Anticoagulation or antiplatelet therapy of bioprosthetic heart valves recipients: an unresolved issue

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Summary

Improvements in the performance and longevity of biological valve prostheses have steadily increased their rates of implantation in recent years. Aortic bioprostheses, which are commonly used in the elderly or when the risks of anticoagulating are high, have generally been associated with low rates of long-term complications. Freedom from anticoagulation, therefore, represents the main theoretical advantage of biological, compared with mechanical, aortic prostheses. While a variety of anticoagulant and antiplatelet drug regimens have been described, a precise antithrombotic protocol for the early postoperative period after bioprosthetic aortic valve replacement has not been developed. There are also important differences between the international guidelines published. This review examines the clinical evidence concerning the use of vitamin K antagonist and antiplatelet therapy in the early management of the antithrombotic complications after bioprosthetic aortic valve replacement.

Keywords: Bioprosthesis; Surgery; Anticoagulation; Acetyl salicylic acid; Antiplatelet therapy

1. Review of current guidelines

1.1. Bioprosthetic heart valve

Improvements in the performance and longevity of biological valve prostheses have steadily increased their rates of implantation in recent years [1—4]. Aortic bioprostheses, which are commonly used in the elderly or when the risks of anticoagulating are high, have generally been associated with low rates of long-term complications [4—6]. Freedom from anticoagulation, therefore, represents the main theoretical advantage of biological, compared with mechanical, aortic prostheses. While a variety of anticoagulant and antiplatelet drug regimens have been described [6—16], a precise antithrombotic protocol for the early postoperative period after bioprosthetic aortic valve replacement (AVR) has not been developed. The 2006 guidelines issued by the American Heart Association (AHA) and the American College of Cardiology (ACC) for valve replacement recommend the prescription of acetyl salicylic acid (ASA) to all recipients of bioprosthetic heart valves (Class I, Level of evidence C) as well as to consider anticoagulating with a vitamin K antagonist (VKA) for 3 months after bioprosthetic AVR, to reach an INR between 2.0 and 3.0, an acceptable alternative but certainly not a primary recommendation (Class IIa, Level of evidence C) [17]. The European Society of Cardiology also recommends the use of a VKA for 3 months after bioprosthetic AVR [18]. The guidelines of the American College of Chest Physicians (ACCP), updated in 2004, recommend the use of a VKA for 3 months after valve replacement (Grade 2C), and long-term ASA (Grade 1C+) [19]. Likewise, the guidelines issued by the Canadian Cardiovascular Society (CCS) in 2004 recommend a VKA for the 3 months after bioprosthetic AVR (Grade 2C) [20]. The British Society of Hematology (BSH) does not recommend the use of oral anticoagulants for the first 3 months for bioprosthetic valves in the aortic position for patients in sinus rhythm (Grade A, Level Ib), although it does not view as a contraindication the prescription of VKA, as practiced in many medical centers [21]. These guidelines were developed to minimize the incidence of thromboembolism during the highest risk period, when fibrin deposits and platelets aggregate on foreign surfaces, such as Dacron sewing rings or valve leaflets devoid of endothelium, until endothelialization has occurred [7,22]. Despite guidelines issued by several professional societies, opinions and medical practices related to the prevention of thrombotic events early after the implantation of aortic bioprostheses remain conflicting (Table 1).

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1.2. Mechanical heart valve

There is growing general interest in anticoagulation of mechanical heart valves as well. AHA/ACC, ESC, ACCP, and CCS guidelines recommend that all recipients of mechanical prosthetic heart valves be orally anticoagulated (Grade 1), with a target INR between 2.0 and 3.0 for both aortic and mitral valve replacement (MVR) [17–20]. Only the AHA/ACC guidelines updated in 2006 recommend the prescription of ASA (75–100 mg daily) combined with VKA [17]. The BSH recommends a target INR of 3.0 for AVR and 3.5 for MVR [21].

2. Optimizing anticoagulation therapy

To diminish the risk of bleeding that can occur at these levels of anticoagulation, successful attempts have been made, in various populations, to lower the target INR, with a highly significant decrease in the incidence of hemorrhagic complications, at the cost of only a slight increase in the incidence of thromboembolic events [23–27]. The therapeutic window of anticoagulation is, nevertheless, narrow and, according to the results of the GELIA study, the most important issue is stability of the INR within the target range [23,24], a goal which mandates frequent measurements and appropriate adjustments. The management of anticoagulation can be optimized by handheld, self-testing devices, which allow reliable measurements of INR with a single drop of whole blood [27–30]. When monitoring themselves, the patients can either perform the test and adjust their treatment, according to a preplanned dose adjustment schedule, or perform the test and call a caregiver to receive the appropriate dose adjustment instructions. A recently published meta-analysis showed that self-management improves the quality of oral anticoagulation. Patients capable of monitoring their INR and of adjusting their own treatment sustained fewer thromboembolic events and had a lower mortality than those who were only capable of monitoring the INR. However, self-monitoring (a) cannot be performed by all patients, (b) requires the identification and education of suitable candidates [31], and (c) is not reimbursed in all countries.

Much of this potential benefit remains unattainable because patients are not anticoagulated, or are not properly anticoagulated. To mitigate the difficulties and disadvantages of chronic anticoagulation, Garcia-Rinaldi [32] reintroduced an antithrombotic protocol for patients with mechanical aortic valves, previously unsuccessfully tested by Schlitt et al. [33] consisting of a combination of ASA and clopidogrel. The authors reported noteworthy results, with no thromboembolic event or clotted prosthesis over a cumulative follow up of 1030 months. Based on this favorable experience, the Medical Carbon Research Institute, LLC (Austin, Texas), manufacturer of the On-X mechanical heart valve, has recently launched a trial approved by the US Food and Drug Administration to test this innovative protocol for mechanical AVR (<http://www.clinicaltrial.gov/>).

3. Literature review

According to a recent survey by the Cardiothoracic Surgery Network (<http://www.ctsnet.org/file/AnticoagulationSurveyFinalResultsSlidesPDF.pdf>), 'Anticoagulation therapy after aortic tissue valve replacement', accessed September 14, 2005), over 60% of cardiac surgeons believe that antiplatelet therapy alone is preferable to oral anticoagulation for patients without major comorbidity. A survey made in Great Britain and Ireland, published in September 2005, showed that 47% of the consultants who participated in the survey treated with VKA patients after bioprosthetic AVR for the first 3 months [34]. In a preliminary survey, we determined that only 25% of European medical centers administer only ASA in the early postoperative period after AVR with a bioprosthesis.

A few retrospective studies and two randomized trials have examined the effects of various regimes on the incidence of postoperative thromboembolisms and hemorrhages after AVR with bioprostheses [22,35–46]. Heras et al. observed an inordinately high rate of early thromboembolic events in patients who were not anticoagulated, particularly after MVR in the first 10 days postoperatively [22]. In this interval, there were five strokes among 424 patients undergoing bioprosthetic AVR, all of which occurred among patients not receiving anticoagulation. The risk fell precipitously, thereafter, to a linearized rate of 3.6% per year between 10 and 90 days, and 1.9% per year, thereafter. They concluded that early anticoagulation to maintain a prothrombin time between 1.5 and 2.0 (INR 3.0–4.5) should be administered for at least 3 months. This high level of anticoagulation might explain the higher rate of bleeding complications observed in these patients compared with previous reports [11,47,48]. They did not, however, distinguish between prostheses in the mitral and aortic positions.

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Table 1: Guidelines for antithrombotic therapy in patients with aortic bioprosthetic valves in absence of risk factors

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>Recommended treatment</th>
<th>Class of evidence</th>
<th>Level of evidence</th>
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<tr>
<td>ACC/AHA [17]</td>
<td>ASA</td>
<td>1</td>
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<td>VKA for first 3 months (INR 2–3)</td>
<td>IIA</td>
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<tr>
<td>ESC [18]</td>
<td>VKA for first 3 months (INR 2–3)</td>
<td>1</td>
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<td>ACCP [19]</td>
<td>ASA</td>
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<td>CCS [20]</td>
<td>ASA</td>
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<td>VKA for first 3 months (INR 2–3)</td>
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<td>BSH [21]</td>
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Curiously, the protective effect of anticoagulation was only slight after mitral valve replacement and was not seen at all among double valve replacement patients. Furthermore, while approximately one-third of the patients were given anticoagulants postoperatively, in two-thirds of those cases the prothrombin time was less than 1.3 s during the high-risk first 10 days when an apparent protective effect was observed.

In 1988, Turpie et al. reported a low rate of serious bleeding complications with low-dose anticoagulation and a target INR kept between 2.0 and 2.3, while in 1995, Orszulak et al. found that the early use of warfarin after bioprosthetic AVR was beneficial only among patients with high-risk characteristics, including a depressed left ventricular function, older age, and preoperative atrial fibrillation or paced rhythm [12]. Nevertheless, in 1998, Tiede et al., in a review article, recommended anticoagulation with warfarin in all patients [49].

Babin-Ebell et al. [37] and Joyce and Nelson [38] found no benefit conferred by early standard anticoagulation with warfarin compared to ASA. Furthermore, in 378 patients who underwent AVR and were treated with ASA, or warfarin, or neither, Blair et al. observed a mean 0.8 ± 0.2% per patient-year incidence of thromboembolisms associated with ASA, lower than the 2.9 ± 1.6% per patient-year recorded with warfarin, or 1.5 ± 0.6% per patient-year with no treatment [39]. Recognizing the limitations imposed by the retrospective nature of their analysis, the authors concluded the article with a recommendation to use ASA alone routinely after AVR. Similar conclusions were reached by investigators in Spain [40,41]. Likewise, in a retrospective analysis of 195 patients who had undergone bioprosthetic AVR, Moinudddeen et al. found no significant differences in rates of cerebral ischemic events (2.8% vs 2.6%) or bleeding complications (9.2% in both groups) among patients treated with warfarin versus patients treated with ASA alone for the first 3 postoperative months [42].

In a prospective study published in 2004, Gherli et al. reported no significant difference in rates of cerebral ischemic events, major hemorrhages, or overall survival among 141 patients who received warfarin for 3 months versus 108 patients treated with ASA alone, chosen according to the surgeon’s preference [35]. Mistiaen et al. [43] analyzed 500 elderly patients receiving a Carpentier-Edwards valve and found on multivariate analysis that the use of VKA actually increases the risk of thromboembolism with a risk ratio of 3.0 after a 4-year follow-up. In a retrospective analysis of 1151 patients who underwent bioprosthetic AVR with (n = 641) or without (n = 510) associated coronary artery bypass grafts at the Mayo Clinic, 624 patients were anticoagulated postoperatively, 411 received antiplatelet therapy, and 116 received neither warfarin nor antiplatelet agents [44]. Postoperative cerebrovascular accidents occurred in 2.4% of the anticoagulated versus 1.9% of the non-anticoagulated patients, a statistically non-significant difference. The rates of bleeding complications in the first 90 days were similar in both groups (1.1% vs 0.8%). Despite several biases inherent to the retrospective character of their analysis, the authors concluded that anticoagulation with warfarin early after bioprosthetic AVR did not protect against adverse neurological events. The results of the Spanish multicenter, randomized, TRAC trial, comparing the antiplatelet agent trifusal with acenocoumarol in the prevention of thromboembolisms after bioprosthetic AVR and MVR, were recently published [45]. Among 193 patients enrolled, 9 (4.7%) experienced thromboembolic events, 6 among the 96 patients assigned to acenocoumarol, and 3 events among the 97 patients assigned to trifusals (ns). There were six major hemorrhages in the group treated with acenocoumarol versus three in the trifusal-treated group (ns). Though the population included in this trial was small and inhomogeneous, its results were noteworthy, suggesting that trifusal was at least as safe and effective as systemic anticoagulation in the prevention of thromboembolisms after valve replacement with a bioprosthesis. In 2005, Colli et al. presented the early results of the WoA Epic Pilot Trial, comparing warfarin versus aspirin after AVR with the Epic TM tissue valve prosthesis (St. Jude Medical, Minneapolis, MN) in 69 patients who had no thromboembolic risk factor [46]. A single postoperative cerebral ischemic event was observed in each treatment group (2.8% vs 2.9%, ns) between 24 h and 3 months after surgery. The rates of major bleeding events, the stroke-free survival, and the overall survival rates were not statistically different between the two study groups. The authors concluded, from these early results, that there is currently no evidence in support of anticoagulation with warfarin for the prevention of valve thrombosis or arterial thromboembolisms in recipients of EpicTM prostheses. More recently, Jamieson et al. presented, at the 42nd Annual Meeting of the Society of Thoracic Surgeons, the results of a retrospective study of 1372 patients who had undergone biological AVR alone, versus biological AVR combined with myocardial revascularization, between years 1994 and 2000 [50]. Although there was an important bias introduced by limiting early events to the first 30 days, instead of first 90 days after surgery, these authors observed a 3.6% incidence of thromboembolism in the non-anticoagulated group, 2.2% in the group treated with antiplatelet agents, and 3.9% in the anticoagulated group (ns). By univariate analysis, antiplatelet therapy was the only protective treatment against major thromboembolic events. By multivariate analysis, preoperative cerebrovascular accidents and concomitant coronary artery bypass graft surgery were indications for anticoagulation. The preliminary results of a study by Di Marco et al., who analyzed the presence versus absence of microembolic signals, showed a correlation between absence of neurologic complications and absence of microembolic signals on transcranial Doppler examination in a subgroup of aortic valve bioprostheses recipients who were treated with ASA instead of warfarin in the early postoperative period (0% microembolic signals) [51].

4. Discussion

These key observations seem to confirm, in patients without thromboembolic risk factors, the sufficiency of antiplatelet therapy as antithrombotic protection during the early postoperative period of AVR with a bioprosthesis.

Nevertheless, no definitive evidence has been proved and this conclusion, which is mainly based on retrospective or small studies, need to be confirmed by a multicenter,
prospective, randomized trial. Furthermore, the postoperative
treatment of atrial fibrillation mandating VKA therapy in
15–20% of patients needs to be considered. All
manufacturers of tissue heart valves currently refer to the
official guidelines, such that no valve implant is recom-
manded with protection by an antiplatelet regimen only. The
AntiCoagulation Treatment Influence ON postoperative
patients (ACTION) trial was designed to determine whether
anticoagulation is preferable, or whether antiplatelet
therapy suffices after bioprosthetic AVR. The study, spon-
sored by a device company (ST. Jude Medical, Minneapolis,
MN) was to be conducted in all European countries. Since ASA
is not labeled as antithrombotic therapy after bioprosthetic
AVR, and since the patients were to be randomly assigned
to two different therapies, several competent authorities have
classified ACTION as a drug trial, with the need of a
declaration to the European Medicine Agency (EMEA). Given
the high interest of the medical community in antithrombotic
therapy after biological valve implant, we have developed
the ACTION Registry, which will collect early postoperative
information without recommending or requesting the use of a
specific antithrombotic regimen, and without random assign-
ment of the patients to a specific therapy. The antithrombo-
tic management for the 3 months after the operation will be
chosen by the surgeons, based on their preferences. This will
offer an opportunity to examine for the first time, in a pan-
European observational registry, which therapy confers the
highest level of protection against thromboembolisms,
providing the basis for a randomized trial, hopefully
supported by professional organizations. This study would
represent the most solid basis on which to develop a critical
revision of the current guidelines. A recommendation
limiting antithrombotic therapy to ASA for recipients of
bioprostheses for AVR could only be made with a Grade 1A
level of evidence after the successful completion of a
randomized trial.
We believe that the confirmation of equivalent safety and
efficacy of ASA in preventing systemic thromboembolisms
would (1) eliminate the need for frequent uncomfortable
blood samplings, and regular monitoring and adjustments of
drug doses, (2) lower the risk of hemorrhage, and (3)
markedly decrease the costs associated with postoperative
antithrombotic therapy, while notably improving patient
care and quality of life.

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