

Shifting paradigms for treatment of symptomatic aortic stenosis in lower risk populations: role of a newer generation balloon-expandable transcatheter aortic valve implantation device

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Provenance: This is a Guest Editorial Commissioned by Section Editor Yue Liu, MD (Department of Cardiology, the First Affiliated Hospital of Harbin Medical University, Harbin, China).

Comment on: Kodali S, Thourani VH, White J, *et al.* Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. *Eur Heart J* 2016;37:2252-62.

Submitted Aug 12, 2016. Accepted for publication Sep 28, 2016.

doi: 10.21037/cdt.2016.11.21

View this article at: <http://dx.doi.org/10.21037/cdt.2016.11.21>

Over the last decade, transcatheter aortic valve implantation (TAVI) has emerged as the treatment of choice for patients with symptomatic severe aortic valve stenosis at a prohibitive or high risk for surgical valve replacement. Since its introduction in 2002 and establishment of the retrograde transfemoral access route in 2005, TAVI procedures underwent several refinements (1-3). Improved prosthesis design and delivery systems, as well as the systematic use of multimodality imaging for accurate patient selection and valve positioning have significantly improved the efficacy and safety of TAVI devices over the last years. Although TAVI is currently approved for the treatment of inoperable or high surgical risk patients with severe symptomatic AS, increased operator experience and improved valve systems have expanded the use of TAVI towards patients with intermediate or lower risk (4-6). However, so far, because of the lack of large scale and randomized data, the expansion of the use of TAVI to lower risk populations warranted careful individual clinical evaluation and decision-making.

The next generation balloon-expandable transcatheter valve (Sapien 3, S3, bovine pericardial leaflets; Edwards Lifesciences, Irvine, California, USA) was introduced in 2013 and subsequently replaced its predecessor the Sapien XT transcatheter heart valve (THV) system as the default balloon-expandable transcatheter valve for TAVI (*Figure 1*). The S3 may be delivered via lower profile expandable 14 or 16 Fr transfemoral delivery sheaths depending on the size

of the implanted valve prosthesis, and can also be delivered via transapical or direct transaortic access routes (7). Since the occurrence of paravalvular leaks remained an important issue associated with the use of earlier generation TAVI devices, the newer generation S3 device has been equipped with a polyethylene terephthalate skirt surrounding the inflow portion of the stent frame in order to efficiently reduce paravalvular leaks (8).

In a recently published issue of the *European Heart Journal*, Kodali and co-authors report the early outcome results from a multicenter non-randomized registry involving 57 centers in North America and enrolling a total of 583 high-risk or inoperable as well as 1,078 intermediate risk patients who underwent TAVI with the new generation S3 THV (9).

Early clinical and echocardiographic outcomes after implantation of a next generation balloon-expandable THV in patients with severe AS

The patients included in this study were enrolled in the context of the Placement of Aortic TraNscathetER Valves (PARTENR) II Sapien 3 trial between October 2013 and December 2014. The study was designed as a multicenter non-randomized prospective trial to evaluate the clinical and echocardiographic short-term outcomes associated with the use of the new generation Sapien 3 valve in high-risk/

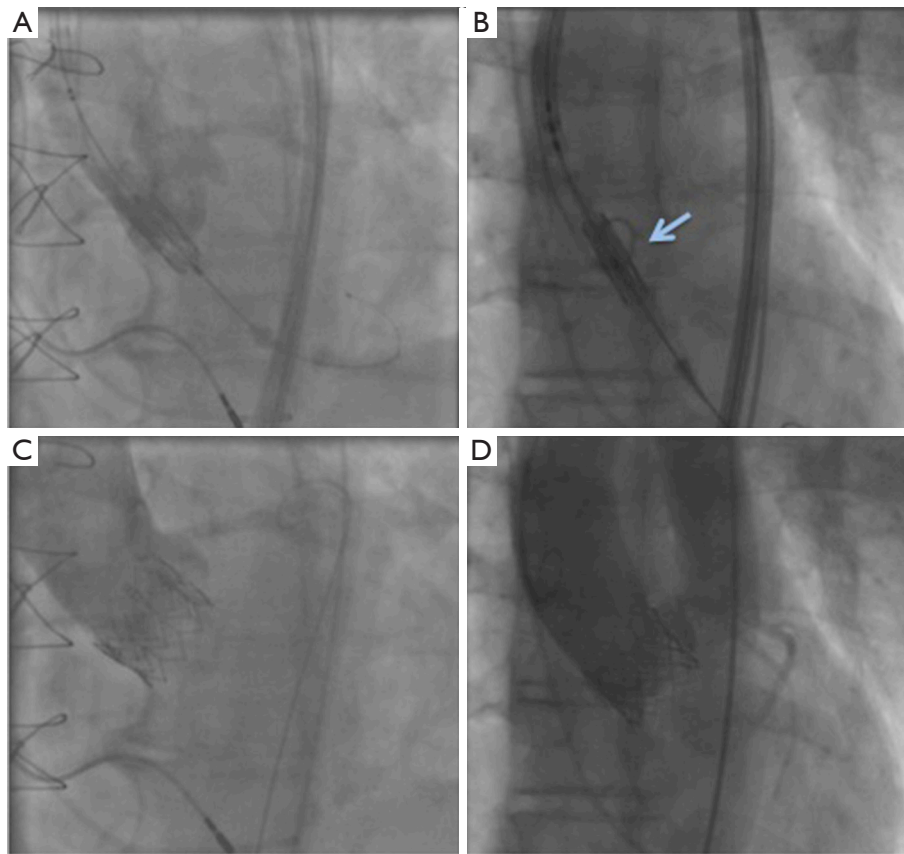


Figure 1 Aortic root angiogram during implantation of a Sapien XT (A and C) and the newer generation Sapien 3 (B and D) transcatheter heart valve. Both heart valves comprise a balloon-expandable cobalt chromium frame and a trileaflet bovine pericardial tissue valve. While the Sapien XT is constituted only of a PET inner skirt, the inflow portion of the Sapien 3 transcatheter heart valve has an additional outer PET sealing skirt on top of the inner skirt which significantly reduces the extent of PVR. Blue arrow indicates position of the central marker of the S3 THV system at the level of the aortic annulus. PET, polyethylene terephthalate; THV, transcatheter heart valve.

inoperable as well as intermediate risk patients with severe symptomatic aortic stenosis. All clinical endpoints were reported according to the VARC-2 endpoint definitions.

Use of the S3 THV system was associated with excellent device success rates and procedural outcomes. Overall rates of valve embolization (0.1%), coronary obstruction (0.3%), aortic rupture (0.1%) and conversion to open heart cardiac surgery (0.2%) were among the lowest reported in patients undergoing TAVI so far. Implantation of an additional valve system during the index procedure was required in only 0.5% of the procedures. Rates of post-dilatation due to residual paraavalvular leak were markedly lower than those reported with the use of earlier generation devices (high-risk/inoperable: 14.8%, intermediate risk: 11.3%, overall: 12.5%), which may be attributed to the introduction of the peri-prosthetic sealing cuff in the new

generation device.

The excellent procedural outcomes associated with the use of the S3 valve translated into improved 30-day outcomes as compared to reports from earlier TAVI studies. While in the PARTNER IA trial patients randomized to TAVI faced higher rates of cerebrovascular events at 30 days as compared to patients randomized in the surgical arm, the current study demonstrates that implantation of the new generation S3 device was associated with low rates of cerebrovascular events in both high-risk/inoperable (2.1%) and intermediate risk (3.2%) populations (10,11). Most importantly rates of major/disabling stroke at 30-days in both groups were as low as 0.9% and 1.0% respectively. This impressive reduction in cerebrovascular complications is particularly relevant in terms of expanding TAVI to lower risk populations, since the incidence of early cerebrovascular

	Improved valve design and delivery system	Implementation of multimodality imaging	Operator learning curve
Less access site and vascular complications	✓✓	✓✓	✓✓
Less cerebrovascular complications	✓✓	✓	✓✓
Less PPM	✓	✓✓	✓
Less PVR	✓✓	✓✓	✓

Figure 2 Improved efficacy and safety profile of new generation TAVI devices: contributing factors. ✓✓, important contribution; ✓, moderate contribution. PPM, patient prosthesis mismatch; PVR, paravalvular regurgitation.

events is strongly associated with a higher risk of short- and mid-term mortality after TAVI (10-12).

Paravalvular regurgitation was frequently observed after TAVI using earlier generation devices and its severity correlates with a worse prognosis (13,14). Analyses from the PARTNER trials have demonstrated that even mild paravalvular regurgitation may be associated with poorer outcome (15). Hence, it is not surprising that newer generation devices such as the S3 were designed to overcome this important limitation and reduce the rate of required post-dilatation. While the adapted design of the new generation THV may account in large parts for the reduction in paravalvular regurgitation, other factors such as operators' experience and routine use of multimodality (3D) imaging for patient selection as well as establishment of sizing algorithms have also substantially contributed to these excellent results (Figure 2).

Downsizing of introducer sheath and delivery system diameters has significantly contributed to lower rates of periprocedural bleeding and vascular complications, both of which are independent predictors of mortality after TAVI. While with first generation devices major vascular complications were reported in up to 16% of the procedures, rates of major vascular complications were as low as 5.5% (high-risk/inoperable patients) and 4.4% (intermediate risk) (9-16). As a result 86% of the procedures described in the current study were performed via transfemoral access route, while in the early PARTNER trials this percentage was much lower. This is particularly important since post-hoc comparisons from both PARTNER I and the recently published PARTNER II trial strongly suggest that the net survival benefit of TAVI is

more pronounced in patients undergoing the less invasive transfemoral rather than the transapical or transaortic procedure (17,18).

Despite those rather enthusiastic results, the current study by Kodali *et al.* raises concerns regarding the higher rates of conduction disturbances observed with the new generation S3 THV system. This observation is in line with previously published results from a smaller registry, which demonstrated higher rates of permanent pacemaker implantation after TAVI using the S3 THV as compared to the earlier XT THV system (8). As mentioned by the authors, this could be explained at least in part by the longer stent frame of the S3, which may protrude deeper into the left ventricular outflow tract, thereby compressing the interventricular septum. Although the initial manufacturer recommendation was to position the middle marker of the deployment balloon in the annular plane, this practice may have led to lower final positioning of the valve prosthesis in the outflow tract thus compromising the conduction system. Interestingly, rates of permanent pacemaker implantations were lower in the intermediate risk population than in patients at high or prohibitive risk of surgery. Most probably the introduction of new recommendations for positioning and prosthesis sizing during the course of the study as well as the later enrollment of the intermediate risk cohort during the trial may account for this difference in permanent pacemaker implantation rates observed between both groups. In the near future, upcoming trials and the increasing amount of data derived from large scale registries enrolling patients undergoing TAVI with new generation devices will add more evidence to our knowledge in order to better evaluate the extent of this problem in daily practice.

In summary, this analysis of a prospective non-randomized registry published by Kodali *et al.* provides—for the first time—large scale data on the short-term efficacy and safety of a newer generation balloon-expandable THV system in patients with severe symptomatic AS who are either at high risk/inoperable or at intermediate risk. The use of the new generation S3 was associated with very low rates of periprocedural complications, 30-day mortality and ischemic events. The use of a newer delivery system and low profile introducer sheaths has expanded the transfemoral access route to a large majority of patients considered for TAVI, rendering the procedure less invasive for most of the patients. Those excellent short-term results were not only observed in high-risk/inoperable patients but also in patients at so called intermediate risk according to their STS score (4–8%), and may pave the way to introducing

TAVI for treatment of symptomatic AS in lower risk populations.

Expanding TAVI to lower risk patients

The study by Kodali *et al.* reports results obtained in one of the largest series of patients undergoing TAVI and who display an intermediate risk profile. TAVI is currently still restricted to patients with severe symptomatic AS unsuitable for surgical valve replacement (recommendation class I, level of evidence B) or have a high surgical risk (recommendation class IIA, level of evidence B). However data derived from most registries have shown that in clinical practice TAVI has already expanded to patients with an intermediate STS score (4–8%) and that short-term clinical outcomes were favorable also in the low and intermediate risk populations (4–6). More recently, the NOTION trial, which enrolled all-comers with symptomatic severe AS, showed that patients with a low to intermediate STS score randomized to either surgical valve replacement or TAVI had similar event rates at 1 year (19). These results suggest at least that TAVI may be non-inferior to surgical treatment in patients with lower surgical risk. A major reason for the discrepancy between current guideline recommendations and real-world data lies in the difficulty met in accurate risk stratification of TAVI patients. Current risk stratification algorithms such as the STS risk score and the EuroSCORE are derived from surgical databases which only included candidates for cardiac surgery. Many elderly patients with AS traditionally have not been offered surgery, with age, frailty and impaired left ventricular function being the most notable factors associated with denial of surgical therapy. A comprehensive clinical evaluation may reveal additional factors not captured in the risk scores such as potential for rehabilitation, cognitive impairment, frailty and anatomic characteristics that may render surgery challenging and highly risky.

Few weeks after publication of the article by Kodali *et al.*, Leon and co-authors presented the results from the PARTNER 2 cohort A randomized trial, in which TAVI with a balloon-expandable system (XT) was compared with conventional surgery in patients with severe symptomatic AS and an intermediate-risk profile (18). The trial demonstrated that TAVI using the Sapien XT device was similar to surgical aortic-valve replacement with respect to the primary end point of death or disabling stroke. Of note, in the transfemoral access cohort, TAVI even resulted in significantly lower rates of death or disabling stroke

than surgery. With regard to secondary endpoints, TAVI was associated with lower bleeding risks, lower rates of acute kidney injury, earlier recovery and shorter duration of hospitalization. Whether those findings can also be generalized to the newer S3 THV needs to be confirmed in future prospective trials. In the mean time, in a recently published propensity score analysis in intermediate risk patients including 963 patients treated with S3 TAVI and 747 patients treated with surgical valve replacement in the PARTNER 2A trial, a significant superiority for the composite outcome (mortality, stroke, \geq moderate aortic regurgitation) with TAVI with the S3 THV compared with surgery has been observed, underlining that TAVI with new generation devices might become the standard of care treatment in intermediate risk patients (20).

In summary, the most recent studies provide important new insights for the future treatment of severe AS in daily practice. First of all performing TAVI in patients with an intermediate risk profile is safe and non-inferior to surgical valve replacement. Second, current subgroup analyses strongly suggest that the increasing number of less traumatic transfemoral TAVI procedures with newer generation devices due to improvement of device design and use of low profile delivery systems may even lead to superior results in intermediate risk patients than conventional surgical valve treatment. In fact, as of August 2016, the new generation self-expandable Evolute R (Medtronic) THV has gained CE mark by European Authorities for treatment of severe AS in intermediate risk patients based on convincing data derived from the NOTION trial and a subgroup analysis from the CoreValve U.S. High Risk Pivotal Trial. Whether TAVI will also expand to younger low-risk patients with severe AS remains a matter of debate. There is no doubt that the technical advances and the growing operators' experience will translate into excellent procedural success rates also in this subset of patients. However concerns may arise regarding the durability of bioprosthetic valves. Our experience derived from surgical bioprostheses shows us that structural valve deterioration is a slow process and that failure rates increase over time, particularly 7 to 8 years after implantation (21–23). Although the initial 5-year outcomes of TAVI are promising, these results cannot yet be extrapolated to predict long-term durability. In addition data from the NOTION and OBSERVANT trials have provided conflicting results regarding the outcome after TAVI in low-risk patients. While in the prospective randomized NOTION trial TAVI and SAVR proved comparable in terms of the composite risk of all-

cause death, MI or stroke at 1 year, analysis of the Italian OBSERVANT registry suggested that surgery may offer a survival advantage with lower MACE rates at 3 years in low-risk patients (24). Thus, caution is required when considering to expand TAVI to younger low-risk patients until more evidence on THV durability is forthcoming and large-scale prospective clinical data are provided. In the mean time, the optimal treatment of symptomatic AS should rely on careful patient screening, individualized comprehensive clinical assessment and interdisciplinary decision making involving all heart team members.

Acknowledgements

None.

Footnote

Conflicts of Interest: Dr. Abdel-Wahab reports receiving institutional research grants from St. Jude Medical and Biotronik and lecture fees from Medtronic and Boston Scientific. Dr. Abdel-Wahab is a proctor for Boston Scientific. Dr. Holy is currently supported by an EAPCI training grant sponsored by Edwards Lifesciences and a research grant from the “Walter and Gertrud Siegenthaler” Foundation of the University of Zurich, Switzerland.

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Cite this article as: Holy EW, Abdel-Wahab M. Shifting paradigms for treatment of symptomatic aortic stenosis in lower risk populations: role of a newer generation balloon-expandable transcatheter aortic valve implantation device. *Cardiovasc Diagn Ther* 2017;7(Suppl 2):S57-S62. doi: 10.21037/cdt.2016.11.21