Controversies in cardiovascular medicine

The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties

Bernard Iung1,2* and Josep Rodés-Cabau3*

1Cardiology Department, AP-HP, Bichat Hospital, 46 rue Henri Huchard, 75018, Paris, France; 2Paris-Diderot University, DHU Fire, Paris, France; and 3Quebec Heart and Lung Institute, Laval University, Quebec City, Quebec, Canada

Received 25 June 2014; revised 6 August 2014; accepted 11 August 2014; online publish-ahead-of-print 8 September 2014

Anti-thrombotic therapy after valve replacement encompasses a number of different situations. Long-term anticoagulation of mechanical prostheses uses vitamin K antagonists with a target international normalized ratio adapted to the characteristics of the prosthesis and the patient. The association of low-dose aspirin is systematic in the American guidelines and more restrictive in the European guidelines. Early heparin therapy is frequently used early after mechanical valve replacement, although there are no precise recommendations regarding timing, type, and dose of drug. Direct oral anticoagulants are presently contraindicated in patients with mechanical prosthesis. The absence of long-term anticoagulant therapy is the main advantage of bioprostheses. Early anticoagulation is indicated after valve replacement for mitral bioprostheses, whereas aspirin is now favoured early after bioprosthetic valve replacement in the aortic position. Early dual antiplatelet therapy is indicated after transcatheter aortic valve implantation, followed by single antiplatelet therapy. However, this relies on low levels of evidence and optimization of anti-thrombotic therapy is warranted in these high-risk patients. Although guidelines are consistent in most instances, discrepancies and the low-level of evidence of certain recommendations highlight the need for further controlled trials, in particular with regard to the combination of antiplatelet therapy with oral anticoagulant and the early post-operative anti-thrombotic therapy following the procedure.

Keywords
- Valve prosthesis
- Mechanical prosthesis
- Bioprosthesis
- Transcatheter aortic valve implantation
- Anticoagulant therapy
- Antiplatelet drugs

Anti-thrombotic therapy in patients with prosthetic valves should be adapted to a variety of situations with regard to the type and site of prosthesis, the period considered, and patient characteristics. Guidelines and consensus papers provide recommendations that rely on low levels of evidence in certain cases, which may account for discrepancies. This review summarizes the current knowledge of the management of anti-thrombotic therapy after valve replacement, paying particular attention to persisting gaps in knowledge.

Mechanical prostheses

Long-term anti-thrombotic therapy

Anticoagulant therapy

The need for lifelong anticoagulant therapy in patients with mechanical heart valve prosthesis is not debated. Observational series have consistently shown that the use of antiplatelet drugs is associated with prohibitive rates of thromboembolic events. A small randomized trial comparing warfarin vs. combined antiplatelet therapy found an excess of thromboembolic events under antiplatelet therapy. Anticoagulant therapy using vitamin K antagonists (VKA) is effective in the prevention of thromboembolic events but exposes patients to an increased bleeding risk. Until the 1990s, a target international normalized ratio (INR) between 3.0 and 4.5 was uniformly recommended for mechanical prostheses. Then, three randomized trials showed that, in selected patients, a target INR between 2.0 and 3.0 lowered the bleeding risk without a significant increase in the thromboembolic risk (Table 1). The GELIA trial led to the same conclusions for aortic prostheses, despite a complex design with overlapping target INRs, but also showed lack of benefit of a low target INR (2.0–3.5) for mitral prostheses. Recent trials reported low event rates and tested lower target
### Table 1  Randomized trials on anti-thrombotic therapy in patients with mechanical heart valve prostheses

<table>
<thead>
<tr>
<th>Comparison of target INR</th>
<th>Mean age (years)</th>
<th>CABG (%)</th>
<th>MVR/double (%)</th>
<th>Aspirin (%)</th>
<th>Target INR</th>
<th>n</th>
<th>All symptomatic thromboembolism (per 100 patients/year)</th>
<th>Major bleeding (per 100 patients/year)</th>
<th>All bleeding (per 100 patients/year)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saour³</td>
<td>91% ≤ 40 years NA</td>
<td>62</td>
<td>0</td>
<td>2.65</td>
<td>122</td>
<td>4.0</td>
<td>3.3</td>
<td>21.3</td>
<td>NA</td>
<td>Three post-operative months excluded</td>
</tr>
<tr>
<td>Altman⁴</td>
<td>52</td>
<td>NA</td>
<td>32</td>
<td>100</td>
<td>2.0–3.0</td>
<td>51</td>
<td>1.9</td>
<td>NA</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>AREVA⁵</td>
<td>59</td>
<td>20</td>
<td>4</td>
<td>0</td>
<td>3.0–4.5</td>
<td>48</td>
<td>4.9</td>
<td>NA</td>
<td>24.7</td>
<td></td>
</tr>
<tr>
<td>GELIA Aortic⁶</td>
<td>60</td>
<td>21</td>
<td>0</td>
<td>NA</td>
<td>2.0–4.5</td>
<td>192</td>
<td>1.7</td>
<td>5.6</td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>GELIA Mitral⁶</td>
<td>61</td>
<td>NA</td>
<td>100</td>
<td>NA</td>
<td>2.0–3.5</td>
<td>675</td>
<td>0.45</td>
<td>0.92</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>ESCAT Aortic⁷</td>
<td>60b</td>
<td>NA</td>
<td>0</td>
<td>7.6b</td>
<td>3.0–4.5</td>
<td>178</td>
<td>1.21</td>
<td>0.24</td>
<td>49.7</td>
<td></td>
</tr>
<tr>
<td>ESCAT Mitral⁷</td>
<td>60b</td>
<td>NA</td>
<td>100</td>
<td>7.6b</td>
<td>2.5–3.5</td>
<td>392b</td>
<td>0*</td>
<td>1.42</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>LOWERING-IT⁸</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5–2.5</td>
<td>197</td>
<td>0.09</td>
<td>NA</td>
<td>1.57</td>
<td></td>
</tr>
<tr>
<td>PROACT⁹</td>
<td>55</td>
<td>27</td>
<td>0</td>
<td>100</td>
<td>1.5–2.0</td>
<td>185</td>
<td>2.67</td>
<td>1.48</td>
<td>2.67</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.0–3.0</td>
<td>190</td>
<td>1.59</td>
<td>3.31</td>
<td>6.62</td>
<td></td>
</tr>
<tr>
<td>Addition of aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turpie⁰</td>
<td>58</td>
<td>17</td>
<td>54</td>
<td>50</td>
<td>3.0–4.5</td>
<td>184</td>
<td>1.9⁵</td>
<td>6.6</td>
<td>22</td>
<td>24% bioprosthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.0–4.5 + ASA</td>
<td>186</td>
<td>8.5⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altman¹¹</td>
<td>57</td>
<td>11</td>
<td>29</td>
<td>100</td>
<td>2.0–3.0</td>
<td>207</td>
<td>0.5</td>
<td>8.5</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.0–3.0 + 100 mg ASA</td>
<td>202</td>
<td>6.5</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meschengieser¹²</td>
<td>53</td>
<td>7</td>
<td>33</td>
<td>50</td>
<td>2.5–3.5</td>
<td>258</td>
<td>1.3</td>
<td>1.1</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.5–4.5</td>
<td>245</td>
<td>1.5</td>
<td>2.3</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*Only major thromboembolism.

bNumbers not detailed for each sub-group.

bMajor embolism or death from vascular causes.

CABG, coronary artery bypass grafting; MVR, mitral valve replacement; NA, not available.
INRs in patients with aortic prostheses: 1.8–2.5 in the ESCAT trial, 1.5–2.5 in the LOWERING-IT trial, and 1.5–2.0 in the PROACT trial (Table 1).7–9 Two of the three trials showed decreased bleeding risk with a lower target INR than 2.0–3.0 with no concomitant increase in thromboembolism.8,9 Statistical power was however limited due to low event rates and small sample sizes.

Association of antiplatelet drugs
The combination of low-dose aspirin with VKA was shown to be beneficial in a randomized trial comprising 370 patients, of whom 76% had mechanical prostheses and 30% had atheromatous disease.10 Patients were randomized to aspirin (100 mg daily) or placebo, associated with VKA with a target INR of 3.0–4.5. The combination of aspirin was associated with a 61% decrease in cardiovascular death, death due to bleeding and stroke. However, mortality reduction was due to a decreased incidence of deaths from heart failure, myocardial infarction, and sudden death, with no difference in stroke rates. These findings raise the question as to whether the benefit of aspirin was due to the prevention of complications of atherosclerosis rather than to a decrease in prosthesis-related thromboembolism. In addition, bleeding rates were higher in patients taking aspirin. The benefit of the addition of aspirin has not been specifically studied in patients without atherosclerosis and with contemporary target INRs (Table 1).11,12 The decrease in thromboembolic risk with the combination of antiplatelet drugs and VKA should be weighed against the inherent increase in the bleeding risk. A meta-analysis of anti-thrombotic therapy in 2428 patients with valve prostheses showed that the combination of antiplatelet drugs was associated with a 57% reduction in the thromboembolic risk, but at the expense of a 58% increase in the risk of major bleeding.13

Guidelines
American and European guidelines advise use of a target median INR value, rather than a range, to avoid considering extreme values in the range as a valid target INR.14,15 A target median INR of 2.5 is consistently recommended for aortic prostheses without additional risk factors for thromboembolism.14–16 A higher target INR is advised in other cases. Except for first-generation prostheses, which are now rare, target INR is 3.0 in American Heart Association (AHA)/American College of Cardiology (ACC) guidelines and in the Ninth American College of Chest Physicians (ACCP) consensus and 3.0 or 3.5 in European Society of Cardiology (ESC)/European Association of Cardiothoracic Surgery (EACTS) guidelines, which makes little difference in practice (Table 2).14–16

However, there is a discrepancy in the indications for the combination of low-dose aspirin with VKA, which is systematically recommended as a class I indication in AHA/ACC guidelines for any type and position of prosthesis, whereas the ACCP Consensus and ESC/EACTS Guidelines are more restrictive, thereby reflecting conflicting evidence (Table 2).14–16

Stability of anticoagulant therapy
Besides target INR, the effective INR is a strong determinant of anticoagulant-related complications. In a study of 1272 patients with a single type of mechanical prosthesis, INR variability was strongly associated in multivariate analysis with all-cause late mortality.17 Late mortality increased of 80% for each 20% increase in INR variability.

Anticoagulant clinics allow for optimized INR monitoring and dose adaptation of VKA. Non-randomized comparisons suggest that patient follow-up in anticoagulant clinics improves INR stability and decreases the risk of major bleeding as compared with standard care.18

International normalized ratio self-monitoring is another option to improve INR stability and to reduce the incidence of complications.19 Advantages of self-monitoring include the possibility to measure INR more frequently and better patient education and adhesion to anticoagulant therapy. Only a few series addressed self-monitoring in the specific case of mechanical prostheses. The use of self-monitoring remains limited due to the lack of reimbursement in most countries and issues related to patient education and the need for quality control of the devices.20

Variability of INR is partly determined by genetic polymorphisms affecting cytochrome P450 2C9 and vitamin K epoxide reductase complex 1.20 Genotyping of patients under VKAs is not

Table 2

<table>
<thead>
<tr>
<th>Site</th>
<th>Mechanical prosthesis</th>
<th>Target median INR</th>
<th>Aspirin</th>
<th>Bioprosthesis</th>
<th>3 post-operative months</th>
<th>&gt;3 post-operative months</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESC/EACTS guidelines</td>
<td>Aortic</td>
<td>2.5</td>
<td>3.0 or 3.5b</td>
<td>Selecteda</td>
<td>Aspirin (Ila)</td>
<td>VKA (Ilb)</td>
</tr>
<tr>
<td></td>
<td>Mitral</td>
<td>3.0 or 3.5b</td>
<td>3.0 or 3.5b</td>
<td>Selecteda</td>
<td>VKA</td>
<td></td>
</tr>
<tr>
<td>AHA/ACC guidelines</td>
<td>Aortic</td>
<td>2.5</td>
<td>3.0</td>
<td>Systematic</td>
<td>Aspirin (Ila)</td>
<td>Aspirin (Ila)</td>
</tr>
<tr>
<td></td>
<td>Mitral</td>
<td>3.0</td>
<td>3.0</td>
<td>Systematic</td>
<td>VKA</td>
<td>VKA</td>
</tr>
<tr>
<td>ACCP consensus</td>
<td>Aortic</td>
<td>2.5</td>
<td>2.5</td>
<td>If low bleeding risk</td>
<td>Aspirin (Ila)</td>
<td>Aspirin (Ila)</td>
</tr>
<tr>
<td></td>
<td>Mitral</td>
<td>3.0</td>
<td>3.0</td>
<td>If low bleeding risk</td>
<td>VKA + aspirin</td>
<td>VKA + aspirin</td>
</tr>
</tbody>
</table>

aRisk factors include AF, previous thromboembolic event, left ventricular dysfunction, hypercoagulable state and for AHA/ACC Guidelines older generation prosthesis.
bAccording to whether prosthesis is at low or intermediate thrombogenicity (high-thrombogenicity prostheses are not represented here).
cPatients with concomitant atherosclerotic disease or with thromboembolism despite adequate INR.

No risk factorsa Risk factorsb
recommended at the present time in the absence of convincing clinical benefit and concerns regarding cost-effectiveness. Management of anticoagulant overdose and bleeding

Overdose of VKA with an INR > 6.0, but no severe bleeding is managed by transient anticoagulant withdrawal and oral vitamin K according to the actual INR and the target INR. Severe bleeding should lead to immediate reversal of anticoagulation using prothrombin concentrates or fresh frozen plasma with a target INR < 1.5 after 30 min, combined with vitamin K. There should not be reluctance to reverse anticoagulation in patients with mechanical prostheses since the risk due to bleeding outweighs the thromboembolic risk.

Management of acute coronary syndromes and stenting

Aspirin and a P2Y12 receptor blocker are recommended for treating acute coronary syndromes and following intracoronary stenting. However, when associated with VKA, double antiplatelet therapy is associated with a three-fold increase in the bleeding risk. Three to six months triple anti-thrombotic therapy should be considered in selected cases after acute coronary syndrome. A combination of clopidogrel with VKA, without aspirin, should be considered after stenting since it decreases the bleeding risk without increasing thromboembolic risk.

Direct oral anticoagulants

Direct inhibitors of factor II or factor X have the advantage of a more stable and predictable anticoagulant effect as compared with VKA. Randomized trials have shown their favourable benefit–risk profile in the treatment of venous thromboembolism and atrial fibrillation (AF). The only trial testing direct oral anticoagulants (DOACs) in patients with mechanical prostheses was the Re-Align phase II trial, in which 252 patients were randomized to VKA or dabigatran using therapeutic doses, with a grade 2C. A review of 28 studies found no difference in thromboembolic events between oral anticoagulation alone, oral anticoagulation plus UFH, and oral anticoagulation plus low-molecular-weight heparin (LMWH). Bleeding was more frequent with oral anticoagulation plus UFH. The observational character of the studies and the absence of standardization of endpoints are sources of bias.

Anticoagulation is often difficult to stabilize during the early postoperative period. LMWH allows for more stable anticoagulation but is off-label in patients with mechanical prostheses. There is no consensus on the type of heparin, the dose, and the administration route because of the lack of appropriate controlled trials.

The association of low-dose aspirin raises the same problems of risk–benefit analysis as for long-term therapy. A randomized trial showed that the association of aspirin markedly decreased the risk of thromboembolic events during the year following mitral valve replacement, but also increased the risk of severe bleeding, thereby leading to a non-significant trend toward a higher all-cause mortality at 1 year.

Management of anticoagulation for non-cardiac surgery

The management of anticoagulant therapy in the case of non-cardiac surgery should take into account the bleeding risk inherent to the intervention, the possibility of controlling local bleeding, and the thromboembolic risk due to changes in anticoagulant therapy.

Most interventions at low bleeding risk can be performed safely without interruption of VKA: dental care, ophthalmologic, and dermatologic surgery. With regard to dental care, management should be adapted to the bleeding risk of the procedure and to target INR. A number of gastrointestinal endoscopic investigations can also be performed under VKA.

In patients undergoing major surgery, INR should be < 1.5, which requires interruption of VKA. Heparin bridging is mandatory in patients with mechanical prosthesis in ESC/EACTS guidelines, while AHA/ACC guidelines allow no bridging for short interruptions (< 5 days) in patients with low-risk aortic prostheses. The low thromboembolic risk associated with short discontinuation of anticoagulation is, however, mainly based on the extrapolation of series of selected patients. Heparin bridging should use UFH or LMWH at therapeutic doses. Intravenous UFH is favoured immediately before and after surgery since it ensures more rapid dose changes and neutralization by protamine sulphate in case of bleeding (Figure 1).

Bioprostheses

Long-term anti-thrombotic therapy

The main advantage of bioprostheses is that long-term anticoagulant therapy is not required, unless there are other indications for anticoagulant therapy. In these cases, indications and target INR should follow the recommendations concerning the associated disease, most often AF. A word of caution is needed concerning the use of DOACs. The presence of a bioprosthesis was an exclusion criteria in all trials on DOACs and their use is therefore off-label. The 2014 AHA/ACC guidelines state that ‘These agents (anti-ila and
anti-Xa) are also not recommended, due to lack of data on their safety and effectiveness, in patients with bioprosthetic valves who require anticoagulation. Specific trials are warranted in this field.

The need for long-term aspirin therapy after the post-operative period is debated. It is a IIaB recommendation in AHA/ACC guidelines while the ESC/EACTS guidelines do not recommend the use of antiplatelet drugs after 3 months if there is no other indication, i.e. most often atherosclerotic disease (Table 2). Post-operative anti-thrombotic therapy

Anticoagulant or antiplatelet therapy

As for mechanical prostheses, thromboembolic risk is increased for bioprostheses during the early post-operative period. Anti-coagulant therapy using VKA was initially recommended during the first 3 months following any bioprosthetic valve replacement due to the time needed for the endothelialization of the sewing ring.

The need for post-operative anticoagulant therapy has been challenged for aortic bioprostheses with sinus rhythm since the thromboembolic risk may not justify the bleeding risk of anticoagulant therapy. A number of small observational retrospective series led to contradictory results and their impact is limited by uncontrolled confounding factors and limited statistical power. A prospective but non-randomized study on 249 patients reported no benefit of VKA over aspirin. The only randomized trial compared VKA with trifusal in 193 patients and found no difference in thromboembolic events but less bleeding in patients treated with trifusal. However, the antiplatelet trifusal is seldom used. Surveys performed when post-operative VKA were recommended showed that they were prescribed in only approximately half of patients (38–63%).

Two large-scale retrospective studies have been recently performed from observational registries. A study on 26,556 patients from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database in the United States found no difference between aspirin alone, used in 49% of patients and VKA alone, used in 12%. The combination of VKA and aspirin was associated with a decrease in thromboembolism at the expense of an increase in bleeding, with a lower adjusted risk of death. The authors recommend a combination of aspirin and VKA in patients at low-risk for bleeding and aspirin alone in patients at high risk for bleeding.

The analysis of the Danish surgical database on 4075 patients showed a higher incidence of thromboembolic events and of cardiovascular mortality in patients discontinuing warfarin during the first six post-operative months. Surprisingly, there was no excess bleeding in warfarin-treated patients. The authors conclude that VKA are indicated during the first 6 months following aortic valve replacement using a bioprosthesis. However, concerns can be raised regarding confounding factors and possible underreporting of complications in administrative databases. Furthermore, the group of patients who discontinued warfarin mixed those without anti-thrombotic treatment with those receiving aspirin. Of the 881 patients who did not receive warfarin, 700 did not have any anti-thrombotic therapy and only 181 received aspirin. Although they represent a small subgroup, patients treated with aspirin did not experience an excess of either thromboembolism or cardiovascular death.

Guidelines
ESC/EACTS and AHA/ACC guidelines, and the Ninth ACCP consensus consistently favour the use of aspirin alone vs. VKA during the post-operative period after aortic valve replacement using a bioprosthesis (Table 2). VKA remain recommended during the first 3 months for mitral bioprostheses, in particular because of the higher rates of post-operative AF thromboembolic events.

Transcatheter aortic valve implantation

Long-term anti-thrombotic treatment

The ACC Foundation/Association for Thoracic Surgery (AATS)/Society for Cardiovascular Angiography and Interventions (SCAI)/STS, AHA/ACC, ESC/EACTS, and Canadian Cardiovascular Society (CCS) guidelines recommended the use of low-dose aspirin as long-term anti-thrombotic treatment (Table 3), and this was also the recommendation in the two pivotal US trials.
The majority (more than half) of TAVI candidates exhibit concomitant co-morbidities such as coronary artery disease, prior stroke, or peripheral vascular disease that require the use of long-term antiplatelet therapy. The burden of AF in TAVI candidates is very important, with additional 10–15% of patients with new episodes of AF following the procedure. This leads to an overall AF burden close to 50%. There are no clear recommendations on the use of long-term antiplatelet treatment on top of anticoagulation therapy in patients with AF undergoing TAVI. However, the potential risk of bleeding complications can clearly outweigh that of thromboembolism when adding antplatelet treatment in such patients. Finally, no data exist on the use of novel anticoagulants in the TAVI field.

Some cases of transcatheter valve thrombosis presenting as valve restenosis have been reported. All cases occurred within the months after the procedure, in patients on antiplatelet (aspirin or aspirin + clopidogrel) treatment, and most of them responded to short-term anticoagulation therapy. While the low number of reported cases does not justify any change in current recommendations, further evaluation of this complication is warranted. Also, anticoagulation therapy should be considered before replacing the transcatheter valve in case of valve restenosis within a few months following TAVI.

### Post-operative anti-thrombotic therapy

The current recommendation is the addition of clopidogrel (75 mg/day) to low-dose aspirin for 1–6 months following TAVI. However, this recommendation is empirical and no studies to date have shown the efficacy of dual antiplatelet therapy following TAVI. To date, three studies have compared the use of aspirin alone vs. aspirin + clopidogrel following TAVI, and the main results are summarized in Figure 2. While the addition of clopidogrel was not associated with any reduction in stroke rate, an increased risk of major or life-threatening bleeding was observed in one study. However, the retrospective nature of one study and the small and underpowered sample size of the two prospective studies preclude drawing definite conclusions. A prospective randomized trial (ARTE trial: clinicaltrial.gov) comparing single vs. dual antiplatelet therapy following TAVI is currently ongoing. Also, the ATLANTIS study will evaluate the efficacy of apixaban as a single therapy following TAVI in 1500 patients (planned to start in 2015) (Collet JP. EuroPCR presentation 2014).

As formerly stated, the high burden of AF observed in TAVI candidates leads to a high proportion of patients requiring anticoagulation therapy. VKA are usually stopped 3–4 days before the TAVI procedure (switching with heparin in cases with high thromboembolic risk) and re-started following the procedure. Switching with intravenous UFH within the hours following the procedure is recommended if high thromboembolic risk. Current guidelines recommend adding single antiplatelet therapy to VKA. Apart from those patients with a history of AF, some studies have also suggested the need for anticoagulation therapy in those patients with transient episodes of new-onset AF following TAVI, especially considering the high risk of stroke.

### Table 3  Current recommendations for anti-thrombotic therapy following transcatheter aortic valve implantation

<table>
<thead>
<tr>
<th>ACCF/AATS/SCAI/STS expert consensus</th>
<th>AHA/ACC guidelines</th>
<th>CCS position statement</th>
<th>ESC/EACTS guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-term anti-thrombotic treatment</strong></td>
<td>Aspirin 81 mg/day indefinitely</td>
<td>Lifelong aspirin 75–100 mg daily (Class III; level of evidence: C)</td>
<td>Low-dose aspirin indefinitely</td>
</tr>
<tr>
<td><strong>Post-procedural anti-thrombotic treatment</strong></td>
<td>Aspirin 81 mg/day + clopidogrel 75 mg/day for 3–6 months</td>
<td>Aspirin 75–100 mg/day + clopidogrel 75 mg/day for 6 months</td>
<td>Low-dose aspirin + a thienopyridine early after TAVI</td>
</tr>
<tr>
<td></td>
<td>If warfarin indicated (AF), then no clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>If oral anticoagulant indicated (AF), avoid triple therapy unless definite indication exists</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Downloaded from https://academic.oup.com/eurheartj/article-abstract/35/42/2942/2293158 by guest on 29 October 2018
thromboembolic risk (mean CHADS score \(\approx 3\)) in patients undergoing TAVI nowadays.\textsuperscript{48,49} The use of triple anti-thrombotic therapy has been associated with a much higher risk of bleeding events in the coronary intervention field,\textsuperscript{24} and this has also been reported in a retrospective evaluation of the German TAVI registry.\textsuperscript{65} Avoidance of the use of triple anti-thrombotic therapy in such patients has been included in the current guidelines of TAVI (Table 3).\textsuperscript{14,15,44,45} No data exist on the use of anticoagulation therapy without any antiplatelet treatment in such patients, but this strategy may be considered in patients at high risk for bleeding while we await randomized data.

In conclusion, the different recommendations for anti-thrombotic therapy after valve replacement are consistent in most cases. Consistent guidelines are issued from randomized trials, as illustrated by target INRs which should be adapted to mechanical prosthesis and patient characteristics. Although recommendations for

\begin{itemize}
  \item Combination of aspirin with VKA in patients with a mechanical prosthesis and contemporary target INRs
  \item Optimal timing, doses, and type of heparin to be used early after mechanical valve replacement
  \item Use of aspirin vs. VKA during the first three post-operative months following aortic valve replacement using a bioprosthesis
  \item Use of DOACs in patients with a bioprosthesis
  \item Use of anti-Xa DOACs in patients with a mechanical prosthesis
  \item Anti-thrombotic therapy after TAVI in patients in sinus rhythm and in AF
\end{itemize}

\textbf{Table 4} Major gaps in evidence in anti-thrombotic therapy after valve replacement

\begin{itemize}
  \item Combination of aspirin with VKA in patients with a mechanical prosthesis and contemporary target INRs
  \item Optimal timing, doses, and type of heparin to be used early after mechanical valve replacement
  \item Use of aspirin vs. VKA during the first three post-operative months following aortic valve replacement using a bioprosthesis
  \item Use of DOACs in patients with a bioprosthesis
  \item Use of anti-Xa DOACs in patients with a mechanical prosthesis
  \item Anti-thrombotic therapy after TAVI in patients in sinus rhythm and in AF
\end{itemize}
post-operative anti-thrombotic therapy are also often consistent, they rely on low level of evidence. This illustrates remaining gaps of evidence that are summarized in Table 4. Appropriate controlled trials are needed to clarify these issues given the number of patients concerned and the potential harms of anti-thrombotic therapy.

Conflicts of interest: B.I. has received consultant fees from Abbott, Boehringer Ingelheim, and Valtech and speaker’s fees from Edwards Lifesciences. J.R.-C. has received consultant fees from Edwards Lifesciences and St Jude Medical.

References


