Head to head transcatheter heart valve comparisons: when theory becomes reality

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Transcatheter aortic valve implantation (TAVI) is nowadays the standard treatment for severe aortic stenosis in symptomatic patients with extreme or high surgical risk (1-3) and a valid alternative to surgery in elderly patients at intermediate risk. This is the consequence of accumulating clinical experience, technological improvements and the promising results of several randomized clinical trials (4-6). Nevertheless, several limitations related to TAVI, such as conduction disturbances and paravalvular leak (PVL) remain an ongoing concern and an opportunity for improvement.

Mechanically expanded Lotus Valve system (MEV, Boston Scientific Corp) was designed to further minimize PVL rates and to insure a safe and controlled deployment. The MEV consists of 3 bovine pericardial tissue valve leaflets and a braided nitinol frame with an adaptive seal, which folds up on itself during valve expansion to fill the paravalvular space and diminish PVL. This device is mechanically expanded and capable to function early during the deployment process. The most interesting feature of this transcatheter heart valve (THV) is that it is capable of being fully retrievable and repositioned if necessary when the valve is already functioning in its final position. While limitation of balloon expandable THV is that the operator only has one chance to position it in the correct site, self-expandable THV may be recaptured and repositioned until 80% of the deployment process. However, there is no possibility to retrieve the valve after it is fully released.

The REPRISE III (Safety and Efficacy Study of Lotus Valve for Transcatheter Aortic Valve Replacement) is a multicenter, randomized clinical trial that compared two competitive THV (7). Fifty-five participant centers from North America, Europe and Australia recruited 912 patients with severe symptomatic aortic stenosis and high or extreme surgical risk, which were randomized 2:1 to receive either MEV (n=607) or the self-expanding CoreValve (SEV, CoreValve Classic or Evolut-R; Medtronic) (n=305). Feldman *et al.* reported 1-year results with particular emphasis in safety and effectiveness in terms of mortality, stroke, bleeding and vascular complications, acute kidney injury and PVL. Authors and supporters should be commended for performing a direct head-to-head comparison between two THVs, which is the best scientific approach to obtain definitive conclusions. Until now, there was only a direct randomized trial comparing two available THVs (8), although several publications indirectly compared some THVs (9-11). With the expansion of the technique to intermediate and lower risk patients and several THVs available in the market, studies with direct comparisons will be necessary in order to define the best treatment and THV choice for each patient.

Major findings of the REPRISE III were that both systems had similar rates of the primary safety end-point (20.3% in the MEV group *vs.* 17.2% in SEV group, P=0.003 for non-inferiority), with some differences in secondary

end-points. While, thrombosis, permanent pacemaker (PPM) implantation and valve hemodynamics favored SEV, rate of significant PVL, valve malpositioning and need for a second valve was less frequent in MEV group. The grade of PVL is linearly related to increased mortality, especially in cases with moderate-to-severe PVL (4). Thus, residual PVL has been the major limitation of TAVI compared to surgery. Technological improvements in prosthesis design as well as anatomical considerations (multimodality imaging, optimized valve sizing) and deployment technique have contributed to lowered post-TAVI PVL severity with newer generation valves (12). A major limitation of the trial is that most patients in the SEV group were treated with the old-generation of the CoreValve system. Residual PVL has been traditionally greater with SEV, especially with previous generation, compared to balloon expandable THV and to newer generation of SEV (9,13,14). In fact, in the REPRISE III, a post hoc analysis with limited number of patients treated with the Evolut-R showed that PVL was below <3% without differences compared to Lotus valve (<1%). This data suggests that Lotus valve reached surgical rates of significant PVL and other THV are in the right direction with almost similar results (7). One may wonder, if this difference in the rate of PVL would remain in a complete comparison versus Evolut-R or Sapien-3.

While several efforts have been made to reduce PVL, conduction disturbances after TAVI have not been given the same attentiveness and their clinical impact may be minimized (15). The impact of conduction disturbances at short-term are increased hospital stay and costs (16,17). Furthermore, left bundle branch block (LBBB) post-TAVI has been associated with higher mortality (18), a trend toward increased hospitalization, a lack of left ventricular ejection fraction (LVEF) recovery, poorer functional class at follow-up, and increased permanent pacemaker (PPM) placement (19). Also, PPM implantation is not innocuous. Right ventricular pacing has been shown to cause reduction in LVEF and cardiac output due to interventricular dyssynchrony (20). Although, some studies revealed similar mid-term mortality in patients with PPM (21), other studies showed higher mortality and heart failure admission rates (22). In addition, recent studies showed poorer outcomes in patients with pacemaker after TAVI at longer follow-up (16). Unfortunately, the rates of PPM implantation have even increased with newer generation THV (15,23) and definitively, this would have an impact when expanding the indications to younger patients. In this study, patients in the Lotus arm had a PPM implantation

rate of 35.5% and 41.4% at 30-day and 1 year, respectively. Previous studies have showed similar results in patients receiving Lotus Valve system, revealing baseline conduction abnormalities, deeper implantation and annular oversizing as predictors of PPM implantation (24). In this trial, depth of implant was similar between MEV and SEV. Unfortunately, data about baseline EKG or prosthesis oversizing was not reported, as well as the incidence of new LBBB. Meanwhile, in other non-randomized studies LBBB exceeded 50% in patients receiving MEV (24). A rate of more than 70% of the patients developing a new conduction disturbance (either pacemaker or *de novo* LBBB) is excessively high and make this TVH difficult to justify when other THV types had a pacemaker rate around 5% to 10% (25,26). Therefore, the benefits and advantages of a fully repositionable THV with a very low aortic regurgitation (AR) rate may be jeopardized by the excessive radial force and damage caused in the conduction system. Second generation MEV: the Lotus Edge valve system device may address this issue with the new Depth Guard™ technology that limit left ventricular outflow tract (LVOT) interaction, which theoretically might reduce conduction abnormalities. Additional design improvements are a flexible delivery system, lower profile access (14F/15F) and more valve sizes (21 and 29 mm). However, first and second-generations MEV are currently off the market. The company released a voluntary recall due to issues with the locking mechanism. The problem stems from premature release of a pin connecting the valve to the delivery system, which is consequence of a manufacturing error that leads to additional pressure in the pin system. Boston scientific has announced the return of Lotus Edge THV but it has been delayed several times, first in November 2017 and February 2018, lastly until 2019, apparently since the company is pending final testing and regulatory approval timelines. Nevertheless, one might speculate if the company could be considering focusing its efforts in other THV technology rather than returning to MEV.

In summary, the more outstanding feature of the REPRISE III is that it is one of the first international head-to-head randomized clinical trial that compare two THVs, demonstrating that MEV and SEV are comparable in terms of the primary safety and effectiveness end-points. PVL and PPM implantation continue to be a drawback for TAVI and may be inversely related. Lotus Valve system achieved the lower PVL rate, probably by increasing the strength to seal the paravalvular space. However, it resulted in larger degree of LVOT compression causing higher conduction

abnormalities. MEV may be particularly useful in patients with severe, asymmetric aortic valve calcification or with high eccentricity annulus index, as in bicuspid aortic valve, with the intention of minimizing malpositioning and PVL. However, a high rate of conduction disturbances should be expected. Thus, future studies will have to determine which valve is the best valve for each specific group of patients.

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Footnote

Conflicts of Interest: L Nombela-Franco has served as a proctor for Abbott and has received speaker honoraria from Edwards Lifesciences Inc. Other authors have no conflicts of interest to declare.

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