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Update on transcatheter aortic valve replacement

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ABSTRACT

Transcatheter aortic valve replacement (TAVR) is currently the treatment modality of choice for patients with symptomatic severe aortic stenosis who are inoperable or at high risk for surgical aortic valve replacement. TAVR has shown a clear mortality benefit compared to conservative treatment in inoperable patients and is at least non-inferior to surgical aortic valve replacement in high-risk operable patients. Through improvements in pre-procedural imaging, refinement in valve technologies, increasing operator and team experience, and continuous valuable research, TAVR has developed rapidly in the past few years and is expected to further boost in the near future. In this review, we highlight the current status of TAVR, summarize recent updates, and discuss briefly the future expectations of this rapidly evolving technology.

Introduction

Calcific aortic stenosis (AS) is the most common form of valve disease in the Western world and represents a major healthcare burden. To date, there are no effective medical therapies that can halt or delay progression of calcific AS, and symptomatic AS is associated with a dismal prognosis when managed conservatively. Surgical aortic valve replacement (SAVR) is generally accepted to prolong survival on the basis of historical comparisons and long experience [1,2]. However, it has been estimated that 33% of all patients aged ≥75 years with severe AS are declined for surgery because of age considerations and/or concomitant co-morbidities that increase the operative risk [3]. Without surgery, the 3-year survival rate of symptomatic severe AS is <30% [4,5].

In this context, and following experimental work in the transcatheter valve field in the 1990s [6], the first-in-human transcatheter aortic valve replacement (TAVR) was performed by Cribier et al. [7] in 2002. This case was followed by several single-center and small multicenter registries and series that included inoperable or very high-risk patients, which were associated with promising results that confirmed the feasibility of TAVR [8–12]. In more recent years, the technology has developed very rapidly and, to date, more than 80,000 transcatheter valves have been implanted worldwide. The results of several large multicenter registries [13–17] and randomized clinical trials [18–21] have provided definitive data confirming this treatment as a real alternative to standard SAVR in inoperable and high-risk surgical candidates. The current article highlights the current status of TAVR, summarizes recent updates, and discusses briefly the future expectations of this rapidly evolving technology.

Transcatheter aortic valve replacement: More than an alternative to high-risk surgery

The Placement of AoRTic TraNscathetER Valves (PARTNER) Trials were the first prospective randomized landmark studies, which compared TAVR using the earlier-generation balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) with medical management in inoperable patients with severe symptomatic AS (PARTNER Trial Cohort IB) [18], and with SAVR in patients considered to be at high surgical risk (PARTNER Trial Cohort IA) [19]. In the inoperable cohort, the 30-day mortality was 5.0% in the TAVR group

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(trans-femoral approach in all patients) and 2.8% in the medical treatment group ($p = 0.41$). Importantly, up to 84% of patients in the medical treatment group had at least one procedure of balloon aortic valvuloplasty during the study period. At 1 year, mortality was 30.7% in the TAVR group compared with 50.7% in the medical treatment group ($p < 0.0001$). In the high-risk PARTNER trial cohort, the 30-day mortality was 3.4% in the TAVR group (trans-femoral approach in 70% of patients) compared to 6.5% in the SAVR group ($p = 0.07$). Mortality at 1 year was 24.2% and 26.8% in the TAVR and SAVR groups, respectively ($p = 0.44$). Based on the results of both trials, the United States Food and Drug Administration (FDA) approved the early-generation balloon-expandable device for inoperable patients in November 2011 and for high-risk operable candidates in October 2012.

In a recently published meta-analysis including two randomized controlled trials and 11 observational reports comparing TAVR with SAVR in patients with severe AS, no significant differences in mortality and stroke between the two treatment groups were identified [22]. However, vascular complications, permanent pacemaker insertion, and residual aortic regurgitation were more frequent after TAVR than after conventional AVR. Conversely, major bleeding was more likely to occur after SAVR than TAVR.

More recently, the results of two further more contemporary TAVR studies were reported [20,23]. The non-randomized CoreValve US extreme-risk pivotal trial compared TAVR with the self-expandable CoreValve device (Medtronic Inc., Minneapolis, MN) to a pre-specified objective performance goal in inoperable patients [23], while the randomized CoreValve US high-risk pivotal trial compared TAVR using the same device (trans-femoral approach in 83%) with SAVR in patients at high risk for surgery. Surprisingly, the CoreValve US high-risk trial demonstrated—for the first time—a significantly higher rate of survival at 1 year with TAVR compared to SAVR. The mortality at 30 days was lower than predicted in both arms (3.3% vs. 4.5%). At 1 year, TAVR was superior to SAVR for the primary end point of all-cause mortality (14.2% vs. 19.1%, $p < 0.0001$ for non-inferiority, $p = 0.04$ for superiority). In addition, TAVR was non-inferior with respect to echocardiographic indices of valve stenosis, functional status, and quality of life, and exploratory analyses suggested a reduction in the rate of major adverse cardiovascular and cerebrovascular events. Importantly, no increase in the risk of stroke was observed [any stroke in 4.9% of the TAVR group and 6.2% of the surgical group at 30 days ($p = 0.46$) and 8.8% and 12.6%, respectively, at 1 year ($p = 0.10$)] [20]. Based on the results of both trials, the FDA approved the self-expandable CoreValve device for inoperable patients in January 2014 and for high-risk operable patients in June 2014. A summary of selected outcome measures from the PARTENR I and CoreValve US trials is provided in Table 1.

The downside of transcatheter valves

With mortality and stroke rates being largely comparable between TAVR and SAVR, two main limitations of the transcatheter approach have been the focus of extensive research: the need for permanent pacemaker (PPM) insertion and residual paravalvular aortic regurgitation (PAR).

New-onset conduction disturbances, particularly new left bundle branch block, occur frequently after TAVR (7–18% with the balloon-expandable Edwards SAPIEN valve and 30–83% with the self-expandable CoreValve) [24]. Direct mechanical injury of the left bundle branch and inflammation created by the stent containing the valve prosthesis are potential mechanisms of these disturbances. Importantly, about half of these conduction disturbances occur during balloon valvuloplasty before valve implantation, and injury to the conduction system is not permanent in all patients [25]. Nevertheless, the rate of PPM implantation after TAVR remains higher compared to SAVR, especially with the self-expandable device [20].

In a recently published meta-analysis comprising seven published studies, the need for PPM following TAVR did not seem to have negative clinical consequences and did not increase the risk of all-cause mortality during follow-up [26]. Indeed, 30-day PPM implantation was a protective factor for the occurrence of unexpected death in a recent study [27]. On the other hand, new PPM implantation does seem to have a negative effect on left ventricular function over time [27]. Interestingly, Pereira et al. [28] recently documented PPM dependency in only 27% of TAVR patients receiving a new PPM. Whether outcomes are related to pacemaker dependence remains unknown and needs to be analyzed in future studies.

On the other hand, data from European registries and observations from the PARTNER trial have consistently identified more-than-mild PAR as an independent predictor of early and late mortality after TAVR [14,29,30]. Transcatheter heart valves (THVs) are implanted in a sutureless fashion using oversizing to anchor the prosthesis stent frame at the level of the aortic annulus. The native valve is not removed but instead crushed by the superimposed bioprosthesis, which can result in an incomplete seal of the bioprosthetic valve and aortic annulus, with subsequent occurrence of PAR. Despite the favorable hemodynamic properties of THVs, PAR remains a rather frequent complication. Significant PAR most commonly results from incomplete prosthesis apposition to the native annulus due to patterns or extent of calcification [31], annular eccentricity [32], under-sizing of the device [33], and/or mal-positioning of the valve. These observations seem to be true for both balloon-expandable and self-expandable THVs [34].

In order to minimize PAR, detailed pre-procedural assessment using various imaging modalities to precisely estimate the size of the aortic annulus and analyze the aortic root anatomy has been implemented. Although annulus sizing using two-dimensional echocardiography has been associated with good clinical results in the early days of TAVR, recent studies have confirmed an underestimation of the true annulus size when two-dimensional echocardiography is compared with multislice computed tomography (MSCT) [35,36]. MSCT studies have demonstrated an oval shape of the annulus in most patients, further highlighting the complexity of aortic annulus measurements [36]. Recently, a prospective study by Binder et al. [37] showed that integration of an MSCT-based three-dimensional annulus-sizing algorithm reduced the incidence of more-than-mild PAR and the composite end point of in-hospital death, aortic annular rupture, and severe PAR. These observations have clearly