Editorial

Early transcatheter valve prosthesis degeneration and future ramifications

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Submitted Jul 14, 2016. Accepted for publication Aug 09, 2016.
doi: 10.21037/cdt.2016.08.04
View this article at: http://dx.doi.org/10.21037/cdt.2016.08.04

Transcatheter aortic valve replacement (TAVR) has become the treatment of choice for patients with severe, symptomatic aortic stenosis with prohibitive risk for valve replacement surgery (SAVR) and is now considered a favourable alternative to surgical management for patients considered to be high risk (1). Recently published results of the PARTNER 2 trial have demonstrated that TAVR is an acceptable treatment option for patients with intermediate surgical risk and may hold an advantage over surgery if feasible via transfemoral approach (2). As we continue to explore the possibility of TAVR for lower risk patients who are typically younger and good candidates for surgical therapy, the durability of the prosthesis becomes an important consideration. Bioprosthetic valve failure after surgical aortic valve replacement (SAVR) is well described and well investigated. Structural valve deterioration is the most common noted cause with incidence of <1%, 10–30%, and 20–50% at 1, 10 and 15 years respectively (3,4). A recent report highlighting concerns regarding the long-term durability of the early SAPIEN prosthesis has certainly compelled the structural heart community to take a step back and better evaluate the future of TAVR for patients at low surgical risk (5). Currently, clinical trials are recruiting patients in the United States to examine the efficacy of TAVR in low risk patients, both studying the Medtronic CoreValve Evolut R System (NCT02701283) and the Edwards S3 system (PARTNER 3 trial, NCT02675114).

The 5-year results of the original PARTNER trial published last year did not reveal any significant structural valve deterioration (6). Recently presented data by Dvir and colleagues studying patients who underwent TAVR with balloon-expandable valves between April 2002 and April 2011 in two centers, at St Paul's in Vancouver, Canada and in Rouen, France, has generated concern regarding the durability of TAVR prostheses (5). Degeneration was defined in the analysis as moderate regurgitation and/or a mean gradient ≥20 mm Hg not present at 30 days post procedure. After all exclusions, 378 patients receiving Cribier-Edwards, Edwards SAPIEN, and SAPIEN XT, mostly via transfemoral access, were included in the analysis. Median survival was found to be 51 months, with increasing age, male gender, atrial fibrillation, and high STS score found to be independent predictors for higher mortality. Almost half the patients were noted to have valve degeneration after 8 years of follow-up. A mean time of 61 months was noted from valve replacement to degeneration, and chronic renal failure (GFR <60 cc/min) was identified as the strongest risk factor for valve degeneration (HR =3.22, CI: 1.45–7.15, P=0.004). The investigators noted gradually increasing calcification in the TAVR valve that progressed to valve degeneration within the first 5 years with a steep increase in valve degeneration after 5 years. This study should only be considered hypothesis generating, as it was somewhat limited, conducted at only two centers, both of which lacked core lab adjudication. The study was also retrospective with a fairly small sample size. Also, the criteria used by Dvir and colleagues to define valve degeneration is far more stringent than the studies on degeneration of surgically implanted aortic bioprosthesis which have relied on parameters like New York Heart Association Functional Classification index, need for reoperation and morbidity to assess for valve degeneration (3,7). Therefore, it is too early to make a fair comparison with the currently available data.

The long term results with CoreValve, though not extensive, have not shown evidence of valve degeneration to date. The 5-year high-risk Italian registry results show sustained clinical outcomes and durability at 5 years with only 5 patients (1.4%) noting prosthesis failure (8). The results of the CoreValve US pivotal study revealed stable aortic valve gradients after three years follow up (9). In addition, the CoreValve ADVANCE study demonstrated stable hemodynamic performance with low aortic valve gradients at 4 years follow-up. Although we can hypothesize about the role of internal mechanical pressure associated with balloon expansion possibly playing a part in the Sapien valve degeneration, it is important to note that the presented data demonstrated most deterioration occurring at 5 years and onwards. Thus, it is too early to judge the durability of the self-expanding CoreValve with the current data.

If more data confirms the findings of Dvir and colleagues, placement of a second transcatheter bioprosthetic valve might become an attractive option in patients with a large aortic annulus, especially in high risk surgical patients. Sapien XT was approved by Food and Drug Administration for high risk patients with failed surgical aortic bioprosthesis in October 2015 after presentation of the 1-year data from PARTNER II valve-in-valve registry. This followed the approval of CoreValve for the same indication earlier in 2015.

In addition to long-term valve deterioration, concerns are arising about leaflet mobility with both balloon-expandable and self-expanding TAVR valves. This phenomenon was first discovered during the PORTICO trial, and it has since been evaluated in both the SAVORY and RESOLVE registries. It has been hypothesized in these cases that rapid increases in transvalvular gradients may be a sign of subclinical valve thrombosis (10,11). Del Trigo *et al.* recently concluded that the absence of anticoagulation at the time of discharge was independently associated with higher valve hemodynamic deterioration and initiating anticoagulation was noted to correlate with improvement in valve hemodynamics (12). The concept of reduced leaflet motion secondary to subclinical leaflet thrombosis became popular during the PORTICO IDE trial when one patient who suffered a stroke following TAVR was noted to have reduced leaflet motion on CT and another asymptomatic patient was discovered to have a similar finding (13). Close scrutiny including multiple CT images revealed that reduced leaflet motion is more common than initially assumed. This led to the formation of two physician-directed registries-RESOLVE and SAVORY. Both are designed to investigate the incidence and significance of reduced leaflet motion after TAVR and SAVR and to evaluate the role of subclinical thrombosis. Cases of reduced leaflet thrombosis seem to resolve with anticoagulation, giving rise to the theory that subclinical thrombosis is the underlying mechanism for the reduced leaflet motion. This hypothesis is further supported by the fact that most of these leaflet mobility problems resolve with long-term anticoagulation with warfarin, while dual anti-platelet therapy has not been observed to reduce this risk. The most alarming aspect of this phenomenon is that many of these patients do not have appreciably increased gradients on transthoracic echocardiography and the diagnosis of leaflet immobility is made only with transesophageal echocardiography or 4-D volume rendered CT. It is also important to note that the registries also studied surgically implanted bioprosthetic valves and found the same issue with leaflet immobility, albeit at a lower rate. It is unknown whether this represents a new complication or simply a benign imaging finding secondary to our ability to see with 4-D CT what could previously not be seen. Also, antithrombotic therapy after surgically implanted bioprosthesis has been well defined. This, however, was not true for antithrombotic therapy after TAVR. Before the results of the PORTICO trial, there was wide variation in the antithrombotic therapy used at different institutions. Ongoing trials, the ARTE trial, GALILEO trial and CLOE trial will shed more light on this issue. The FDA now requires all patients who receive TAVR as part of a clinical trial in the US have follow-up CT scans to evaluate for leaflet immobility. This will help answer the question of the true prevalence of this phenomenon.

In the meantime, although we should proceed with caution in considering expanding indications for TAVR to low risk patients, the data is too sparse to draw any conclusion about the fate of TAVR in this risk category. Randomized controlled trials have demonstrated the outstanding clinical performance of TAVR with both the SAPIEN and CoreValve prostheses in those at high, and prohibitive surgical risk. Recently, data has shown feasibility of TAVR in intermediate risk patients as well (2,14). Future study, namely the ongoing studies of low surgical risk patients, will answer many of the questions regarding TAVR prosthesis durability and help determine the utility of this technology in lower risk patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Arora S, Ramm CJ, Misenheimer JA, Vavalle JP. Early transcatheter valve prosthesis degeneration and future ramifications. Cardiovasc Diagn Ther 2017;7(1):1-3. doi: 10.21037/cdt.2016.08.04

