Valve in Valve:

Another Milestone for Transcatheter Valve Therapy

Running title: Tuzcu et al.; Transcatheter valve in valve replacement

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The first mechanical heart valve prosthesis designed by Dr Charles Hufnagel was implanted to the descending aorta of a 30 year old woman with severe aortic regurgitation in 1952\(^1\). Eight years after the initial successful prosthetic valve implantation, Dr Harken sutured a prosthetic valve (Starr Edwards Valve) to the aortic anulus after removing the diseased native valve. During the ensuing years different types of valves made from pyrolytic carbon were tried. Though successfully remedied the aortic valve disease, mechanical prosthesis required lifelong anticoagulation resulting in high rates of bleeding and thrombosis complications.

In the 1960s valves with leaflets that were made from animal tissue were developed as an alternative without an anticoagulation requirement. Indeed, they were superior to mechanical prosthesis in that regard but they did not last nearly as long. In randomized trials of bioprosthesis or mechanical valves which started enrollment in 1970s, primary valve failure and reoperation rates were higher in patients receiving bioprothetic valves especially in patients less than 65 years of age\(^2-4\). Since these initial reports, several important advancements have been made in design and tissue processing to improve valve hemodynamics and durability. With these improvements, the age cutoff to use bioprothetic valves was gradually lowered to avoid lifelong anticoagulation. Large studies with prospectively collected data and long term follow-up are not yet available to determine the clinical impact of such a trend\(^5\).

Until recently reoperation was the only choice for symptomatic patients with degenerated aortic bioprosthesis. Advanced age and multiple comorbidities put some patients at a higher risk for a repeat open heart surgery and for many this risk is so prohibitive that there is no other treatment option\(^6-9\). Advancements in transcatheter aortic valve replacement (TAVR) and the first successful reported case of VIV (valve in valve) in 2007\(^10\), brought a new hope for these patients.
The study by Dvir et al published in this issue of Circulation provides us a reality check\textsuperscript{11}. On the one hand it shows the remarkable efficacy of the transcatheter valve replacement without removing the previously placed, now dysfunctional prosthesis. On the other hand it presents the unique pitfalls and the challenges of a new techniques.

Dvir et al report stems from a registry of VIV procedures in 202 patients from 33 canters in 4 continents. Information was prospectively collected after December 2010. Older data were gathered retrospectively. Although patients were of advanced age and had multiple comorbidities and high surgical risk scores, it is not clear if some or all of them were inoperable by a heart team. The findings are based on site reported data and not independently adjudicated. There was no core laboratory. Nevertheless, this comprehensive look provides valuable insights to the transcatheter VIV replacement.

Since this initial experience does not have a control group, the relative risk and efficacy compared to conventional surgical approach remains undefined. However, this series provides some benchmarks when transcatheter VIV therapy is considered for bioprosthetic valve failure. The 30-day rates of mortality (8.4\%) and stroke (2\%) are not much different from what was observed in the early experience of TAVR for inoperable patients. On the other hand, 3 issues were more frequent and consequential than for TAVR for native AS, including high transvalvular gradients, coronary occlusions and valve malpositioning.

**High Transvalvular Gradients**

Overall 28\% of patents had a mean transvalvular gradient of $>20$ mmHg. following TAVR. In patients with small surgical prosthesis (internal diameter $<20$ mm) this rate was doubled. High gradients were also more common when the Edwards valve was used. These findings represent less than ideal hemodynamic results.
The bioprosthesis, unlike the native aortic anulus, provides a rigid boundary for the new valve that is placed inside it. Accordingly, the size of the surgically placed valve has a paramount importance in the planning and outcome of the VIV procedure. Determining the true internal diameter of a given valve is not an easy task. The sizes that are given by the manufacturers frequently correspond to the sewing ring diameter but do not represent the actual internal diameters. The magnitude of discrepancy between the manufacturer’s size and the actual measurements vary among the different valves. In the Global VIV Registry reported by Dvir and colleagues, >75% of the bioprosthesis were < 23 mm. There is a large variation in internal diameter of bioprosthetic valves ranging from 17 to 20 mm for a 21 mm and 15 to 19 mm for a 19 mm valve based on intraoperative measurements. This measurement not only depends on the valve type, but also on whether the bioprosthetic valve is placed supra or intra-annularly and whether valve pledgets are placed above or below the annulus. Understanding the complexity of the dimensions and knowing the true internal diameter of the prothetic valve are critical in the planning of VIV procedure.

The opening that will accomodate the new prosthesis is also determined, albeit to a lesser extent, by presence and severity of pannus formation, bulky nature of the degenerated and calcified prosthetic valve leaflets and the severity of stenosis. The issue of internal diameter size of the diseased valve is more important for the Edwards Sapien valve because of its “intra - anular” positioning unlike for the CoreValve which has functioning leaflets above the minimum internal diameter.

Creating a relatively small effective orifice area and consequently high transvalvular gradients will frequently lead to patient prosthesis mismatch (PPM). Whether this less than optimal orifice translates into higher long-term mortality or functional impairment remains to be
seen. Available data in the surgical literature suggest that there may be a price to pay for larger residual gradients. With that said, for patients with no surgical option due multiple co-morbidities, expectations may be different. For the time being, VIV for a “no option” patient with severely dysfunctional 19 mm or 21 mm prosthesis may not be a perfect solution but it may offer an acceptable result with improvement in symptoms, particularly with a supra-annular valve.\textsuperscript{15}

**Coronary occlusion**

The data in the registry highlight another critical procedural problem and point to the importance of careful patient selection and procedure planning. Coronary artery occlusion with attendant 57% mortality occurred more frequently in the stentless valves and valves with leaflet mounted on the outside of the frames (Figure 1). It is not clear whether or not there is an “interaction” between the diseased prosthesis and the type of TAVR used although there was no difference in the frequency of the coronary occlusion between the 2 types of transcatheter valve. To prevent this frequently lethal complication, we need to examine the relationships between the coronary artery ostia, the bioprosthetic valve sewing ring, the leaflets, the sinotubular junction and Sinuses of Valsalva. For the time being we should either avoid or use extreme caution in using VIV technique in the particular prosthesis mentioned above that leaves little space between the prosthetic leaflets and coronary ostia.

**Malpositioned valve**

The malpositioning rate of 15.3% and the need for a second TAVR valve in 8.4% of patients are surprisingly high. The valve that moves cranially during deployment up the aorta can often be managed via catheter techniques. But, if it moves in toward the left ventricle open-heart surgery may be necessary. These complications can potentially be prevented by clear understanding of
the anatomy of different valves, pre-procedural planning with CT scan and use of guiding
intraprocedural radioscopic software for positioning\textsuperscript{13}.

**Long-term outcome**

There appears to be no loss of improved valve function in a small number of patients who had 1-year echocardiograms. Follow up is too short and very limited to draw comfort for durability of the VIV technique. The longer term follow up from larger TAVR cohorts cannot be readily used for VIV procedures. For the time being, the impact of the frequently constrained conditions of the functioning VIV, interaction between 2 different prosthetic surfaces on the durability of the transcatheter valve is not clear.

**Bioprosthesis now, TAVR later?**

The question at hand is: does TAVR offer a reasonable solution to the difficult problem of the severely symptomatic patient with malfunctioning aortic prosthesis who is not a surgical candidate or at very high risk for surgical mortality and morbidity. The answer is a qualified “yes”; not all surgical prostheses are suitable and much improvement in technology and procedural technique is needed.

The question for future is: Should we take the option of VIV-TAVR technique into consideration when deciding the surgical valve type for aortic valve disease patients of all ages? The answer is a cautious “maybe”. In the future, availability of newer iterations of TAVR devices specifically for VIV will make this approach more feasible as long as the durability issue is addressed. But the size of the surgically implanted valve will continue to be the most important determinant of the success of the VIV procedure. Accordingly, surgeons who envision a prospective TAVR procedure if a valve bioprosthesis fails should make sure a large valve is implanted during the first surgery\textsuperscript{16}. This may require wider use of the root enlargement
Valve in valve is another milestone in the advance of transcatheter valve therapies. Dvir et al should be congratulated for reporting the initial global experience. They show us the promise and the pitfalls of the new technique and point to the hard work ahead to overcome the challenges.

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**References:**


**Figure Legend:**

**Figure 1.** A) a stented bioprosthesis with leaflets mounted inside the frame struts. B) a stentless valve is sewn to the aortic wall with coronary ostia above open to the stentless valve rim aorta with reduction in aortic root dimensions(Subcoronary Insertion) . C) a stentless valve root replacement with mobilized coronary ostia sewn to the stentless valve root with consequent reduction in the aortic root and coronary sinuses (Root Replacement). D) a stented valve with leaflets mounted outside of the frame struts. Valve- in- valve are shown in the bottom panels for respective valves. Calcific deposits on the valve (blue arrows) and prosthetic valve annulus pannus formation (yellow arrows) on the valve could potentially affect the expansion of the transcatheter valve. It is also possible that limited space in the aortic root in stentless valves and in valves with leaflets mounted outside could potentially compromise flow to the coronary arteries.
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