Transcatheter aortic valve replacement (TAVR): expanding indications to low-risk patients

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Abstract: Aortic stenosis (AS) is the most common cardiac valve disease in developed countries. Transcatheter aortic valve replacement (TAVR) for the treatment of severe symptomatic AS is an accepted therapy option for elderly patients with symptomatic severe AS. Nowadays, TAVR has revolutionized the treatment of AS with an exponential growth worldwide. Both the development of new generation valves and the experience of the operating teams have contributed significantly to decrease the complications rate after TAVR. Several randomized trials have reported similar short- and mid-term results, and even better than surgical aortic valve replacement (SAVR) in patients with high- or intermediate-risk. In addition, two comparison trials in low-risk patients have reported promising results. Therefore, in the future TAVR indications will expand, treating younger and younger patients, with less comorbidities and lower risk. However, the long-term durability of percutaneous prostheses is a matter of debate. The aim of this manuscript is to review available data that support to treat AS in low-risk patients and provide our perspective on the topic.

Keywords: Aortic stenosis (AS); transcatheter aortic valve replacement (TAVR); surgical aortic calva replacement; low surgical risk

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Introduction

Aortic stenosis (AS) is the most common cardiac valve disease in developed countries. Its prevalence increases with advanced age to reach 9.8% between 80–89 years (1). Transcatheter aortic valve replacement (TAVR) started in 2002 as a therapy for high-risk patients with severe AS and no other options (2). The procedure is an accepted therapy option for elderly patients with symptomatic severe AS. Nowadays, this new technology has revolutionized the treatment of AS with an exponential growth worldwide. Development of new generation valves and the experience of the operating teams have definitely contributed to decrease the complications rate during TAVR (3). Complication of the vascular access is one of the most feared; its rate has been reduced with the rigorous selection of the patient, the development of increasingly small-size arterial sheaths, as well as the design of new vascular closure devices (4-6).

Several randomized trials reported similar short- and mid-term results even better than surgical aortic valve replacement (SAVR) in patients with high (7-9) or intermediate surgical risk (10-12). In addition, two comparison trials in low-risk patients have reported promising results (13,14). Thus, it is expected future TAVR indications to expand, treating younger and younger patients, with less comorbidities and lower surgical risk

(13-15). For these reasons, TAVR programs are developing a minimalist approach to simplify the procedure, with the objectives to reduce complication rates, optimization of procedure time, recovery facilitation and earlier mobilization of the patient, as well as the achievement of a shorter hospital stay, with the decrease of healthcare resource consumption and the reduction of the waiting lists (16,17). However, the long-term durability of percutaneous prostheses is still controversial (18).

The aim of this paper is to review the therapy options to treat AS in low-risk patients and provide our perspective on the topic.

TAVR in low-risk patients

Low-risk patients with severe AS represent approximately the 80% of the total of patients with severe AS undergoing SAVR (19). Nowadays, there is a trend to propose TAVR to lower age and risk patients with severe AS (12). The development of new generation valves and the experience of the operators have contributed significantly to decrease the complications rate after TAVR (3-6). Despite recent promising results after TAVR, it should be noted that SAVR outcomes have also improved with a lower mortality than predicted in intermediate-risk patients and comparable to predicted in low-risk patients. However, the median hospital stay after TVAR is 2 days compared to 8 days after SAVR (19).

The NOTION trial (15) is a randomized trial, which compared TAVR *vs*. SAVR in an all-comers patient cohort; where 280 patients with severe AS with low- and intermediate-risk were randomized to receive a self-expanding TAVR *vs*. SAVR. Most patients (81.8%) were considered at low surgical risk. The mean STS score was 3%. No significant differences were observed between the two groups considering the composite endpoint of death form any cause, stroke or myocardial infarction after 1 year. Patients who underwent TAVR showed larger improvements in effective valvular orifice area, higher degree of aortic valve regurgitation; they needed more frequently a pacemaker (PM) implantation and presented worse New York Heart Association functional class at 1 year. Patients who underwent SAVR showed more major or life-threatening bleeding, cardiogenic shock, acute kidney injury and new-onset of atrial fibrillation (15).

Waksman *et al.* (20), conducted a non-randomised study in low-risk patients with symptomatic severe AS, which included 200 patients undergoing TAVR whose results were compared with an inverse probability weighting-adjusted control cohort of 719 patients who underwent SAVR using the STS database. At 30 days, there was 0 all-cause mortality in the TVAR group compared to 1.7% in the SAVR group. There was 0 in-hospital stroke rate in the TVAR group *vs*. 0.6% stroke in the SAVR group. Permanent PM implantation rates were similar between groups (20). In a number of studies, the transfemoral access and the minimalist approach, which includes conscious sedation, valve implantation without pre-dilation, overstimulation with intravenous PM and the use of radial access as a contralateral approach are all variables associated with the acceleration of patient recovery and ambulation (16,21,22).

Recently, two contemporary trials in low-risk patients with severe AS have been reported (13,14). The PARTNER 3 trial (13), randomized 1,000 patients at low 30-day mortality risk (mean STS score was 1.9% and the mean age was 73 years) to TVAR with the balloon-expandable Sapien 3 prosthesis or SAVR. The assigned procedure was performed in 950 patients (496 in the TVAR group and 454 in the SAVR group). The primary combined endpoint at 1 year (all-cause mortality, stroke, or re-hospitalization) was 8.5% with TVAR and 15.1% with SAVR (P<0.001). The combined endpoint of death and disabling stroke at 1 year was 1% with TVAR and 2.9% with SAVR. Hospital stay was shorter with TVAR than with surgery (3 *vs*. 7 days, P<0.001) and quality of life improved more quickly. Both groups presented similar PM implantation rates, although TVAR was associated with more-frequent new left bundle-branch block [24% *vs*. 8%, hazard ratio (HR) 3.43; 95% confidence interval (CI): 2.3–5.1] and mild paravalvular regurgitation (29% *vs*. 2%).

The Evolut Low trial (14) is a randomized trial that included 1,468 patients to any of three self-expanding TVAR prostheses or SAVR (mean age was 74 years and STS score was 1.9%). In a prespecified 1-year interim analysis of 784 patients, TVAR and SAVR were estimated to have comparable rates of death or disabling stroke (2.9% and 4.6%, respectively). At 30 days, both groups presented similar rates of death (0.5% and 1.3%) and disabling stroke (0.5% and 1.7%). However, TVAR was associated with a higher 30-day rate of PM implantation (17.4% *vs*. 6.1%) and moderate/severe paravalvular aortic regurgitation (3.5% *vs*. 0.5%).

In summary, both trials in patients at low-risk provide data for an early safety, a shorter hospital stay, faster recovery and ambulation, and less re-hospitalizations with

TAVR in comparison to SAVR. For that reasons, patients who are considered for the treatment of AS undergoing aortic valve replacement with a bioprosthesis should be informed about the two options (TAVR *vs.* SAVR) to get a correct shared decision-making.

Moreover, the randomized NOTION 2 trial (23) is currently enrolling younger patients (<75 years old) with severe AS and low-risk with a Society of Thoracic Surgeons (STS) score <4% to be randomized to transfemoral TAVR *vs.* SAVR. Any CE mark-approved valve is allowed. The primary end-point at 1 year is the composite of all-cause mortality, myocardial infarction and stroke. Finally, the DEDICATE trial (24), will include 1,600 patients with severe AS and low- to intermediate-risk to compare TAVR *vs.* SAVR in order to assess if TAVR is non-inferior to SAVR regarding short- and long-term mortality.

TAVR in low-risk patients: challenges

PM implantation

The incidence of atrioventricular conduction disorders after TAVR is highly variable, ranging from 10% to 30% depending on the type of valve implanted (25). The current evidence indicates that both the development of atrioventricular conduction disturbances and the need for definitive PM implantation after TAVR are influenced by anatomical, electrical, type of implanted prosthetic valve and periprocedural factors (26). For the first generation of valves, the PM implantation rate for CoreValve® ranged from 16.3% in the Italian Registry to 37.7% in the CHOICE trial (27). For the SAPIEN® valve, the PM implantation rate varied from 2.3% in the PARTNER EU trial to 17.3% in the CHOICE trial.

For the new generation of valves, the PM implantation rate after TAVR is highly variable and is influenced by anatomical electrical factors and periprocedural factors (28). According to a meta-analysis of 40 studies (26), for the SAPIEN® 3 valve the rate of PM implantation ranged from 4% to 24%; for the Lotus® valve from 27.9% to 36.1% and for the Direct Flow® valve the rate was 17%. According to different series, the rate of PM implantation for the CoreValve Evolut R® was 26.7% (11), for the Portico® valve was 13.5%; for JenaValve® 14.4%; and for ACURATE® the rate varied from 2.3% to 10.2%.

In the study conducted by Jørgensen *et al.* (29), 1,190 patients treated with TVAR were included. TVAR patients with new onset of left-bundle-branch block had an increased risk for all causes of early mortality compared with patients who did not have atrioventricular conduction disturbances; the risk of hospitalization for heart failure was increased, as well as all causes of late mortality.

In the NOTION trial (15), the rate of PM implantation was five times higher in the TAVR group compared to the SAVR group (41.8% *vs.* 8.4%). At 5 years, all-cause mortality was 38.2% in the group with PM implantation after procedure *vs.* 21.7% in the group that did not need PM implantation. In the Evolut Low Risk trial (14), at 30-day follow-up, the PM implantation in the TVAR group was 17.4% *vs.* 6.1% in the SAVR group (difference, 11.3 percentage points; credible interval for the difference, 8 to 14.7). In the PARTNER 3 trial (13), there were no significant differences between TAVR *vs.* SAVR regarding the new PM implantation at 30 days.

With new-generation TAVR devices, the rates of success, need of second valve implantation, the presence of paravalvular leak and the conversion to SAVR have been reduced. However, the PM implantation rates continues being high (26). In a study of 1,263 patients undergoing TAVR, the new PM implantation was associated with greater morbidity and mortality at long-term follow-up (30). Main complications after PM implantations are infection, endocarditis and left ventricular dyssynchrony or dysfunction. In addition, the new PM implantation is associated with poorer evolution of left ventricular ejection fraction and it is considered as an independent predictor of lower ejection fraction at 1-year follow-up (31).

Vascular complications

These complications could lead to bleeding and/or ischaemic complications. New delivery valve systems and smaller sheath diameters are aimed to reduce vascular bleeding complications. However, a recent meta-analysis of randomized trials, which compare TAVR *vs.* SAVR in low-risk patients, showed that TAVR was associated with increased risk for intermediate-term mortality compared to SAVR [17.2% *vs.* 12.7%; relative risk (RR): 1.45, 95% CI: 1.11–1.89, P=0.006]. Nevertheless, TAVR patients showed less acute kidney injury and bleeding complications, but higher vascular complications and PM implantation rates (32).

In most centers, percutaneous closure of the vascular access of TAVR has become a routine procedure. Percutaneous closure is a much less invasive technique than surgical closure and allows shortening patient's hospital stay by promoting early mobilization and recovery (33).

The first percutaneous closure device used was the Prostar® closure, later came the Proglide® with a pre-closure system that led to technical simplification and lower costs. The closure of vascular access using two Proglide® devices carries a lower risk of vascular complications compared to closure with Prostar® (34). The collagen closure device MANTA® is now available with similar results to suture-based closure devices (35).

Percutaneous vascular access technique must be rigorous to limit potential complications in the access area. The puncture site in the common femoral artery should preferably be selected by computed tomography scan before the procedure. During the procedure, the femoral puncture should be guided by ultrasound or angiography, thus reducing complications (17). Notably, most vascular complications could be treated percutaneously with adequate experience of the operating team. This point is essential to simplify the TVAR procedure by facilitating earlier recovery of the patient.

Paravalvular leak

The NOTION trial (15) showed that TAVR groups showed a rate of 15.7% of moderate or moderate-to-severe aortic regurgitation; whereas SAVR group showed a rate of 0.9%, persisting at 5-year follow-up. It is widely known that moderate and severe aortic regurgitation is associated with increased mortality; however, the impact of mild paravalvular leakage on outcomes remains uncertain. The PARTNER 2 trial (10) showed that moderate and severe aortic regurgitation was associated with increased late mortality. The PARTNER 3 trial (13) showed similar rates of moderate or severe paravalvular regurgitation in both groups (TAVR and SAVR).

Technological advances in transcatheter prostheses designs have decreased the differences between TAVR and SAVR regarding the rate of moderate-to-severe aortic regurgitation. Nevertheless, specific anatomical factors, such as bulky eccentric or asymmetric calcifications of the annulus and the left ventricular outflow tract, bicuspid aortic valves and non-circular annulus could lead to reduced aortic regurgitation with surgical treatment.

Prostheses thrombosis

Chakravarty *et al.* (36), conducted an observational study, where subclinical leaflet thrombosis was detected on computed tomography, as leaflet thickening or reduced leaflet motion, between 10–15% of TAVR patients and in 4% of SAVR patients. Despite that subclinical leaflet thrombosis may improve with anticoagulation, this fact remains uncertain, so that several studies are actually being conducted in order to identify the adequate antithrombotic treatment after TAVR.

Severe bicuspid aortic valve stenosis

Bicuspid aortic valve is the most common congenital valve disease and is associated with accelerated valve degeneration and concomitant aortic disease (37). There is lack of data on TAVR in bicuspid aortic valve disease. The use of TAVR in a bicuspid aortic valve may result in uneven prosthetic valve expansion and suboptimal function. Bicuspid valves usually present a higher degree of root calcification than the tricuspid aortic valve, increasing the risk of complications (38). In patients with bicuspid aortic valves treated with the first-generation of TVAR, paravalvular leakage grade ≥2 was present in the 28.4% of patients, requiring the 3.6% of patients another valve (39). Last valve generation, with a sealing skirt, is associated an improvement of results. Procedural complication rates in patients with severe AS were similar when comparing bicuspid and tricuspid aortic valves (40). Compared with tricuspid aortic valves, the annulus in a bicuspid aortic valve tends to be more elliptical and has more annular calcification with irregular distribution that can affect prosthesis expansion and may increase the risk of paravalvular leakage (41). Notably, concomitant aortopathy; such as dilated ascending aorta, aneurysm or coarctation, which can be associated to this pathology, definitely requires surgical treatment.

Prosthetic valve endocarditis

Prosthetic valve endocarditis after TAVR is challenging to diagnose. Its incidence is similar to the rates after SAVR: between 0.3% and 1.2% per patient-year. Nevertheless, there is a higher incidence, up to 3.4% per patient-year reported in some series, what may be related to the presence of residual paravalvular leaks and patient comorbidities (42).

Prostheses durability

The long-term TAVR durability remains uncertain. Prostheses valve durability depends on several factors as age at implantation (43). Most patients in contemporary trials that underwent TAVR were elderly and high-risk patients

with a life expectancy inferior to the predicted durability of a biological prosthesis. Lastly, there is a trend to standardize definitions of structural deterioration and valve failure when assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves (44). Nevertheless, there are no available data on TAVR durability in younger patients, in whom it is well known that the durability of surgical bioprosthesis is reduced (45).

Conclusions

Recent available data on TAVR at low-risk patients may lead to this procedure to be quickly approved as an alternative to SAVR for patients that will prefer a less-invasive approach. For that reasons, the role of the heart team will be relevant in the decision-making process when referring a patient for aortic valve replacement. However, despite the exponential growth of TAVR, SAVR should remain as the standard treatment for severe AS in patients with active endocarditis, young patients, which would benefit more from a mechanical prosthesis due to the lack of data on the TAVR durability, and patients with indication of coronary artery bypass grafting or other concomitant procedures, like additional valve or aortic surgery.

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