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The temptation of anticoagulant therapy after transcatheter aortic valve implantation

Laura Gatto[1,2]* and Lorenzo Scalia[2]

[1]Emergency Cardiology, San Giovanni Addolorata Hospital, Rome; and [2]Centro per la Lotta contro l'Infarto Onlus, ONLUS Foundation, Rome

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The choice of the best antithrombotic strategy after transcatheter aortic valve implantation (TAVI) must be based on the careful balance between the ischaemic risk and the bleeding risk and on the evaluation of some concomitant conditions, such as atrial fibrillation or coronary artery disease which may lead to the choice of anticoagulant treatment or antiplatelet therapy. Another element to consider is the possibility, albeit remote in post-TAVI patients, of thrombosis of the valve leaflets, an event whose clinical impact has yet to be fully clarified and which however appears to present a lower incidence in patients treated with anticoagulants. Recent evidence has shown that in patients who do not require anticoagulant therapy, single therapy with aspirin represents the best treatment compared to dual antiplatelet or to the addition of anticoagulant which in post-TAVI patients should be reserved only for those with a clear indication such as atrial fibrillation. It is still much debated whether in this case the choice should fall on vitamin K antagonists or on the new direct-acting anticoagulants, as the comparison studies have produced inconclusive results.

Introduction

Transcatheter aortic valve implantation (TAVI) is now a valid treatment option in patients with severe aortic stenosis as several clinical trials have demonstrated results comparable to those of traditional surgery in large series of subjects with different risk profiles. Like other operations performed percutaneously, TAVI is also burdened by an ischaemic and haemorrhagic risk, both peri-procedural and in the longer-term follow-up; for this reason, the choice of the best antithrombotic strategy is often challenging, and it must be based on the characteristics of the patient, his comorbidities, and the need for concomitant therapies.

Transcatheter aortic valve implantation and ischaemic and haemorrhagic risk

Although most of the patient candidates for TAVI have concomitant coronary artery disease (from 30 to 70% according to the different series), the risk of myocardial infarction is very low (from 1 to 3% during the first year).[1]

On the contrary, ischaemic stroke certainly represents the prevalent thromboembolic event in patients undergoing TAVI and is burdened by considerable mortality and morbidity. In the pilot trials on TAVI, the incidence of major and disabling stroke at 30 days was around 5%; today, it is known that the incidence is directly correlated with surgical risk, going from <1% in low-risk patients up to 7% in high-risk individuals. Most cerebral ischaemic events occur early: a quarter within the first few days and half within the first month. The pathogenesis of early strokes is mainly to be found in procedural aspects and has decreased over the last few years thanks to the use of smaller delivery systems and brain protection devices. On the contrary, the ischaemic events that occur above all after the third month are mainly of thromboembolic origin and can be due to atrial fibrillation (AF) (especially if of new onset) or to thrombi that develop on the leaflets of the bioprosthesis due to a delay or a failed endothelialization process, exposure of thrombotic material, tissue damage, and haemodynamic changes across the valve.[2]

As far as the bleeding risk is concerned, the incidence of major and disabling bleeding varies from 3 to 11% during the first year. Of these, about 50% are related to the procedure, despite the correct definition of the vascular

*Corresponding author. Email: lgatto@hsangiovanni.roma.it

access and the use of ultrasound-guided puncture and small-diameter catheters. Advanced age and the presence of numerous comorbidities such as anaemia and renal insufficiency that characterize the general frailty of the candidate patient for TAVI increase the bleeding risk, as do the acquired von Willebrand factor deficiency and moderate thrombocytopenia that are often observed after the valve implant. All these factors must necessarily be taken into consideration in choosing the best antithrombotic strategy.[3]

Oral anticoagulant therapy and the risk of post-transcatheter aortic valve implantation valve thrombosis

Clinically evident bioprosthesis thrombosis, usually associated with thromboembolic episodes or the onset of heart failure, is a very rare event in patients undergoing TAVI (<1% in the first 2 years), requiring immediate treatment with vitamin K antagonists (VKA) and/or with unfractionated heparin and in some cases a reoperation.[4]

Most valve thromboses are instead subclinical, do not alter the haemodynamics of the valve, and are diagnosed in one-third of patients treated with antiplatelet therapy alone through the use of imaging methods such as transoesophageal echocardiography or computed tomography (CT). In this case, they appear as hypoattenuated leaflet thickening (HALT), and in the recent definition of the Valve Academic Research Consortium 3, they were classified according to their extension and the reduced leaflet mobility (RLM).[5]

The review of the literature has allowed to identify the subexpansion of the stent during implantation, and above all, the non-use of anticoagulant therapy, as some of the risk factors for the formation of thrombi affecting the bio prosthesis. For example, in the RESOLVE and SAVORY registries, CT revealed the presence of valve thrombosis in 12% of cases, with a significantly lower incidence in patients treated with anticoagulation than in those receiving dual antiplatelet therapy (4% vs. 15%, $P < 0.0001$). Furthermore, it has been shown that thrombosis resolved in all patients treated with oral anticoagulants [both VKA and direct-acting oral anticoagulants (DOAC)], while it was persistent in subjects who did not receive such treatment. Probably the most interesting datum is that the incidence of stroke and transient ischaemic attacks was significantly higher in patients with radiological evidence of valvular thrombosis than in those without thrombosis (7.85% vs. 2.36%, $P = 0.001$),[6] association also suggested by some meta-analyses and non-randomized studies.

However, data regarding the clinical consequences of valve leaflet thrombosis are conflicting, and in a recent registry that included 836 patients, subclinical thrombosis, diagnosed on CT in 12.3% of patients, was an independent predictor of mortality, but not of ischaemic events. Also in the CT substudies of the PARTNER-3[7] and Evolute Low-Risk,[8] no association was observed between the presence of subclinical valve thrombosis and thromboembolic events. However, it should be emphasized that none of these studies was designed with adequate statistical power for this type of endpoint.

On the basis of these results, the use of anticoagulant to prevent valve leaflet thrombosis in all post-TAVI patients does not appear reasonable, and it is not even clear whether such treatment should be started once the diagnosis has been made. The guidelines of the European Society of Cardiology on the treatment of heart valve disease recommend Class IIA anticoagulant treatment in patients with HALT and RLM with high gradients at least until resolution of the thrombosis.[4] The rationale for this choice lies not only in the prevention of thromboembolic events but could also be related to the duration of the device. In fact, the degeneration of the prosthesis is supported by the formation of the thrombus with consequent intimal hyperplasia, fibrosis, tissue remodelling, expression of proteases, and finally calcification of the leaflets.[1] Just as there is no clear consensus on the treatment of thrombosis, there is also no clear consensus on whether this finding should be routinely investigated using more defined imaging methods. The guidelines recommend the execution of CT in the suspicion of prosthesis degeneration when the echocardiogram shows an increase in the mean gradient >10 mmHg compared with the post-implantation resulting in a mean gradient >20 mmHg with a concomitant reduction of the valvular area >0.3 cm^2 or >25%.[4]

Patients undergoing transcatheter aortic valve implantation with an indication for anticoagulant therapy

About 30% of patients undergoing TAVI are affected by AF, and it has been estimated that in 10% of cases, this arrhythmia occurs after surgery. Transcatheter aortic valve implantation patients with concurrent AF are as deserving of anticoagulant therapy as all patients with AF, but which is the best anticoagulation strategy (VKA vs. DOAC) is a matter of debate, as TAVI has been an exclusion criterion in trial registrars of DOACs.

Some observational data in TAVI patients with AF have shown conflicting results. In a Danish registry, the 3-year risk of thromboembolic events, bleeding, and all-cause mortality was similar in 219 DOAC-treated patients and 516 VKA-treated patients.[9] A large German registry that enroled 962 subjects demonstrated an equal rate of bleeding, but a higher risk of infarction, cerebrovascular events, and all-cause mortality at 1 year in the DOAC group.[10] On the contrary, the French registries (FRANCE-TAVI and FRANCE 2), which included 8962 TAVI patients treated with VKA and 2180 TAVI patients treated with DOAC, showed a higher 3-year risk of mortality and major bleeding for traditional anticoagulants.[11]

Only two randomized clinical trials have tested the use of DOACs in the post-TAVI AF setting. The Edoxaban Compared to Standard Care After Heart Valve Replacement Using a Catheter in Patients With Atrial Fibrillation (ENVISAGE-TAVI AF) is a non-inferiority study comparing edoxaban to VKA. In 1426 randomized patients, the primary efficacy and safety endpoint including all-cause mortality, myocardial infarction, ischaemic stroke, systemic thromboembolism, valve thrombosis, and major bleeding was non-inferior in the edoxaban group vs. the VKA group [hazard ratio (HR) 1.05; 95% confidence interval (CI) 0.85–1.31]; however, major bleeding was significantly increased in patients treated with DOAC (HR 1.40; 95% CI 1.03–1.91). This result was mainly driven by an increase

in gastrointestinal bleeding in the edoxaban arm, with no significant differences in fatal and intracranial bleeding.[12]

The most recent Anti-Thrombotic Strategy After Trans-Aortic Valve Implantation for Aortic Stenosis (ATLANTIS) included 1500 post-TAVI patients randomized to apixaban or to standard therapy represented by VKA (Stratum 1) or antiplatelet agents (Stratum 2) as needed or less of anticoagulation. Overall, the trial failed to demonstrate superiority of apixaban over standard of care in terms of safety and efficacy: the primary endpoint (composite of all-cause death, myocardial infarction, stroke, systemic embolism, valvular or intracardiac thrombosis, deep vein thrombosis/pulmonary embolism, and major bleeding) occurred in 138 (18.4%) subjects receiving apixaban and 151 (20.1%) receiving standard of care (HR 0.92; 95% CI 0.73–1.16). In the subgroup of patients indicated for anticoagulant therapy (223 randomized to apixaban and 228 randomized to VKA), apixaban was not superior to VKA (HR 1.02; 95% CI 0.68–1.51) even with regard to safety; in fact, the incidence of major, life-threatening, and disabling bleeding was comparable between the two groups.[13]

It has been debated whether, in this setting, it might make sense to add an antiplatelet to the anticoagulant, but the results of the POPular TAVI seem to discourage this therapeutic approach. In Cohort B of this trial, 326 post-TAVI and AF patients with no recent history of percutaneous coronary revascularization were randomized to anticoagulation alone or to anticoagulation plus clopidogrel for 3 months. The primary endpoint evaluating all bleeds was significantly reduced in the anticoagulant only arm (risk ratio 0.63; 95% CI 0.43–0.90), as was the incidence of major, life-threatening, disabling, and site-related bleeding vascular access. Also with regard to the efficacy endpoint relating to ischaemic events, the anticoagulant alone was non-inferior to the combination therapy.[14]

The AVATAR trial is ongoing, a randomized study aimed at defining whether a single anticoagulant strategy (VKA or DOAC) is superior to a combined anticoagulant/aspirin strategy in net clinical benefit that included ischaemic and bleeding endpoints. The results are expected by the end of this year.

Patients undergoing transcatheter aortic valve replacement without indication for anticoagulant therapy

In patients with no indication for anticoagulant therapy, the guidelines suggest the use of low doses of aspirin.[3] This recommendation is based on findings from POPular TAVI Cohort A, in which 665 post-TAVI patients were randomized to either a single antiplatelet therapy strategy with aspirin or a dual antiplatelet therapy strategy with aspirin and clopidogrel for 3 months followed by only aspirin. Single antiplatelet therapy proved to be non-inferior in the prevention of ischaemic events and superior in avoiding haemorrhagic events.[15]

In the TAVI setting without any indication for anticoagulant therapy, the use of this treatment has been studied several times, and in particular, the behavior of DOACs has recently been tested in three different randomized clinical trials. The first was the Global Study Comparing a Rivaroxaban-Based Antithrombotic Strategy to an Antiplatelet-Based Strategy After Transcatheter Aortic Valve Replacement to Optimize Clinical Outcomes (GALILEO), a study in which 1664 post-TAVI patients with no indication for anticoagulant therapy were randomized to a strategy of low-dose rivaroxaban (10 mg/day) plus aspirin for the first 3 months followed by rivaroxaban alone or a dual antiplatelet therapy strategy (aspirin + clopidogrel) for the first 3 months followed by aspirin alone. The trial was stopped early for safety reasons; indeed, after a follow-up of approximately 17 months, the primary efficacy endpoint, a composite of death and thromboembolic events, occurred more frequently in the rivaroxaban group (HR 1.35; 95% CI: 1.01–1.81; $P = 0.04$) and also showed an increase in major, disabling, and life-threatening bleeding (HR 1.50; 95% CI: 0.95–2.37; $P = 0.08$). Probably most concerning was all-cause mortality, which increased by 69% in patients in the DOAC arm, a finding the authors were unable to explain since it does not appear to be related to haemorrhagic events. However, although GALILEO demonstrated that the antithrombotic strategy based on low-dose rivaroxaban in combination with aspirin failed in this setting, a subanalysis showed, once again, that there was a significantly lower incidence in the DOAC arm of subclinical valve leaflet thrombosis diagnosed on CT scan at 90 days (2.1% vs. 10.9%, $P = 0.01$), with fewer patients with symptomatic valve thrombosis (3 vs. 7).[16]

In Stratum 2 of the ATLANTIS trial, more than 1000 patients with no indication for anticoagulant therapy were enrolled, 526 of whom were randomized to the standard dose of apixaban and 523 to dual or single antiplatelet therapy. Also in this subgroup, apixaban was not superior to antiplatelet therapy with respect to the primary endpoint (HR 0.88; 95% CI 0.66–1.17) and was associated with a higher non-cardiovascular mortality rate (HR 2.99; 95% CI 1.07–8.36). There were no significant differences between the two treatment strategies regarding safety; in fact, major, disabling, and life-threatening bleeds were similar (HR 1.09; 95% CI 0.69–1.69). Also in this case, the use of apixaban significantly reduces subclinical valve thrombosis (HR 0.19; 95% CI 0.08–0.46), without however this entailing a benefit in terms of reduction of systemic embolic events or overall mortality.[13]

To try to clarify whether valve leaflet thrombosis is an endpoint that should really be taken into consideration and whether anticoagulant therapy can modify its clinical impact, the Anticoagulation Versus Dual Antiplatelet Therapy for Prevention of Leaflet Thrombosis and Cerebral Embolization After Transcatheter Aortic Valve Replacement (ADAPT-TAVR) has been performed, a randomized study comparing edoxaban with dual antiplatelet therapy (aspirin and clopidogrel) which enrolled 229 patients undergoing TAVI and without indication for oral anticoagulation. The primary endpoint was the incidence of CT-diagnosed valve leaflet thrombosis at 6 months. As secondary endpoints, the number and volume of new ischaemic brain lesions highlighted on MRI and the changes in neurological and neurocognitive functions evaluated between the immediately post-TAVI period and the sixth month of follow-up were considered. The authors found a non-significant reduction in the incidence of subclinical valve leaflet thrombosis in the edoxaban group compared to the dual antiplatelet therapy group (9.8% vs. 18.4%, $P = 0.076$). There was no difference between the two

treatments in the percentage of patients who presented new ischaemic brain lesions in the follow-up (25% vs. 20.2%) and these lesions were similar in number and volume between the two groups. Furthermore, no significant correlation was found between the presence and extent of valve thrombosis with new cerebral ischaemias and the worsening of neurological and neurocognitive functions.[17]

Conclusions

The choice of the best antithrombotic strategy in patients undergoing TAVI must be based on a correct assessment of the ischaemic and haemorrhagic risk. While, in subjects without indications for anticoagulant therapy, there is clear agreement that the best treatment is aspirin monotherapy, in those with AF, the debate is still very open. At the moment, the choice of anticoagulant therapy alone seems to be the most valid option, but there is a lack of robust data to favor the DOAC over the VKA. On the basis of the ATLANTIS results, apixaban is the one that has shown the best tolerability profile although not superior to the VKA. In the TAVI setting, anticoagulant therapy proved to be more effective in reducing valve thrombosis without, however, a real benefit on the clinical endpoints; therefore, outside of AF, it should only be used in particular patients such as those who show significant degeneration of the prosthesis with increased gradients and reduction of the valve area.

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Data availability

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