Antithrombotic therapy after bioprosthetic aortic valve replacement: 
ACTION Registry survey results

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Abstract

Aims: A variety of antithrombotic regimens have been described for the early postoperative period after bioprosthetic aortic valve replacement (AVR). This study reviews antithrombotic practice for patients undergoing bioprosthetic AVR with or without coronary artery bypass graft (CABG) amongst the centers participating in the ACTION (Anticoagulation Treatment Influence on Postoperative Patients) Registry.

Methods and results: An antithrombotic therapy questionnaire was answered by the 49 centers participating in the ACTION Registry located in Europe, Middle East, Canada and Asia. The 43% of centers prescribe vitamin K antagonist (VKA), 20% prescribe VKA and acetyl salicylic acid (ASA), 33% prescribe only ASA and 4% do not prescribe any therapy after bioprosthetic AVR. For patients undergoing bioprosthetic AVR and CABG 39% of the centers prescribe VKA and ASA, 37% prescribe VKA and 24% prescribe ASA. After the first three postoperative months following bioprosthetic AVR, 61% of the centers prescribe only ASA, while 39% do not prescribe any therapy. Patients with bioprosthetic AVR and CABG receive ASA in 90% centers, in 2% centers VKA and ASA, and 8% centers do not prescribe any antithrombotic.

Conclusion: This study demonstrates that, despite guidelines published by several professional societies, medical practice for the prevention of thrombotic events early after bioprosthetic AVR varies widely among cardiac surgical centers.

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1. Introduction

Despite improvement in valve design, patients undergoing prosthetic valve replacement are at risk of developing valve thrombosis and systemic thromboembolism. The need for lifelong anticoagulant therapy is well established in all patients with mechanical heart valves and in patients with bioprosthetic heart valves in the presence of thromboembolic risk factors like atrial fibrillation, left ventricular dysfunction, previous thromboembolism, left atrial thrombus at surgery or hypercoagulable conditions. The use of antithrombotic therapy in the early postoperative period after bioprosthetic aortic valve replacement (AVR) is controversial. The decision whether to use anticoagulation or antiplatelet therapy, the duration and level of anticoagulation are all areas of debate. The 2006 guidelines issued by the American Heart Association (AHA) and the American College of Cardiology (ACC) for valve replacement recom-
mend the prescription of acetyl salicylic acid (ASA) to all recipients of bioprosthetic heart valves (Class I, Level of evidence C) as well as the consideration to use vitamin K antagonists (VKA) during the first 3 months after bioprosthetic AVR. The guidelines maintain an INR-range between 2.0 and 3.0, as an acceptable alternative but certainly not a primary recommendation (Class IIa, Level of evidence C) [1]. The European Society of Cardiology recommends the use of a VKA for 3 months after bioprosthetic AVR [2]. The guidelines of the American College of Chest Physicians (ACCP), updated in 2004, recommend the use of a VKA for 3 months after tissue heart valve replacement (Grade 2C) and long-term ASA (Grade 1C+) [3]. Also the guidelines issued by the Canadian Cardiovascular Society (CCS) in 2004 recommend VKA for the 3 months after bioprosthetic AVR (Grade 2C) [4]. The British Society of Haematology (BSH) does not recommend the use of oral anticoagulants during the first 3 months for bioprosthetic valves in the aortic position if patients are sinus rhythm (Grade A, Level Ib), although it does not see the prescription of VKA as a contraindication, as practiced in many medical centers [5].

The current survey was carried out in order to review the antithrombotic regimen used by the centers participating in the ACTION Registry located in Europe, Middle East, Canada and Asia before the start of the enrollment.

2. Methods

Following focus group discussions between members of the steering committee of the ACTION Registry, a standard therapy survey was developed with the aim to ascertain the different antithrombotic management following isolated bioprosthetic (excluding autografts and homografts) AVR (±concomitant coronary artery bypass graft; CABG.) adopted in the recruiting centers. The participants were asked to describe their standard antithrombotic protocol focusing on the timing, dosage, route (intravenous, subcutaneous and oral), type of molecule (unfractioned or low-molecular weight; LMWH) of heparin. Information on the desired INR target or range, timing of vitamin K antagonist therapy, type, dosage and timing of antiplatelet agents was also collected. The ACTION Registry aims at collecting data on patient who are at least 18 years of age in sinus rhythm before surgery, requiring first time aortic valve replacement with SJM Epic™ and SJM Epic™ Supra porcine bioprosthetic heart valve. Clinical non-inclusion criteria include the presence of previous implanted prosthetic valve; double valve implantation; concomitant CABG; intra-aortic balloon pump at any time before, during or after intervention; use of ASA or VKA therapy or any other antithrombotic drug; recent positive pregnancy test, breast-feeding, or the possibility of a future pregnancy; active infective endocarditis; aortic dissection; history of cerebral ischemia; coagulopathy; history of gastrointestinal bleeding or increased bleeding risk; vascular disease requiring medical or surgical treatment; previous chronic anticoagulation therapy; allergy or contraindication to ASA and/or VKA. The ACTION Registry is an open registry, in which every participating investigator can prescribe whatever he/she considers appropriate in terms of postoperative antithrombotic therapy. The sample size for the ACTION Registry is 1014 patients in total. The responses on the standard therapy forms were collected and analyzed. The survey was submitted to each participating centre starting from April 2006 up to February 2007.

The standard therapy forms were entered by a dedicated team at St. Jude Medical. Data were stored on a secured server and was managed using Oracle Clinical. If necessary, queries were raised using Oracle Clinical. All captured data were analyzed by quoting the frequencies and percentages. As the sample size calculation for ACTION Registry was not based upon this separate topic, no formal statistical comparisons were performed.

3. Results

In total 49 standard therapy forms were received from 48 centers spread over 13 countries (Belgium, Canada, Germany, France, India, Israel, Italy, Netherlands, Norway, Portugal, Spain, Switzerland and UK. In one center 2 investigators followed a different standard therapy (Fig. 1). In Table 1 the center’s were categorized into VKA/ASA or VKA or ASA or something according to the prescription behavior between hospital discharge and the 3rd post-operative month. For patients with bioprosthetic AVR without CABG, 43% of centers prescribe VKA, 33% prescribe ASA, 20% prescribe VKA and ASA and 4% do not prescribe anything from discharge until month 3. For patients with bioprosthetic AVR and CABG, 39% of centers prescribe both VKA and ASA, 37% prescribe ASA, 24% prescribe VKA between discharge and month 3. Figs. 2 and 3 show a large variability in the antithrombotic therapy not only among different countries but also within the same country. All centers using VKA reported an international normalized ratio (INR) target of 2.5. After bioprosthetic AVR, 29% of centers reported the routine use of intravenous heparin, 27% LMWH, 12% subcutaneous heparin and 16% do not prescribe any specific antiplatelet therapy. Following bioprosthetic AVR and CABG, 30% of centers prescribe intravenous heparin, 30% LMWH, 29% do not prescribe anything and 12% prescribe subcutaneous heparin.

Following surgery, LMWH or heparin was reported as being used by the most of the centers (AVR, 65%; AVR and CABG, 67%). The majority of centers started LMWH or heparin on
postoperative day (POD) 0 (AVR, 72%; AVR and CABG, 76%), although some centers started heparin on POD 1 (AVR, 25%; AVR and CABG, 21%). All the centers discharge patients without LMWH therapy. In centers prescribing ASA, its administration begins in the majority of cases on POD 1 (AVR, 96%; AVR and CABG, 86%). The use of VKA started in the majority of centers on POD 2 (AVR, 87%; AVR and CABG, 87%). All the centers stop prescribing VKA after 3 months for all patients with isolated AVR, 61% of them prescribe ASA long-life and 39% do not prescribe anything. For patients with AVR and CABG, 90% centers prescribe ASA after the first 3 postoperative months, 2% prescribe VKA and ASA and 8% do not prescribe any antithrombotic therapy (Table 2).

In case of comparison of new onset atrial fibrillation (AF) all the centers anticoagulate patients. However, 26.5% of centers give VKA and ASA in patients with isolated bioprosthetic AVR. In patients undergoing bioprosthetic AVR and CABG and experiencing new onset AF we have observed that 63.3% of the centers give VKA and ASA, and 30.6% give only VKA, 4.1% give VKA ASA and Clopidogrel, and 2% gives VKA and Clopidogrel.

4. Discussion

Prosthetic valve thromboembolism is a complex phenomenon, occurring through an interaction between prosthetic type and patient-related factors. The pathologic events leading to thromboembolism start immediately after surgery. Damaged paravalvular tissue and deposition of fibrinogen on the valve surface activate platelets as soon as blood starts flowing across the valve leading to immediate platelet adhesion and aggregation [6,7]. Within 24 h after surgery, platelet deposition on the Dacron sewing ring can be imaged radiographically [8] however, these platelets are highly sensitive to shear forces and they are prone to continued activation and destruction. With continuing cycles of platelet aggregation, patients with mechanical valves have shorter platelet survival, a marker of thromboembolic risk, than patients with biological valves [9]. Also coagulation factors are activated after valve implantation, leading to further clot formation. This is inherent to the thrombogenicity of the prosthetic material (suture material, Dacron sewing ring, struts, and hinge points) and sites of debrided tissue (valve excision site) [10]. Transprosthetic turbulent flow leads to regional increase in shear stress, structural damage of the endocardium and causes a loss of local resistance to thrombosis. Turbulent areas on the outflow side of the prosthesis create flow stagnation, trapping damaged platelets and activated factors [11]. This provides an ideal substrate for thrombus formation and subsequent embolization. Thrombin can also be formed on platelet membranes after their activation, further promoting the organization and growth of platelet fibrin thrombus [12].

The insertion of an artificial device in contact with the bloodstream exposes the patient to a continuous risk of thrombosis and thromboembolism. This risk is proportional to the surface area of the foreign material, which is in contact with blood, making patients with mitral valve prostheses more prone to thromboembolic complications [9]. In general, a recent heart valve prosthesis implantation is a strong risk factor for thromboembolic complications [15,16], especially in the first 3–6 months after surgery [15]. The reasons for this are the following: first, the pathologic sequelae of the patients’ inherent to valvular disease (atrial fibrillation, dilated left atrium, and dilated left ventricle) may predispose to areas of stasis and thrombus formation. Secondly, the increased thromboembolic risk early after valve implantation

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of therapies between discharge and month 3</th>
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<tbody>
<tr>
<td></td>
<td>Without CABG N = 49</td>
</tr>
<tr>
<td>n   (%)</td>
<td>n   (%)</td>
</tr>
<tr>
<td>VKA/ASA</td>
<td>10   20.4</td>
</tr>
<tr>
<td>VKA</td>
<td>21   42.9</td>
</tr>
<tr>
<td>ASA</td>
<td>16   32.7</td>
</tr>
<tr>
<td>Nothing</td>
<td>2    4.1</td>
</tr>
</tbody>
</table>

Fig. 2. Standard therapies at discharge for patients without CABG.

Fig. 3. Standard therapies at discharge for patients with CABG.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Prescribed medication at discharge and month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without CABG N = 49</td>
</tr>
<tr>
<td>n   (%)</td>
<td>n   (%)</td>
</tr>
<tr>
<td>VKA/ASA → VKA/ASA</td>
<td>0   0</td>
</tr>
<tr>
<td>VKA/ASA → ASA</td>
<td>9   18.4</td>
</tr>
<tr>
<td>VKA/ASA → nothing</td>
<td>1    2.0</td>
</tr>
<tr>
<td>VKA → ASA</td>
<td>7    14.3</td>
</tr>
<tr>
<td>VKA → nothing</td>
<td>14   28.6</td>
</tr>
<tr>
<td>ASA → ASA</td>
<td>14   28.6</td>
</tr>
<tr>
<td>ASA → nothing</td>
<td>2    4.1</td>
</tr>
<tr>
<td>Nothing → nothing</td>
<td>2    4.1</td>
</tr>
</tbody>
</table>
may reflect incomplete endothelial proliferation on the raw intracardiac surfaces, sewing ring and suture knots in the initial postoperative period [6,7,9]. The presence of an endothelial lining on the valve surface effectively prevents thrombus formation, but it may require more than one year after implantation for this in-growth to fully form [13,14]. However, in the absence of endothelial organization, the development of a mature platelet fibrin coating on the valve surface may also be favorable in terms of non-thrombogenicity and explain the absence of thrombotic deposits in explanted valves in which tissue in-growth is incomplete [13,14]. Therefore, it is believed that the lack of host endothelial cell in-growth and mature platelet fibrin coating on the valvular surface in the postoperative period may promote early thrombus formation and contribute to the elevated early thromboembolic risk [17].

The optimal antithrombotic prophylaxis for aortic valve bioprostheses remains controversial. Five international medical associations have addressed this issue over the last 10 years in specific consensus documents. Regardless of the earlier consensus recommendations, there is widespread use of ASA as an alternative to anticoagulation for 3 months in patients with no other indications for anticoagulation with bioprosthetic AVR. There are almost no randomized studies to support the safety of this management. It is yet to be clearly determined whether antithrombotic therapy is protective against TE events in patients with an aortic bioprosthesis during the first 90 postoperative days after AVR.

The ESC has reported three times over the last 12 years recommending to anticoagulate patients with an INR range between 2.0 and 3.0 during the 3 months after surgery. The 1998 ACC/AHA guidelines recommend [18] anticoagulation for 3 months after bioprosthetic AVR with an INR target of 2.5 to 3.5. The 2006 ACC/AHA guidelines [1] are now recommending aspirin alone in patients with AVR bioprostheses and no risk factors (Class Ia, Level of evidence C and also consider anticoagulation with a vitamin K antagonists (VKAs) for 3 months after bioprosthetic AVR with an INR target range 2.0 and 3.0; an acceptable alternative but certainly not a primary recommendation (Class IIa, Level of evidence C). The American College of Chest Physicians in 2001 [19] also recommended anticoagulation for 3 months with a reduced INR target of 2.0—3.0. In the 2004 updated release of the ACCP it is recommend to use VKA for 3 months after valve replacement (Grade 2C) followed by long-term ASA (Grade 1C+) [3]. The only consensus document that did not recommend anticoagulation was the British Society of Haematology, reporting in 1998 [5]. The Canadian Cardiovascular Society Consensus on Surgical Management of Valvular Heart Disease in 2004 recommend VKA during the first 3 months after bioprosthetic AVR (Grade 2C) [4]. There is a general consensus that anticoagulation should be utilized in the early postoperative period and at long-term for bioprostheses patients with accompanying risk factors for TE such as atrial fibrillation, left ventricular dysfunction, previous TE and hypercoagulable condition [1—4].

In 2004 a survey conducted and reported on the Cardiothoracic Surgery Network web page (<http://www.ctsnet.org/file/AnticoagulationSurveyFinalResultsSlidesPDF.pdf>, "Anticoagulation therapy after aortic tissue valve replacement", accessed June 26, 2007) demonstrated that ASA is considered by many surgeons a good alternative to anticoagulation in patients who are in sinus rhythm having a biological AVR and without demonstrable risk factors. The survey intended to establish the level of awareness of the ACC/AHA guidelines among the 726 participating surgeons and the adherence to the guidelines in their daily practice. In each country (mainly the United States and Europe), the percentage of respondents acquainted with or unaware of the guidelines was equally distributed, with an overall prevalence of awareness (79% versus 21%). Three main issues emerged from the study: (1) more than 60% of surgeons are convinced that oral anticoagulation therapy administration prolongs hospital stay with approximately 2—3 days; (2) more than 60% believe that antplatelet therapy alone represents a valuable alternative, in absence of comorbidities, granting patients’ safety and reducing overall stay and cost of care; they no longer consider VKA to be the gold standard of early antithrombotic therapy for biologic valves; and (3) approximately 50% of surgeons adopt antplatelet therapy in their current practice instead of VKA and use it in 90% of patients without comorbidities. At the opposite end of the spectrum, more than 25% of surgeons do not only administer VKA after aortic tissue valve replacement but also maintain long-term anticoagulant therapy, even in the absence of comorbidities.

A survey reviewing the anticoagulation practice among cardiac surgeons consultants members of the Society of Cardiothoracic Surgeons of Great Britain and Ireland was published in September 2005. The authors showed that 53% of consultants never use VKA after bioprosthetic AVR and that 47% of the consultants treated their patients with VKA for the first 3 months [20]. Brueck et al. [21] presented the results of a retrospective double institutional study comparing the necessity of antplatelet treatment by ASA with no postoperative antplatelet therapy in terms of survival, major bleedings and cerebral thromboembolism for patients undergoing biological AVR without thromboembolic risk factors. Two hundred and eighty-eight patients were evaluated and divided into two groups, 132 patients received ASA and 156 patients did not receive antplatelet therapy. There were no statistically significant differences for cerebral ischemia within 3 months after AVR (ASA 0.8% vs no ASA 1.3%; p = 0.884) and 3—12 months after AVR (ASA 0.8% vs no ASA 0%; p = 0.933). Major bleeding occurred in two ASA treated patients and in one patient without antplatelet therapy (p = 0.884). The authors concluded that in patients without thromboembolic risk factors undergoing biological AVR administration of ASA no advantage was conferred compared to the absence of antplatelet therapy. Functional status, thromboembolic events and survival were not adversely affected by withholding any antplatelet therapy. Di Marco et al. [22] who analyzed the presence vs absence of microembolic signals, showed a correlation between absence of neurologic complications and absence of microembolic signals on transcranial Doppler examination in a small subgroup of aortic valve bioprostheses recipients who were treated with ASA instead of VKA in the early postoperative period (0% microembolic signals).

Recently two complete systematic reviews on the topic of antithrombotic management after bioprosthetic aortic valve replacement have been published [23,24]. Both reviews conclude that due to the lack of data from prospective
randomized trials, the optimal antithrombotic or anticoagulation regimen in patients following bioprosthetic aortic valve replacement remains unclear. It is evident that several studies have shown equivalence between antiplatelet therapy and anticoagulation whilst no studies have demonstrated that anticoagulation leads to a reduction or increase in adverse outcomes. However, some of the current guidelines are still weighted in favor of oral anticoagulant therapy based on observational studies previously discussed.

VKAs are used to treat a variety of conditions including deep venous thrombosis, pulmonary embolism, atrial fibrillation and patients undergoing valve replacement. Due to the narrow therapeutic window of all anticoagulants, the decision to anticoagulate a patient using VKA can be multifactorial, especially for bioprosthesis valve replacement and is generally based on such factors as age, the presence or absence of atrial fibrillation, left ventricle dysfunction, left atrial dimensions, previous thromboembolism, and hypercoagulable state.

In the ACTION Registry we decided to include only patients undergoing isolated biological AVR or biological AVR combined with CABG but without thromboembolic risk factors. The participating centers were asked to explain precisely their routine antithrombotic strategies for patients undergoing a bioprosthetic AVR without considering all the special conditions in which anticoagulation or antiplatelet therapy would have absolutely indicated or contraindicated for the risk of thromboembolism or hemorrhage, respectively.

The present results clearly show that there is a great variability in antithrombotic management after bioprosthetic AVR. This variability can be observed among different countries and inside the same country as well: we could not identify a geographical factor resulting in a common practice. There are centers who anticoagulate the patients (43%), others give anticoagulants and antiplatelet therapy (20%), others prescribe only ASA (33%) and finally some centers do not prescribe any specific therapy (4%). These differences are observed and amplified for patients undergoing biological AVR and CABG also. For this specific group of patients there are centers that give only VKA for the first 3 postoperative months (24%) where the 33% of these do not give any antithrombotic therapy for the rest of the patient’s life. This particular finding is very different from the common general practice in patients with coronary artery disease. The ACCP and ESC guidelines [2,3] recommend the use of ASA (Grade 1A) for all patients with coronary artery disease and who undergo CABG, also in presence of a prosthetic heart valve. The same guideline also underlines that the use of clopidogrel is recommended only for patients who are allergic to ASA or in patients with a coronary drug-eluting stent. Nevertheless, despite strong evidence supporting its administration after CABG, ASA continues to be underused by many surgeons worldwide. This chaos is reflected also in the presence of many different guidelines with different suggestions for isolated bioprosthetic AVR and without clear specific recommendations for combined bioprosthetic AVR and CABG. Given the high grade of variability in antithrombotic therapy after biological valve implant, we think that the ACTION Registry, with all its limitations (no randomization, lack of preoperative and follow-up cerebral CT scan for all patients) will collect early clinical postoperative information on the use of a specific antithrombotic regimen offering an important opportunity to examine for the first time, in an international population, which therapy confers the highest level of protection against thromboembolism. We also hope that future results of the ACTION Registry will provide the basis for an international randomized trial comparing antiplatelet therapy versus anticoagulation versus no antithrombotic therapy, hopefully supported by professional organizations.

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References


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Appendix A. Participating centers and investigators

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CHU Strasbourg – Hôpital de Hautepierre (Kindo, Michel)
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Universitätssklinikum, Freiburg (Schlensak, Christian)
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Soroka Medical Center, Beer Shiva (Sahar, Gideon)

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Ospedale San Filippo Neri, Roma (Gentili, Carlo)
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Derriford Hospital, Plymouth (Unsworth-White, Michael Jonathan)
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Blackpool Victoria Hospital, Blackpool (Tang, Augustine)
Walsgrave Hospital, Coventry (Patel, Ramesh)
St. Georges Hospital, London (Chandrasekaran, Venkataraman)