Anticoagulation Treatment After Transcatheter Aortic Valve Replacement
Striking the Right Balance*

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Recommendations pertaining to antiplatelet treatment after transcatheter aortic valve replacement (TAVR) in patients in sinus rhythm stem from a consensus of experts and are based essentially on the assumption that stent implantation requires dual-antiplatelet treatment (DAPT) for at least 6 months.

No randomized study has been carried out so far to elucidate this issue. However, since the first case was performed by Alain Cribier in 2002 and, as a result of growing center experience, the use of antiplatelet treatment has been gradually reduced.

Currently, pre-treatment is no longer administered at most centers, and the duration of DAPT has been shortened to 3 months or even 1 month. Moreover, at certain centers, aspirin alone is prescribed after TAVR (1–3), with a similar rate of thromboembolic events and a strong trend toward a decrease in bleeding risks. This hypothesis is currently being explored in the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) study (4), a randomized study of 300 patients not on oral anticoagulation (OAC) who will be treated after TAVR with DAPT with aspirin for at least 6 months and clopidogrel for 3 months or single-antiplatelet therapy with aspirin alone for at least 6 months. The primary endpoint will be a composite of death, myocardial infarction (MI), ischemic stroke or transient ischemic attack, and life-threatening or major bleeding at 3 months.

This is an even more complex problem in the 25% to 30% of TAVR candidates with atrial fibrillation (AF) who are already on long-term OAC. The question as to whether they should receive concomitant antiplatelet treatment remains crucial. In this issue of JACC: Cardiovascular Interventions, Abdul-Jawad Altisent et al. (3) should be commended for exploring in detail and addressing accurately this unresolved issue in an international, multicenter, nonrandomized study involving more than 600 patients, the results of which are reported in this issue of the journal.

As I will comment later, though only observational, the investigators’ findings elicit broader considerations, beyond the problem of patients with AF who are eligible for TAVR.

The first important lesson to be drawn from this study is that prescribing antiplatelet therapy for patients with AF who are already on long-term anticoagulation does not confer any benefits. Indeed, the investigators show that after a median follow-up period of 13 months, the risk for stroke, major cardiac events, or death was similar, regardless of the treatment implemented. Conversely, the risk for major or life-threatening bleeding was almost twice as high (hazard ratio: 1.85; 95% confidence interval: 1.05 to 3.28; p = 0.04). One case of stroke or major bleeding could, therefore, be avoided by not combining antiplatelet therapy with long-term anticoagulant treatment in only 10 patients. This hypothesis is currently being investigated in cohort B of the POPular-TAVI (Antiplatelet Therapy for Patients Undergoing Transcatheter Aortic Valve Implantation) trial (5). This multicenter open-label study conducted in 1,000 patients is currently testing the hypothesis that monotherapy with aspirin or OAC after TAVR is safer than the addition of clopidogrel for 3 months, without compromising clinical

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benefits. In cohort A, patients not on OAC are randomized 1:1 to aspirin versus aspirin plus clopidogrel. In cohort B, patients on OAC are randomized 1:1 to OAC versus OAC plus clopidogrel. The primary outcome is freedom from non-procedure-related bleeding at 1 year, and the secondary net clinical benefit outcome is freedom from the composite of cardiovascular death, non-procedure-related bleeding, MI, or stroke at 1 year.

The study by Abdul-Jawal Altisent et al. (3) provides a second important piece of information by demonstrating that recipients of combined antiplatelet and anticoagulation treatment are at similar risk for major or life-threatening bleeding regardless of whether they are prescribed aspirin and clopidogrel or aspirin alone, while clopidogrel alone combined with long-term anticoagulant medication reduces significantly the risk for major or life-threatening bleeding (p = 0.002). Therefore, if an oral anticoagulant must be combined with an antiplatelet treatment, it seems preferable to choose clopidogrel rather than aspirin. This combination of an anticoagulant and clopidogrel alone versus triple therapy with clopidogrel and aspirin was shown to be superior in terms of bleeding and major adverse cardiac events after coronary stenting in the randomized WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) study (6).

Finally, this study indirectly raises the issue of short- or midterm anticoagulation therapy after TAVR for patients in sinus rhythm. Indeed, although rare cases of valve thrombosis successfully treated with anticoagulant agents have been reported, several studies published since 2015 (7,8) have shown that systematic follow-up using multislice computed tomography after TAVR revealed the presence of partial thrombosis of 1 or several cusps in 10% to 15% of cases, which, though asymptomatic and successfully treated with anticoagulant medications, could potentially increase the risk for valve thrombosis or stroke. Similar data had already been reported in relatively recent studies involving surgical bioprostheses (9-11) which suggested that anticoagulation treatment should be implemented for 3 to 6 months after implantation of a surgical prosthesis (12) while avoiding combination with aspirin, which is associated with excess bleeding. The Frequency of Reduced Leaflet Motion After Surgical Aortic Valve Replacement and Transcatheter Aortic Valve Replacement study (13) is currently investigating this hypothesis. It is a prospective, randomized pilot study that will compare OAC with OAC and clopidogrel for 3 months after surgical aortic valve replacement or TAVR.

As things currently stand, new anticoagulation agents are being investigated in these settings. The results observed in patients with AF look very promising (14), especially with apixaban and dabigatran, for which the benefit ratio between efficacy and safety seems very favorable. In addition, their antithrombotic properties could prove interesting for patients with coronary artery disease, who account for 25% of TAVR patients. The use of new anticoagulation agents not only in patients with AF but also in those in sinus rhythm (instead of antiplatelet treatment) after TAVR is currently being investigated in 2 prospective randomized trials: ATLANTIS (Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis) (15) and GALILEO (Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes) (16). In ATLANTIS, patients already on vitamin K antagonists will be randomized to a vitamin K antagonist or apixaban and those not on vitamin K antagonists to DAPT or single-antiplatelet therapy versus apixaban. This study will include 1,510 patients with a composite primary endpoint of death, MI, stroke or transient ischemic attack, systemic embolism, intracardiac or bioprosthesis thrombus, episode of deep vein thrombosis or pulmonary embolism, and life-threatening or disabling bleeding or major bleeding according to the Valve Academic Research Consortium 2 definitions over 1-year follow-up. A total of 1,500 patients without AF after successful TAVR will be enrolled in the GALILEO study, with a primary efficacy composite endpoint of death, stroke, MI, valve thrombosis, pulmonary embolism, deep vein thrombosis, and systemic embolism and a primary safety endpoint of life-threatening, disabling, or major bleeding events. Patients will be randomized to receive either rivaroxaban 10 mg once daily plus aspirin 75 to 100 mg once daily for 3 months, followed by rivaroxaban 10 mg once daily alone, or clopidogrel 75 mg once daily plus aspirin 75 to 100 mg for 3 months, followed by aspirin 75 to 100 mg once daily alone.

In view of the results already reported and given the potential findings of the ongoing studies, one can anticipate that current guidelines will be completely overhauled within the next 2 to 3 years.

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REFERENCES


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