JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 8, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.02.042

EDITORIAL COMMENT

# Transcatheter Aortic Valve Replacement in Bicuspid Aortic Stenosis

## Early Success But Concerning Red Flags*

Robert A. Guyton, MD,[a] Muralidhar Padala, PhD[b]

Perlman et al. (1) report in this issue of *JACC: Cardiovascular Interventions* a series of 51 patients who underwent transfemoral or transcarotid (2 patients) transcatheter aortic valve replacement (TAVR) in bicuspid aortic stenosis with excellent early clinical results: reduction in the mean aortic gradient from 50 to 11 mm Hg, post-implantation aortic insufficiency that was mild or less in all patients, and a 30-day mortality rate of 3.9% in a group of higher risk patients whose Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) was 5.2%.

SEE PAGE 817

This extension of TAVR to bicuspid aortic stenosis involved a new-generation TAVR device, the SAPIEN 3 (S3) valve (Edwards Lifesciences, Irvine, California). This device has an outer fabric skirt that has been shown to reduce dramatically the incidence of paravalvular aortic insufficiency, a major problem in the application of previous TAVR devices to bicuspid aortic stenosis. This study strongly suggests that this new device is effective in preventing paravalvular aortic insufficiency after TAVR in bicuspid arctic stenosis, as it has been in tricuspid senile aortic stenosis.

The reported outcomes from this study do raise 3 important concerns that will require special attention as we consider the extension of TAVR in bicuspid aortic stenosis to lower risk patients: higher mortality, increased new pacemaker requirement, and a high rate of asymmetrical stent deployment. First, the mortality benefit of the S3 device in the PARTNER (Placement of Transcatheter Aortic Valves) II SAPIEN 3 trial, intermediate-risk cohort (S3i), was impressive: an actual 30-day mortality rate of 1.1%, 21% of the STS PROM in tricuspid S3 patients (2). The actual mortality in this series of bicuspid S3 patients was 3.9%, 75% of the STS PROM. The STS PROM was similar in the 2 groups (STS PROM 5.3%, mean age 82 years in PARTNER II S3i patients; STS PROM 5.2%, mean age 76 years in this study). The numbers in this study are small, but there remains a not unexpected signal that TAVR in bicuspid aortic stenosis is more challenging than TAVR in tricuspid senile aortic stenosis.

Second, the need for a new pacemaker in this study was 25%, excluding the 4 patients who had pacemakers in place at the time of the procedure. The S3 device is intentionally longer than the previous SAPIEN valves and has been associated with a disturbing increase in pacemaker need compared with the previous models, with the rate increasing from 4% to about 10% in tricuspid S3 patients (2). By intentionally placing the S3 device higher in the left ventricular outflow tract, the need for a new pacemaker can be reduced. Indeed, in a series of S3 valves placed only with transapical or transaortic delivery routes, the need for a new pacemaker was only 3.7% (3). In that series, the investigators intentionally attempted high placement of the S3

*Editorials published in *JACC: Cardiovascular Interventions* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Interventions* or the American College of Cardiology.

From the [a]Carlyle Fraser Heart Center, Division of Cardiothoracic Surgery, Department of Surgery, Emory University School of Medicine, Atlanta, Georgia; and the [b]Structural Heart Research & Innovation Laboratory, Emory University School of Medicine, Atlanta, Georgia. Dr. Guyton is national surgical principal investigator for the Edwards Lifesciences Early Feasibility Trial of Transcatheter Mitral Valve Replacement and an investigator for Edwards Lifesciences in the PARTNER trial. Dr. Padala has reported that he has no relationships relevant to the contents of this paper to disclose.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 9, NO. 8, 2016
APRIL 25, 2016:825–7

valve, and the ease of exact positioning is somewhat better with transapical or transaortic delivery than it is with the longer delivery devices required for transfemoral delivery.

Patients with bicuspid aortic stenosis seem to be more vulnerable to conduction system disturbances with TAVR than patients with trileaflet senile aortic stenosis. The 25% new pacemaker rate in this series, as the investigators point out, is similar to other reports of new pacemaker requirements in bicuspid aortic stenosis treated with TAVR. In the present series, even when the S3 valve was implanted high in the left ventricular outflow tract, there was a 10% need for a new pacemaker. This might be related to the anatomic location of the conduction system relative to the commissure of the most common type of bicuspid aortic valve, the Sievers type 1 valve with left-right leaflet fusion. This configuration accounted for 60% of the patients in this series. In this situation, the open non-right commissure is immediately adjacent to the membranous septum, which in turn is adjacent to the vulnerable conduction pathway.

A final major concern is the fact that 38% of the patients in the series had stents that were identified on angiography as asymmetrically expanded. Systolic leaflet opening and diastolic closure are clearly related to intercommissural separation in the native aortic valve and in surgical bioprosthetic valves (4). Asymmetrical intercommissural separation causes leaflet bunching in systole and leaflet pin wheeling in diastole, both of which result in suboptimal valve hemodynamic status and accelerated structural deterioration of the leaflets in surgical valves (5). Although intercommissural separation in the TAVR valve after deployment was not reported in this study, it is reasonable to expect that the commissures are not symmetrically spaced in an eccentrically shaped stent. Biomechanical studies of such leaflet configurations are suggestive of elevated strains and stresses in the leaflet belly, possibly from misalignment and slight prolapse of the leaflets relative to one another (6). Furthermore, leaflets in TAVR valves are relatively thinner than surgical bioprosthetic valves, potentially reducing their ability to sustain such suboptimal loads for prolonged periods without fatigue damage and structural failure (7). Current standards for valve testing require completion of 5 years' equivalent of valve function in a symmetrical, circular, completely expanded stent configuration. The high rate of incomplete stent expansion and resulting asymmetrical valve geometry in this trial suggests that in vitro durability testing for such clinically relevant stent configurations would be appropriate prior to expanded clinical use (8).

As we consider extension of TAVR to lower risk patients, these 3 concerns—a higher mortality rate, a pacemaker rate of 10% to 25%, and incomplete stent expansion in 38% of patients—become magnified in importance. In patients with 5- or even 10-year life expectancy, permanent pacemakers may not be a huge concern. However, in a patient with life expectancy more than 15 to 20 years, the need for a permanent pacemaker becomes a major liability with regard to both quality and length of life. Similarly, a decrease in valve durability from 15 to 20 years down to 7 to 10 years becomes a major concern in those patients with longer life expectancy. This is especially true in patients receiving size 23 or smaller TAVR valves, as the feasibility decreases for successfully repeated valve-in-valve procedures.

The concerns raised by this study about new pacemakers and valve durability should have some impact on the proposed primary endpoint for future studies of TAVR versus surgical valve replacement in low-risk patients. The primary endpoint perhaps should not just be successful initial implantation with patient survival at 1, 3, and 5 years with satisfactory valve function. Optimally, the primary endpoint should include absence of a requirement for a new pacemaker and absence of asymmetrical or incomplete stent expansion. It is highly likely that a requirement for a new pacemaker and asymmetrical or incomplete stent expansion will have a clinically significant impact on the quality and duration of life in patients who have life expectancy of more than 15 to 20 years.

This trial confirms the safe use of S3 TAVR in high-risk patients with bicuspid aortic stenosis. But the red flags strongly raised by this study with regard to new pacemakers and incomplete stent expansion suggest that patients with bicuspid aortic valves should not be included in upcoming trials comparing surgical valve implantation and TAVR in low-risk patients.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Robert A. Guyton, Carlyle Fraser Heart Center, Division of Cardiothoracic Surgery, Department of Surgery, Emory University School of Medicine, 1365 Clifton Road, NE, Suite A2213, Atlanta, Georgia 30322. E-mail: rguyton@emory.edu.

## REFERENCES

**1.** Perlman GY, Blanke P, Dvir D, et al. Bicuspid aortic valve stenosis: favorable early outcomes with a next-generation transcatheter heart valve in a multicenter study. J Am Coll Cardiol Intv 2016;9:817–24.

**2.** Kodali S. Clinical and echocardiographic outcomes at 30 days with the SAPIEN 3 TAVR system in inoperable, high-risk and intermediate-risk AS Patients. Paper presented at: Annual Meeting of the American College of Cardiology; March 15, 2015; San Diego, CA.

**3.** Wendt D, Al-Rashid F, Kahlert P, et al. Low incidence of paravalvular leakage with the balloon-expandable SAPIEN 3 transcatheter heart valve. Ann Thorac Surg 2015;100:819–26.

**4.** Jatene MB, Monteiro R, Guimaraes MH, Veronezi SC, Koike MK, Jatene FB. Aortic valve assessment. Anatomical study of 100 healthy human hearts. Arq Bras Cardiol 1999;73:81–6.

**5.** Gunning PS, Saikrishnan N, Yoganathan AP, McNamara LM. Total ellipse of the heart valve: the impact of eccentric stent distortion on the regional dynamic deformation of pericardial tissue leaflets of a transcatheter aortic valve replacement. J R Soc Interface 2015;12:20150737.

**6.** Abbasi M, Azadani AN. Leaflet stress and strain distributions following incomplete transcatheter aortic valve expansion. J Biomech 2015;48:3663–71.

**7.** Martin C, Sun W. Comparison of transcatheter aortic valve and surgical bioprosthetic valve durability: a fatigue simulation study. J Biomech 2015;48:3026–34.

**8.** Duraiswamy N, Weaver JD, Ekrami Y, Retta Sm, Wu C. A parametric computational study of the impact of non-circular configurations on bioprosthetic heart valve leaflet deformations and stresses: possible implications for transcatheter heart valves. Cardiovasc Eng Technol 2016 Feb 10 [E-pub ahead of print].

**KEY WORDS** aortic stenosis, transcatheter aortic valve replacement, valvular heart disease