

## **Chapter 19: Current controversies, ongoing trials, new valves, and future directions**

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Transcatheter Aortic Valve Replacement (TAVR) is one of the most exciting recent advances in cardiac disease management. Two devices, the SAPIEN 3 Valve (Edwards Lifesciences, Irvine, CA) and the Corevalve EvolutR Valve (Medtronic Inc, Minneapolis, MN) have received approval for use in inoperable, high and intermediate risk patients with aortic stenosis. Expanding clinical indications and a wide variety of newer devices are currently in different stages of clinical trials in this rapidly evolving field. As with any new therapy, there are controversies and challenges that need to be addressed especially with potential use of TAVR in lower risk and younger patients. In this chapter, we will review some of these controversies, newer valve systems and future directions of TAVR.

### **Current Controversies**

#### Subclinical and clinical valve thrombosis

Subclinical and clinical valve thrombosis of both transcatheter and surgical bioprosthetic aortic valves has been increasingly noted with the advent of 4D computerized tomographic (CT) scans, closer surveillance, and systematic echocardiographic analysis after valve implantation. (Figure 1) Recent studies have suggested an incidence of subclinical valve thrombosis between 7% to 14%, with a reduced incidence in patients already on anticoagulants and resolution of imaging abnormalities in almost all patients with systemic anticoagulation.<sup>1,2</sup> The clinical significance of subclinical bioprosthetic valve thrombosis, impact on durability, and the role of empiric oral anticoagulation in all patients with bioprosthetic valves is unclear. This issue is being investigated in two US clinical trials comparing surgical (SAVR) vs. transcatheter aortic valve implantation in low-risk patients, with a subset of the patients undergoing 4D CT analysis in both studies. The role of novel oral anticoagulants (rivaroxaban and apixaban) in patients undergoing TAVR are also ongoing (GALILEO and ATLANTIS trials) and discussed further in the chapter on post-operative management of TAVR patients.

#### Stroke and Embolic protection

Silent ischemic embolic events are detected on MRI in ~90-100% of patients post TAVR<sup>3</sup>. (Figure 2) Use of embolic protection devices in TAVR has been associated with a reduction in the number of new lesions as well as the volume of lesions on diffusion weighted MRI, fewer neurological deficits, and improved cognitive function in some domains at discharge and at 30 days<sup>4</sup>. However, a recent randomized trial of the Sentinel Cerebral Protection System (Claret Medical, Santa Rosa, CA) did not meet the primary endpoint of reduction of radiographic infarcts. Despite this, the FDA has recently approved the device for TAVR. The effect of embolic protection devices on hard clinical endpoints including stroke and all-cause mortality remains unclear and is being evaluated in currently enrolling trials (REFLECT 3).

#### Conduction abnormalities post TAVR

Despite a decrease in overall complication rates with TAVR, the occurrence of new conduction abnormalities as well as the higher risk of permanent pacemaker (PPM) implantation with TAVR as compared to SAVR remains an important clinical issue, especially as we move towards lower risk and younger patients. Several studies have characterized the high-risk features which predispose patients to high-degree AV block and need for PPM post TAVR.<sup>7</sup> However, in patients with conduction abnormalities without high-grade AV block after TAVR (e.g. new or worsening LBBB) controversy remains on the long term clinical impact as well as the appropriate monitoring, management, timing, and indications for pacemaker implantation. Further studies are needed on appropriate risk stratification of these patients with conduction studies to identify patients at higher risk of arrhythmic mortality and need for new PPM implantation after TAVR.

### Durability

The long-term durability of TAVR valves is a lingering question in the cardiovascular community. The effect of leaflet crimping, balloon post-dilatation, increased leaflet stress due to stent under-expansion from severely calcified valves, and observed subclinical/clinical leaflet thrombosis all drawn into question the long-term durability of transcatheter valves. At 5 years, none of the patients in the PARTNER 1 trials had a structural valve deterioration.<sup>8,9</sup> However, since there were very few patients at risk in the later years of the study due to the high mortality rate and elderly age of those patients, long term durability is still unknown. More valve durability data both from randomized trials and registries, such as the Transcatheter Valve Therapy registry, are needed as we move to implant these devices in younger and lower risk patients.

### **New Clinical Trials**

#### Low risk, severe aortic stenosis

TAVR has been shown to be superior to medical management in inoperable patients and is non-inferior to SAVR in high-risk and intermediate risk patients. This has led to increasing interest in the safety and efficacy of TAVR in low risk patients with severe AS. The Nordic Aortic Valve Intervention Trial (NOTION) trial was the first trial to study TAVR in low risk patients, and showed no significant differences in the primary outcome of death from any cause, stroke, or MI in 280 low risk patients at 1 year.<sup>5</sup> Patients undergoing TAVR had a higher risk of conduction abnormalities and paravalvular regurgitation, but had a lower risk of major or life threatening bleeding, cardiogenic shock, acute kidney injury or atrial fibrillation. Two currently enrolling FDA approved trials are investigating the role of TAVR vs SAVR in low risk patients (Partner 3 Trial and EVOLUT Low Risk Trial).

Asymptomatic, severe aortic stenosis: Asymptomatic patients with severe aortic stenosis have traditionally been treated with a “watchful waiting” strategy unless they have very critical AS, drop in LVEF to <50%, undergo concomitant cardiac surgery, or have symptoms unmasked by stress tests. With the advent of trials evaluating TAVR vs. SAVR in low-risk patients, there has been interest in understanding the safety and efficacy of pursuing TAVR versus “watchful waiting” in asymptomatic patients in a randomized trial manner. Previous studies in asymptomatic patients include only

observational data, with the most prominent being the CURRENT AS registry from Japan. This registry, which included 582 patients, showed a significant reduction in five-year mortality (15.4% vs. 26.4%,  $p = 0.009$ ) and heart failure hospitalizations (3.8% vs. 19.9%,  $p < 0.001$ ) with isolated SAVR versus watchful waiting using a propensity matched model.<sup>6</sup> The currently enrolling EARLY TAVR randomized trial aims to evaluate outcomes of TAVR vs. clinical surveillance in asymptomatic patients with severe AS with a normal exercise treadmill stress test.

### Moderate aortic stenosis with impaired left ventricular function

#### Bicuspid aortic valve disease

Bicuspid aortic valve disease is present in about 1-2% of the US population and presents an anatomic challenge in patients undergoing TAVR. SAVR with or without root replacement remains the gold standard in patients with concomitant aortopathy. Challenges for successful TAVR implantation include appropriate sizing methodology due to a more elliptical annulus, higher risk of moderate to severe paravalvular leak, higher risk of aortic injury as well as higher rate of pacemaker implantation. Newer generation TAVR systems along with the use of appropriate CT methodology for sizing has helped overcome several of the challenges. A definitive comparison with SAVR has not yet been performed, but may be an area of investigation in the future.

### **New Valve Systems**

#### Portico

The Portico TAVR (Abbott Vascular, Santa Clara, CA) system is a nitinol based self-expanding stent with bovine pericardial leaflets which has achieved CE Mark and is now being studied in the US in a randomized trial of 758 high-risk or extreme risk patients at 70 sites against a commercially available control TAVR valve.

#### Lotus

The Lotus® valve system (Boston Scientific, Natick, MA) is repositionable and has an adaptive seal surrounding the ventricular portion of the device to reduce para-valvular aortic regurgitation. The REPRISÉ III trial randomized 912 extreme-risk or high-risk patients to Lotus valve or Corevalve/Evolut in a 2:1 manner and showed the Lotus valve to be non-inferior in the primary safety end-point (composite of all-cause mortality, stroke, life-threatening/major bleeding, stage 2/3 acute kidney injury, and major vascular complications at 30 days: 20.3% vs. 17.2%, non-inferiority  $P=0.003$ ) and superior in the primary efficacy outcome (composite of all-cause death, disabling stroke, and moderate or greater paravalvular aortic leakage (PVL) at 1 year 16.7% vs 29%).<sup>10</sup> There were no cases of moderate to severe paravalvular regurgitation. Clinical outcomes at thirty days revealed all-cause mortality in 4.2%, strokes in 5.9%, and new pacemaker implantation in 42% of the patients at risk.

## Symetis

Symetis ACURATE TAVR (Boston Scientific, Natick, MA) system is a self-expanding valve system with porcine pericardial tissue valve and a sealing skirt mounted on a nitinol based stent frame. The valve system has a self-seating, self-sealing mechanism and has been implanted by both trans-apical and transfemoral routes. The CE Mark trial of the ACURATE TA system showed a 30-day mortality of 7% and stroke rate of 3%.<sup>11</sup> The introduction of this valve in the U.S. is anticipated in 2018 through a research protocol.

## Venus A Valve

Venus A (Venus Medical, Hangzhou, China) is a self-expanding valve that is the first TAVR valve approved in China

## Inovare

Inovare (Braile Biomedica, Sao Paulo, Brazil) is a Brazilian bovine pericardial TAVR valve with good early clinical results

## **Future Directions**

TAVR is poised for an exciting future with ongoing trials in low-risk and asymptomatic patients with severe AS as well as trials in patients with moderate AS with heart failure (TAVR UNLOAD). Several centers are reporting anecdotal experience with concomitant/staged TAVR and other minimally invasive approaches for mitral and tricuspid valves including the MitraClip device and the Watchman device for left atrial appendage occlusion. However, further studies are needed to explore the safety and outcomes of these approaches. Additionally, newer TAVR and neuroprotection devices are being evaluated in different stages of clinical trials. As we continue into expanded indications and younger patients with severe AS, concerns remain about subclinical leaflet thrombosis, durability, and conduction abnormalities associated with TAVR. Further studies in appropriate anticoagulation management, use of 4DCT imaging for surveillance and clinical follow up, as well as devising novel TAVR-specific scoring systems for better patient and device selection are needed to further improve outcomes with TAVR.

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#### Figure Legends

Figure 1. Subclinical valve thrombosis (left) with resolution after 3 months of warfarin therapy (right)

Figure 2. Typical findings of “silent” cerebral infarction on diffusion weighted magnetic resonance imaging (DW MRI) after TAVR