiplatelet agent, with oral anticoagulation (n = 96), maintaining INR between 2.0 and 3.0, for 3 months following bioprosthetic valve replacement (aortic, n = 181; mitral, n = 10) with a median follow-up of 6 months was carried out by Aramendi et al. [26]. There was no significant difference in the incidence of TE over the first 6 months postoperatively, but there was a significantly lower incidence of bleeding episodes with trifusal (p = 0.048).

In a prospective non-randomised study, Eichinger et al. [48] evaluated the haemodynamic function of the Mosaic bioprosthetic heart valve in the aortic (n = 444) and mitral (n = 98) position. They found a relatively high rate of haemorrhage in the aortic group (0.8% per patient-year) that they attributed to the large proportion of patients (61.5%) receiving antithrombotic therapy at 5 years follow-up.

11. Conclusion

Due to the lack of prospective randomised trial data, the optimal antithrombotic or anticoagulation regime in patients following bioprosthetic aortic valve replacement remains unclear. What is clear is that whilst several studies have showed equivalence between antiplatelet therapy and anticoagulation, to date, no studies have demonstrated anticoagulation leads to a reduction or increase in adverse outcomes. There is no study specifically examining the safety of omitting warfarin after AVR and, therefore, guidelines remain weighted in favour of early anticoagulation. The guidelines are based on observational studies, most being retrospective case series. Certainly evidence derived from surveys suggests that guidelines and clinical practice are out of step. Several authors have called for large prospective randomised trials. In conclusion, only two prospective randomised trials compare oral anticoagulants and antiplatelet agents following bioprosthetic AVR, both of which suggest equal efficacy. However, many current guidelines are still weighted in favour of oral anticoagulant therapy based on observational studies previously discussed.

Acknowledgement

We would like to thank Miss Frances Williams for her assistance and review of this manuscript.

References


