REVIEW

Transcatheter Aortic Valve Implantation (TAVI) and Mitral Valve Transcatheter Edge-To-Edge Repair (TEER): Current Frontiers and Horizons

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Abstract

During the last two decades transcatheter aortic valve implantation (TAVI) and mitral valve transcatheter edge-to-edge repair (TEER) have evolved in parallel to provide percutaneous interventional treatment solutions for patients with the two most common valvular heart diseases, aortic stenosis and mitral regurgitation, respectively. Having initially been conceived and used to treat patients considered inoperable, TAVI indications have been expanded to include high operative risk and more recently moderate or even low risk patients. The TAVI techniques have also improved to permit tackling challenging complex anatomies and bioprosthetic valve degeneration and structural failure. Similarly, TEER has been initially used to treat inoperable patients with severe symptomatic primary mitral regurgitation (MR), but recently published data have shown that it can provide benefit in carefully selected patients with refractory to optimal medical treatment (OMT) symptomatic severe secondary MR. Furthermore, apart from TEER with the traditional MitraClip system and its iterations, a second TEER system (Pascal) has provided promising results in initial clinical trials and can alternatively be used. We attempt herein a concise overview of the TAVI and mitral valve TEER current state of play. ***Rhythmos 2021;16(3): 57-61.***

Key words: aortic valve stenosis; TAVI; mitral valve regurgitation; MitraClip; TEER

Abbreviations: LVEF: left ventricular ejection fraction; MR: mitral regurgitation; OMT: optimal medical therapy; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; TEER: transcatheter edge-to-edge repair

TAVI in Low-Risk Patients

Several studies have recently compared transcatheter aortic valve implantation (TAVI) to surgical aortic valve replacement (SAVR) among patients with symptomatic severe aortic stenosis of lower surgical risk. Two randomized studies that compared TAVI to SAVR for low-risk patients stand out. PARTNER 3 tested SAVR versus TAVI with a balloon expandable valve (Sapien 3) and Evolut Low Risk tested SAVR versus TAVI with a self-expanding valve (Evolut – CoreValve).[1,2] In both studies mean age was around 73 years, while EuroSCORE II and STS scores were on average 1.5 and 1.9, respectively. The primary end-point was the composite of mortality, stroke and hospitalizations for PARTNER 3 and the composite of mortality and stroke for Evolut Low Risk. Both have been designed as non-inferiority studies and yet have shown positive results in favor of TAVI. PARTNER 3 has shown superiority of TAVI versus SAVR with the primary end-point occurring in 8.5% vs 15.1% (p=0.001) respectively at 1 year follow-up. In Evolut Low Risk the primary end-point at one year was 2.9% with TAVI versus 4.6% with SAVR (p=0.002). Furthermore, with TAVI, strokes were less frequent, atrial fibrillation incidence post-intervention was 2-3 times less probable and notably in PARNER 3 aortic regurgitation and pacemaker implantation rates were comparable to those of SAVR (**Table 1**). The duration of hospitalization post-intervention was 2 times longer with surgery with direct return home in 96% of cases after TAVI versus only in 2 out of 3 cases after SAVR. For the first 6 months after the intervention the quality of life with TAVI was much better compared to SAVR. Of note, the limitations of these studies include the relatively short 1-year follow-up (but data of extended follow-up have started to accumulate) and the fact that only transfemoral TAVI cases have been included.

Table 1. Comparison of SAVR versus TAVI in PARTNER 3 and Evolut Low Risk studies.

Outcome	**PARTNER 3** (1000 patients) *TAVI vs SAVR*	**Evolut Low risk** (469 patients) *TAVI vs SAVR*
Mortality	1% vs 2.5%	2.4% vs 3%
Stroke	1.2% vs 3.1%	0.8% vs 2.4%
AF	11.6% vs 20.3%	9.8% vs 38.3%
PVL	0.6% vs 0.5%	4.3% vs 1.5%

AF = atrial fibrillation; PVL = paravalvular leak

The expansion of TAVI indications towards lower risk populations with reassuring results regarding efficacy and safety has opened the door to lowering the age limit where TAVI can be offered as an option. However, this brings to the surface other issues, such as the access to the coronary arteries if subsequently indicated because of coronary artery disease manifestations, the durability of the various percutaneously implanted bioprosthetic valves and the interventional options in case of bioprosthetic valve failure in the future.

For a long time, data regarding valve durability have been limited by the short follow-up of the initial TAVI studies. Recently the NOTION study that included low surgical risk patients has been the first to present results of

the comparison of TAVI with the self-expanding CoreValve versus SAVR at 5 years and beyond and has shown that the need for reintervention for bioprosthetic valve failure was low and without difference between the two arms.[3] These results have been subsequently confirmed by two registries from France and Germany using standardized definitions for bioprosthetic valve failure. [4,5] Access difficulties to the coronary arteries has been reported in 2% of patients, with some differences depending on the type of valve used. The issue of future coronary access has to be seriously considered in order to decide for which valve to implant and the implantation technique to be used, and this is especially important for young patients with preexisting coronary artery disease and/or risk factors.

Challenging Patient Subgroups for TAVI

Bicuspid aortic valve has been for long regarded as a relative contraindication for TAVI, due to positioning and implantation difficulties, the asymmetry regarding the cusps anatomy and calcifications that increase the risk of significant paravalvular leak and create concerns about a potential premature structural valve deterioration. These concerns are less justified with the last generation of TAVI valves. In a study comparing outcomes of 561 patients with a bicuspid aortic valve to outcomes of 546 patients with a tricuspid one and otherwise identical characteristics, the 320 patients with a first generation valve (Sapien XT or CoreValve) had more often conversion to surgery (2 vs 0.2%), decreased procedural success (85.3% vs 91.4%) and more often at least moderate paravalvular leak (19.4% vs 10.5%). To the contrary, these differences were not observed with second generation valves (Sapien 3, Evolut R or Lotus).[6] The good results obtained with TAVI for bicuspid aortic valve stenosis with the new generation valves have been confirmed by the results of the TVT registry.[7,8] Thus currently, TAVI can be performed with good results for patients with bicuspid aortic valve after thorough evaluation of the valve anatomical details and dimensions (**Fig. 1**).

The treatment of aortic bioprosthetic valve failure has been revolutionized by the advent of TAVI based on the fact that patients previously treated with SAVR and bioprosthetic valve failure consist a very high-risk patient group for re-do surgery. Numerous studies have recently compared percutaneous versus surgical treatment for these patients. Their results have been included in several metanalyses with the most recent showing that valve-in-valve TAVI is effective and safe, with a complication rate more favorable and a 30-day survival rate superior compared to surgical re-SAVR.[9] However, TAVI valve-in-valve has been related to a higher risk of mismatch and higher transvalvular gradients, which imposes great attention in selecting the appropriate TAVI bioprosthesis. Consequently, selecting a self-expanding bioprosthesis with supra-annular function would be the logical choice in order to obtain the lowest transvalvular gradient possible at the end of the procedure. Similarly, and depending on the type of the initial surgical bioprosthetic valve, its fracturing (or "cracking") with a high-pressure non-compliant balloon inflation could be demanded before or after the implantation of the TAVI bioprosthetic valve in order to obtain good expansion and an optimal hemodynamic result. It should be emphasized that an accurate evaluation of the initial surgical valve before TAVI planning is always required, especially in case of regurgitation, in order to verify that it is intra-valvular and thus treatable with TAVI and not paravalvular in which case treatment with a percutaneously implanted plug or surgical re-do should be considered. In general, currently TAVI can be performed with good results for patients with failed surgical bioprosthetic valves after thorough evaluation of anatomical details and dimensions and taking necessary measures to tackle potential procedural risks (**Fig. 2**).

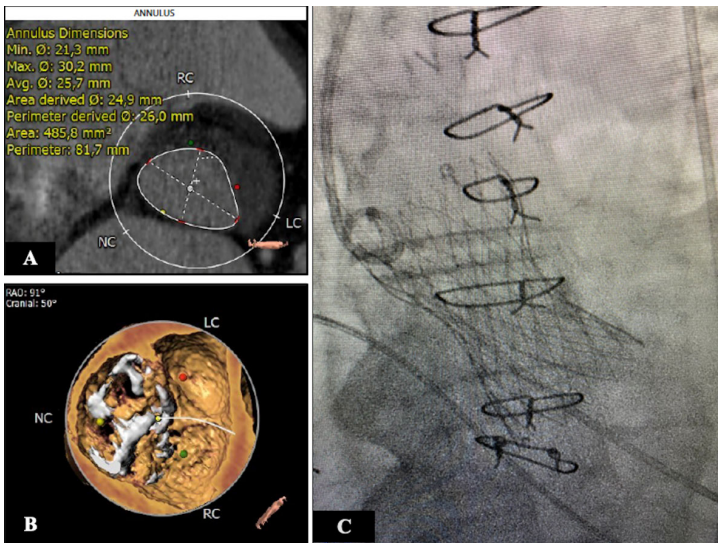

Figure 1. TAVI for bicuspid aortic valve. **A**. Annulus definition and computed tomography measurements, **B**. Bicuspid type 1 valve, L-R subtype, **C**. Successfully implanted self-expanding valve (Evolut R 34mm).

Mitral Valve Transcatheter Edge-To-Edge Repair (TEER) for Severe Mitral Regurgitation

Mitral regurgitation (MR) currently constitutes the most prevalent valvular heart disease in Europe and the second most operated after severe aortic stenosis. Severe symptomatic MR, if not treated, has an ominous prognosis

with a mortality rate of 20% at 1 year and 50% at 5 years, as well as a hospitalization rate of 41% at 1 year and 90% at 5 years.[10]

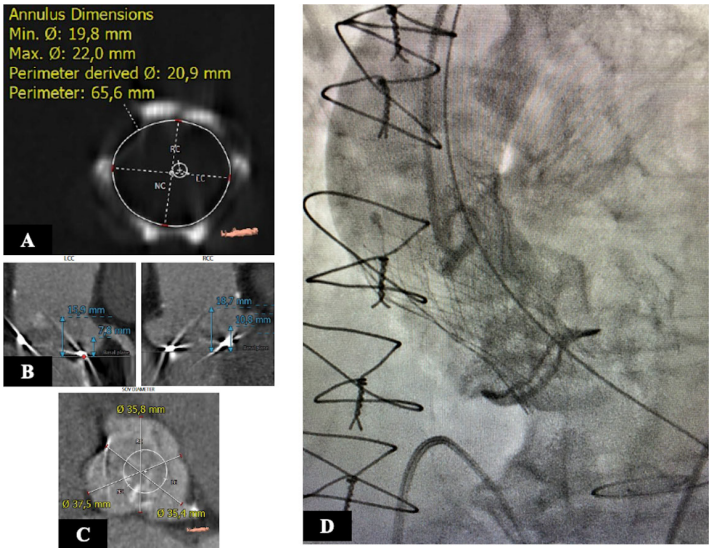

Figure 2. Valve-in-valve TAVI. **A**. Computed tomography measurements to check dimensions of a failed previous Sorin 23mm valve, **B** & **C**. Coronary ostia heights and sinus of Valsalva diameters measurements in order to verify if coronary protection is needed, **D**. Successfully implanted self-expanding valve (Evolut R 26mm).

Despite the fact that the standard treatment for severe symptomatic primary MR is surgical in almost half of the patients, surgery is rejected due to perceived high operative risk.[11] The technique of transcatheter mitral valve edge-to-edge repair (TEER) has evolved in parallel with TAVI during the last 2 decades. Currently TEER is indicated for patients with severe primary MR rejected for surgery or at high risk for surgery and for patients with a secondary MR refractory to optimal medical therapy (OMT). It is the technique mostly applied for the percutaneous treatment of severe MR and the only one supported in the most recent guidelines for the treatment of valvular heart diseases.[12,13] Experience with transcatheter annuloplasty, transapical chordal implantation or valve replacement is still limited and general recommendations cannot yet be made.

The mitral valve TEER procedure is performed with general anesthesia and under transesophageal echocardiographic guidance to apply the Alfieri stitch principle percutaneously by pulling the edges of the anterior and posterior mitral leaflets to one another with the use of one or more clips. Different models and sizes exist to allow an interventional strategy adapted to the anatomy of each valve and the site and severity of each regurgitant jet. A good patient selection depends on clinical and anatomical criteria and determines procedural success and the actual clinical benefit (**Table 2**).

Table 2. Criteria of feasibility of mitral valve TEER with MitraClip

	Ideal anatomic characteristics	**Not ideal anatomic characteristics, but feasible**
Any MR type	Central jet at segment 2 Valvular surface >4 cm^2 Posterior leaflet length > 10 mm Leaflet thickness <5mm No leaflet calcifications	Jets at segments 1 or 3 Valvular surface >3 cm^2 (sufficient leaflet mobility) Posterior leaflet length 7-10 mm Calcifications but not on the grasp area
Primary MR	Prolapsus depth <10 mm Prolapsus width <15 mm	Prolapsus width >15 mm (but multiple clips possible)
Functional MR	Leaflet central coaptation $\geq$ 2 mm Tenting height <11 mm	Tenting height >11 mm

MR = mitral regurgitation; TEER = transcatheter edge-to-edge repair

TEER for Primary Severe MR

The reference treatment for primary severe MR has historically been surgical. The Everest II randomized trial has been the first to compare mitral valve TEER with MitraClip to surgical treatment among 279 patients with severe MR (grades III-IV). Major adverse events occurred in 15% of patients in the percutaneous-repair group and 48% of patients in the surgery group at 30 days (P<0.001).[14] At 5 years follow-up, the mortality was similar between the 2 groups, while more frequent MR grade $\geq$ 3+ and reintervention were found in the TEER group, but keeping in mind that they were the result of the initial experience of the operators that could use only one clip.[15] In the last European recommendations (published in 2017), TEER for severe primary MR is indicated for patients with left ventricular ejection fraction (LVEF) $\leq$ 30%, refractory symptoms despite OMT and a low probability for surgical repair or not low surgical risk (class IIb-C indication).[13] In the most recent ACC/AHA guidelines for the treatment of valvular heart disease (published in 2021), TEER is proposed as a reasonable option (class IIa-B indication) in severely symptomatic patients (NYHA class III or IV) with primary severe MR and high or prohibitive surgical risk, if mitral valve

anatomy is favourable for the repair procedure and patient life expectancy is at least 1 year.[12]

TEER for Secondary Severe MR

In case of secondary MR, the treatment is mainly medical and determined by guidelines regarding heart failure with reduced LVEF, as well as ablation for atrial fibrillation and resynchronization therapy when indicated. Mitral valve TEER with MitraClip was evaluated in two randomized studies published in 2018. The French study MITRA-FR compared TEER on top of OMT to OMT alone among symptomatic patients with severe secondary MR (regurgitant orifice area >20mm^2 or regurgitant volume >30 ml) and LVEF 15-40%. The study was negative without difference between the two groups regarding all-cause mortality and hospitalization for heart failure at 1 and 2 years.[16] The United States study COAPT has also evaluated the benefit of TEER on top of OMT versus OMT alone among patients with MR even more severe than in MITRA-FR (regurgitant orifice area >30 mm^2 or regurgitant volume >45 ml) and LVEF 20-50%. In this study, TEER with MitraClip was associated with a decrease of MR severity, fewer hospitalizations for heart failure, improved functional status and quality of life at 1 year and most importantly decreased mortality at 2 years.[17]

These obviously discordant results of the two studies have been explained by differences in selection criteria, which depend on the respective contribution of MR and left-ventricular systolic dysfunction to the heart failure symptoms of patients. The COAPT population gained greater benefit with TEER because MR was more severe and the LV less dilated, showing the most significant role of MR. Actually the European recommendations that were published before those 2 studies (in 2017) indicate that percutaneous treatment of secondary MR with TEER can be considered for patients who remain symptomatic despite OMT without indication for surgical revascularization and having LVEF >30%, with not low surgical risk or for patients with LVEF <30% after discussion for the possibility of cardiac transplantation and circulatory assistance (recommendation class IIb-C).[13] In the most recent ACC/AHA guidelines for the treatment of valvular heart disease (published in 2021, after MITRA-FR and COAPT), TEER is regarded reasonable for patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF <50%) who have persistent symptoms (NYHA class II, III, or IV) while on OMT, appropriate anatomy as defined on transesophageal echocardiography and with LVEF between 20% and 50%, LV end-systolic dimension (LVESD) ≤70 mm, and pulmonary artery systolic pressure ≤70 mmHg (recommendation class IIa-B).[12]

The Pascal system is the second system for performing mitral valve TEER that is currently available. It is based on the Alfieri principle as well but with some specific features, such as the possibility to separately mobilize each of the two clip arms and a middle spacer that permits to the leaflets to coapt upon it and not directly on one another, thus decreasing traction exerted on them. The Pascal device has been tested in the CLASP study that included 109 patients with severe symptomatic MR despite being on OMT.[18] Among included patients, at 6 months, 98% had less than moderate MR, which was paralleled by significant functional and quality of life improvement. The results were confirmed at 1 year follow up with a 92% survival and 88% freedom from heart failure hospitalization. The two TEER systems are actually compared in studies in both primary and secondary severe MR.

Conclusions

The improvements of the technique and the diversity of the available percutaneously implanted bioprosthetic valves have led to the expansion of TAVI indications to a larger population with lower risk and anatomically more complex cases. Ongoing studies are expected to define the limits of this technique and the patient subsets that should still resort to SAVR. Mitral valve TEER (with the historically established MitraClip system or the recently available Pascal system as alternative) has a dominant role in transcatheter treatment of severe symptomatic MR not amenable to surgery. The Heart Team approach has a pivotal role for both TAVI and TEER to orient and guide each patient to the treatment more suitable for his/her profile.

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