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STRUCTURAL

A Strategy of Underexpansion and Ad Hoc Post-Dilation of Balloon-Expandable Transcatheter Aortic Valves in Patients at Risk of Annular Injury

Favorable Mid-Term Outcomes

John S. Tan, MBBS,* Jonathon Leipsic, MD,* Gidon Perlman, MD,* Dion Stub, MBBS,* Danny Dvir, MD,* Nicolaj C. Hansson, MD,† Bjarne L. Norgaard, MD,† Philipp Blanke, MD,* Anson Cheung, MD,* Jian Ye, MD,* Christopher R. Thompson, MD,* Robert R. Moss, MBBS,* Sandra Lauck, PhD,* David Wood, MD,* John Webb, MD*

ABSTRACT

OBJECTIVES The aim of this study was to evaluate a strategy of intentional underexpansion of excessively oversized balloon-expandable transcatheter heart valves (THVs) in terms of clinical outcomes, valve function, and frame durability at 1 year.

BACKGROUND Transcatheter aortic valve replacement requires the selection of an optimally sized THV to ensure paravalvular sealing and fixation without risking annular injury. However, some patients have "borderline" annular dimensions that require choosing between a THV that may be too small or another that may be too large.

METHODS We evaluated 47 patients at risk of annular injury who underwent transcatheter aortic valve replacement (TAVR) with an oversized, but deliberately underexpanded, THV followed by post-dilation if required. Clinical evaluation, echocardiography, and cardiac computed tomography were performed pre-TAVR, post-TAVR, and at 1 year.

RESULTS Deployment of oversized THVs with modest underfilling of the deployment balloon (<10% by volume) was not associated with significant annular injury. Paravalvular regurgitation was mild or less in 95.7% of patients, with post-dilation required in 10.7%. THV hemodynamic function was excellent and remained stable at 1 year. Computed tomography documented stent frame circularity in 87.5%. Underexpansion was greatest within the intra-annular THV inflow (stent frame area 85.8% of nominal). There was no evidence of stent frame recoil, deformation, or fracture at 1 year.

CONCLUSIONS In carefully selected patients with borderline annulus dimensions and in whom excessive oversizing of a balloon-expandable SAPIEN XT valve (Edwards Lifesciences, Inc., Irvine, California) is a concern, a strategy of deliberate underexpansion, with ad hoc post-dilation, if necessary, may reduce the risk of annular injury without compromising valve performance. (J Am Coll Cardiol Intv 2015;8:1727–32) © 2015 by the American College of Cardiology Foundation.

From the *St. Paul's Hospital, Vancouver, British Columbia, Canada; and the †Aarhus University Hospital, Aarhus, Denmark. Drs. Cheung, Dvir, Lauck, Leipsic, Webb, Wood, and Ye have received consulting fees and grant support from Edwards Lifesciences, Inc. Drs. Hansson and Norgaard have received grant support from Edwards Lifesciences, Inc. Drs. Blanke and Moss have been consultants for Edwards Lifesciences, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

CT = computed tomography

NYHA = New York Heart Association

PVR = paravalvular regurgitation

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

TTE = transthoracic echocardiogram

Transcatheter aortic valve replacement (TAVR) is a proven alternative to conventional surgical aortic valve replacement (1). Selection of an appropriately sized transcatheter heart valve (THV) is a complex component of the TAVR procedure. Excessive undersizing may lead to paravalvular regurgitation (PVR) and poor device fixation (2–4). Excessive oversizing may result in coronary obstruction, atrioventricular block, mitral valve injury, periaortic hematoma, septal rupture, or aortic root rupture (4,5). Aortic annular rupture has proved to be a particular concern when oversizing with balloon-expandable valves (6).

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SAPIEN XT and SAPIEN 3 balloon-expandable THVs (Edwards Lifesciences, Inc., Irvine, California) are manufactured in 4 sizes, with nominal expanded diameters of 20, 23, 26, and 29 mm. The manufacturer's sizing guidelines allow for a gray area with considerable overlap, where patients with "borderline" annular dimensions may be candidates for either of 2 available THV sizes. Often neither of the 2 sizes is ideal; the smaller THV may result in undersizing, and the larger THV may result in excessive oversizing. The difficulty is compounded by the uncertainty involved in noninvasively estimating aortic annular dimensions and compliance as well as the presence of adverse aortic root features (such as subannular calcification) (7).

In such difficult clinical scenarios in which optimal sizing cannot be achieved, we previously described a strategy of deliberate THV stent underexpansion by reducing the volume of the deployment balloon (7). The risk of annular injury is potentially reduced, and the underexpanded valve can subsequently be post-dilated and fully expanded if assessment of PVR suggests that this is necessary and safe. We demonstrated that underfilling the deployment balloon by 5% to 10% resulted in a predictable reduction in THV expansion. Although this strategy showed no adverse effects on short-term clinical or echocardiographic outcomes, questions remain regarding the intermediate- and long-term durability of underexpanded THVs.

To further increase our understanding of clinical outcomes and the durability of underexpanded THVs, we undertook 12-month clinical, echocardiographic, and computed tomography (CT) follow-up of a cohort of patients at increased risk of annular injury who underwent TAVR with an underfilled deployment balloon.

METHODS

Forty-seven consecutive patients with severe aortic stenosis and borderline annular sizing at risk of annular injury who underwent TAVR with an intentionally underexpanded SAPIEN type balloon-expandable THV were included in this prospective study at 2 centers. Our criteria for intentional THV underexpansion were previously reported (7). These included >20% predicted annular area oversizing or >10% predicted annular area oversizing in patients with adverse root features (moderate to severe left ventricular outflow tract calcification, shallow sinuses of Valsalva), extreme age, previous chest irradiation, or relatively small body size. The predicted oversizing was determined by comparing the pre-procedural CT-derived annulus area with the manufacturer's stated THV cross-sectional area. Annular area was preferred over annular perimeter for valve sizing as this measurement has been shown to predict PVR after balloon-expandable TAVR more accurately (4). It is recognized that, with improved smoothing algorithms, perimeter measurements may result in comparable outcomes.

The manufacturer's recommended nominal filling volume of the deployment balloon for the 20-, 23-, 26-, and 29-mm transfemoral Novaflex+ delivery system (Edwards Lifesciences, Inc.) are 11, 17, 22, and 33 ml, respectively. The nominal filling volumes for the 23-, 26-, and 29-mm transapical Ascendra+ delivery system (Edwards Lifesciences, Inc.) are 16, 20, and 30 ml, respectively. Our strategy was to intentionally underexpand THVs by underfilling the deployment balloon by 5% to 10%. **Table 1** represents a very general guide to achieving modest underexpansion for currently available balloon-expandable valves.

All patients underwent pre- and immediate post-procedure transthoracic echocardiography and cardiac CT (7). In the present study, we performed clinical, echocardiographic, and CT assessment at 12 months post-procedure. Clinical follow-up was performed by a telephone interview or clinic visit to determine the patient's New York Heart Association (NYHA) functional class. If the patient was deceased, a cause of death was obtained from the patient's primary care provider or medical records. A transthoracic echocardiogram (TTE) was obtained to assess mean transaortic pressure gradient, aortic valve area, PVR, and left ventricular ejection fraction. PVR was graded as none, mild, moderate, or severe according to Valve Academic Research Consortium 2 criteria (8). Noncontrast CT assessment of THV geometry was also performed. The stent frame of each THV was assessed at 3 cross-sectional levels (inflow, midportion, and

outflow) in diastole at 75% of the R-R interval. The minimal external stent diameter, the maximal external stent diameter, and the external stent area were measured at each level by tracing along the external margins of the stent frame. An experienced level 3 cardiac CT reader measured all stent levels 3 times, and the data represent the mean of the 3 measurements. The CT reader was blinded to the degree of underfilling in addition to all outcome measures of this study including the TTE as well as clinical outcome data.

STATISTICAL ANALYSIS. Continuous variables are reported as mean ± SD. Categorical variables are reported as frequencies and percentages. Continuous variables were compared using the paired Student *t* test. A p value <0.05 was considered significant. Analyses were performed using SPSS statistics software version 16.0 (SPSS Inc., Chicago, Illinois).

RESULTS

The baseline clinical, echocardiographic, and CT characteristics are summarized in Table 2. The mean age was 82.0 ± 7.6 years, 53.2% were female, and the mean Society of Thoracic Surgeons (STS) predicted risk of mortality was 7.8 ± 3.5%.

Procedural variables are listed in Table 3. Access was transfemoral in most (91.5%) patients and transapical in 8.5%. The THV implanted was the SAPIEN XT in 44 of 47 patients (93.6%) and the SAPIEN 3 in 3 (6.4%). The THV deployment balloon was underfilled by 1, 2, 3, and 4 ml in 8 (17.0%), 26 (55.3%), 11 (23.4%), and 2 (4.3%) patients, respectively. Postdilation was performed in 5 patients (10.7%). PVR was mild or less in 45 of 47 patients (95.7%). Two patients (4.3%) had moderate PVR. Complete heart block developed post-TAVR in 2 patients (4.3%), and they required placement of a permanent pacemaker. There were no cases of severe PVR, annular rupture, or valve embolization.

CLINICAL OUTCOME AT 1 YEAR. At 12 months, 40 of 47 patients (85.1%) were alive. In the 7 patients who died, the cause of death was cardiac failure in 1, malignancy in 2, pneumonia in 1, stroke in 1, a fall with hip fracture in 1, and unknown in 1. Of those alive, 24 of 40 (60.0%) were NYHA functional class I, 7 (17.5%) were NYHA II, 8 (20.0%) were NYHA functional class III, and 1 (2.5%) was NYHA functional class IV (limited by dyspnea secondary to severe lung disease).

ECHOCARDIOGRAPHY AT 1 YEAR. A TTE was obtained in 38 of 40 patients (95%) alive at 12 months. Two patients (5%) did not return for a repeat TTE due to frailty. The mean transaortic gradient was 11.6 ± 3.8 mm Hg immediately post-implantation and 12.5 ± 6.5 mm Hg at 12 months (p = 0.46). Mean aortic valve area was 1.6 ± 0.3 cm^2 immediately post-implantation and 1.6 ± 0.4 cm^2 at 12 months (p = 0.53). PVR was mild or less in 45 of 47 patients (95.7%) immediately post-implantation and in 36 of 38 patients (94.7%) at 12 months. Two patients had moderate PVR at 12 months. The mean left ventricular ejection fraction was 53.4 ± 11.8% immediately post-implantation and 55.2 ± 11.5 at 12 months (p = 0.24).

TABLE 1 Balloon Volumes Required to Achieve Modest Underexpansion of Currently Available Balloon-Expandable Valves

	Nominal Balloon Volume, ml	Final Balloon Volume, ml	Volume Subtracted, ml	Underfilling, %
SAPIEN XT*				
20 mm	11	10	1	9.1
23 mm	17	15.5	1.5	9.4
26 mm	22	20	2	9.1
29 mm	33	30	3	9.1
SAPIEN 3*				
20 mm	11	10	1	9.1
23 mm	17	15.5	1.5	9.4
26 mm	23	21	2	8.7
29 mm	33	30	3	9.1

*Edwards Lifesciences, Inc., Irvine, California.

TABLE 2 Baseline Characteristics, Transthoracic Echocardiographic, and CT Findings (N = 47)

Age, yrs	82.0 ± 7.6
Male	22 (46.8)
STS score, %	7.8 ± 3.5
NYHA functional class	
II	8 (17.0)
III or IV	39 (83.0)
GFR <60 ml/min	32 (68.1)
Peripheral vascular disease	6 (12.8)
Permanent pacemaker	6 (12.8)
Extensively calcified aorta	3 (6.4)
Echocardiographic findings	
Mean aortic gradient, mm Hg	46.4 ± 17.7
Aortic valve area, cm^2	0.64 ± 0.17
Left ventricular ejection fraction, %	54.1 ± 11.8
Aortic regurgitation ≥ moderate	5 (10.6)
CT annulus	
Maximal diameter, mm	27.7 ± 3.2
Minimal diameter, mm	21.6 ± 2.3
Mean diameter, mm	24.3 ± 3.2
Area, cm^2	4.9 ± 0.9

Values are mean ± SD or n (%).

CT = computed tomography; GFR = glomerular filtration rate; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

TABLE 3 Procedural Variables

Access	
Transfemoral	43 (91.5)
Transapical	4 (8.5)
Prosthesis type	
SAPIEN XT*	44 (93.6)
SAPIEN 3*	3 (6.4)
Prosthesis size, mm	
20	1 (2.1)
23	7 (14.9)
26	21 (44.7)
29	18 (38.3)
Underfilling of deployment balloon, ml	
1	8 (17.0)
2	26 (55.3)
3	11 (23.4)
4	2 (4.3)
Post-dilation	
Nominal volume in balloon	3 (6.4)
Underfilled balloon	2 (4.3)
Paravalvular regurgitation	
Mild or less	45 (95.7)
Moderate	2 (4.3)
Severe	0 (0.0)
New permanent pacemaker	2 (4.3)
Valve embolization	0 (0.0)
Valve-in-valve	0 (0.0)
Annular rupture	0 (0.0)
Transvalvular regurgitation	0 (0.0)

Values are n (%). *Edwards Lifesciences, Inc., Irvine, California.

CT AT 1 YEAR. Cardiac CT was performed in 24 of 40 patients (60.0%) alive at 12 months. Of the 16 patients who did not undergo repeat cardiac CT, 14 of 16 (87.5%) were not local to the implantation site and 2 of 16 (12.5%) lived in a care facility.

The percentage of THV stent expansion (defined as CT-derived stent frame area divided by the manufacturer's nominal stent frame area × 100) is shown in Figure 1A. THV expansion immediately post-implantation and at 12 months was 85.8 ± 5.9% and 85.5 ± 6.3%, respectively at the stent inflow ($p = 0.46$), 88.9 ± 6.3% and 89.4 ± 5.8%, respectively, at midstent ($p = 0.15$), 92.4 ± 7.1% and 92.4 ± 4.2%, respectively, at stent outflow ($p = 0.33$).

The percentage of THV eccentricity (defined as: 1 − [minimal external stent diameter divided by maximal external stent diameter] × 100) is shown in Figure 1B. THV eccentricity immediately post-implantation and at 12 months was 3.2 ± 2.8% and 4.0 ± 4.8%, respectively, at stent inflow ($p = 0.43$), 3.4 ± 2.9% and 3.7 ± 2.9%, respectively, at midstent ($p = 0.33$), 2.4 ± 2.0% and 2.9 ± 1.9%, respectively, at stent outflow ($p = 0.12$). At 12 months, 23 of 24 THVs (95.8%) were circular (defined as eccentricity <10%) at the stent inflow, 22 of 24 (91.7%) were circular at midstent, and 24 of 24 (100%) were circular at stent outflow.

DISCUSSION

We evaluated outcomes in patients at increased risk of annular injury who underwent TAVR with an oversized, intentionally underexpanded balloon-expandable THV as part of a strategy intended to mitigate the risk of annular injury and PVR. Early clinical outcomes were good, with no evidence of annular injury other than a low (4.3%) need for new pacemakers. Importantly, valve function was not compromised.

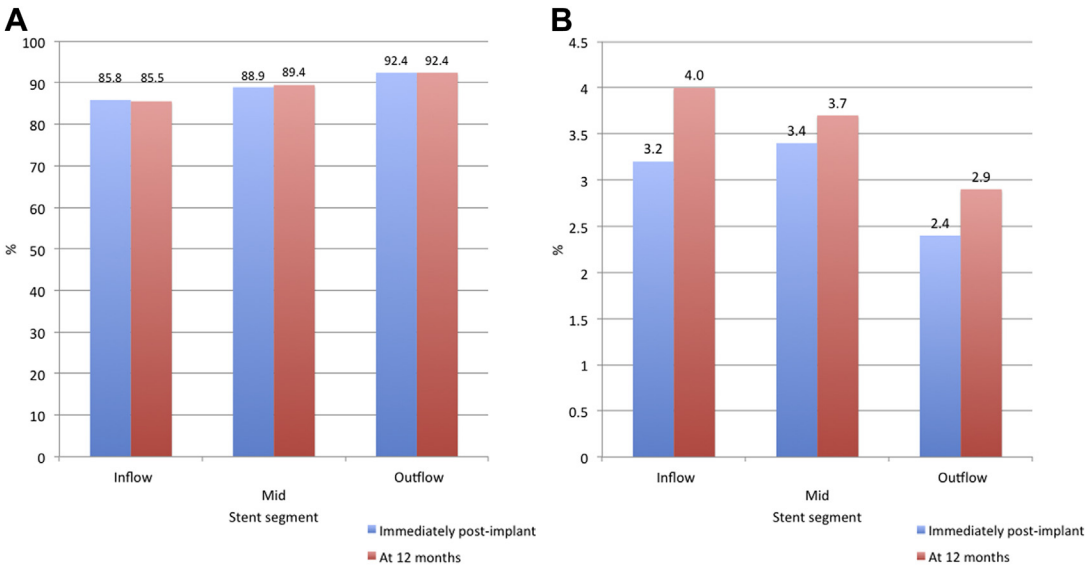
At 1 year, clinical outcomes were also good. The 1-year mortality rate of 14.9% was comparable to the 12.3% to 28.2% mortality rates reported in other reports on high-risk patients (9). The majority of patients (77.5%) remained in NYHA functional class I or II. At 1 year, there was no echocardiographic evidence of progressive deterioration of valve function, with low transvalvular gradients, low rates of PVR, and no CT evidence of stent recoil, deformation, or fracture.

The commonly recommended strategy of full expansion of balloon-expandable THVs is intended to approximate their nominal diameters (currently 20, 23, 26, or 29 mm). However, in some patients, this may result in a difficult choice between 2 different size valves, 1 potentially too large and 1 too small. These concerns may be greater in patients with features that predict an increased risk of annular injury (e.g., subannular calcification, irradiation, advanced age) or PVR (e.g., bulky leaflet calcification, eccentricity). Concerns may be further compounded when the dimensions of the annulus are uncertain due to suboptimal annular imaging.

Concerns about underexpanding balloon-expandable THVs are well founded. In vitro studies have shown that marked underexpansion of the valve stent frame can result in frame eccentricity, suboptimal leaflet coaptation, and contact between the leaflets and the frame, potentially affecting hemodynamic performance and leaflet durability. However, it appears that modest underexpansion (underfilling the deployment balloon by 5% to 10% by volume) does not have a major impact on midterm hemodynamic function or durability.

PARAVALVULAR REGURGITATION. A potential concern is that suboptimal stent expansion might result in poor sealing and PVR. However, this sizing strategy

FIGURE 1 THV Stent Expansion and Stent Eccentricity



(A) Stent expansion defined as CT-derived stent frame area divided by the manufacturer's nominal stent frame area × 100. **(B)** Stent eccentricity defined as: 1 − (CT-derived minimal external stent diameter ÷ CT-derived maximal external stent diameter) × 100. There was no statistically significant difference between measures immediately post-implantation and at 12 months (all p values > 0.05). CT = computed tomography; THV = transcatheter heart valve.

was associated with surprisingly little PVR following SAPIEN XT implantation. PVR was mild or less in 95.7% of patients immediately post-implantation and 94.7% of patients at 12 months. No patient had severe PVR.

Potentially, an oversized but underexpanded THV may not achieve perfect circularity and may conform better to a noncircular, calcified annulus. However, if the selected THV is too small, it might not appose the annulus well, resulting in PVR, even when fully expanded. Selecting a larger, but underexpanded, THV allows for greater flexibility in terms of what can be accomplished with post-dilation. Perhaps surprisingly, post-dilation was required in only 10.7% of patients because of residual PVR.

STENT FRAME GEOMETRY. Nombela-Franco et al. (10) demonstrated a minor degree of acute balloon-expandable frame recoil as seen on fluoroscopy at the time of balloon deflation. Our group has demonstrated durable expansion and circularity of balloon-expandable THV frames at an average of 2.5 years, with no evidence of late recoil (11). The current study demonstrates that modest frame underexpansion does not result in a loss of frame strength sufficient to result in progressive stent recoil, deformation, or fracture as assessed by matched post-implantation and 1-year CT imaging.

With modest (<10%) underfilling of the deployment balloon, the inflow portion of the stent frame was the segment with the most marked underexpansion, with a cross-sectional area ~86% of nominal compared with 92% at the outflow. The smaller inflow can likely be attributed to the localized constraint of the annulus and the fabric sealing cuff. A localized effect on the stent frame inflow might be considered desirable if the intent is to reduce the risk of annular injury.

Circularity was generally excellent, although noncircularity was documented in the stent frame inflow in 1 patient (4.2%) and the midportion in 2 patients (8.3%). In neither case was there an apparent adverse effect on valve performance. As discussed previously, there was no significant change in stent frame eccentricity at either THV inflow, midportion, or outflow at 1 year.

STUDY LIMITATIONS. The relatively small sample size is a limitation of this study. CT follow-up was not complete. CT lacks the spatial resolution to completely exclude stent fracture, although it is adequate to exclude a displaced fracture. Although

durability at 12 months post-TAVR is reassuring, longer term follow-up is required.

In future, newer balloon-expandable THV platforms with improved sealing and a greater variety of sizes may reduce the need to consider a strategy of controlled underexpansion. Improved sealing achieved with the outer sealing skirt incorporated into the next generation of SAPIEN 3 THV (Edwards Lifesciences, Inc.) may allow less need for oversizing to minimize PVR. Should this allow newer sizing strategies, then a strategy of ad hoc underfilling may be less necessary. There are additional concerns that underexpansion of the SAPIEN 3 THV may result in significantly less foreshortening, with unknown implications.

CONCLUSIONS

In carefully selected patients in whom excessive oversizing or undersizing of a SAPIEN XT THV is a concern, a strategy of intentional underexpansion may reduce the risk of annular injury and rupture without compromising valve performance, durability, or frame integrity at mid-term follow-up.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. John Webb, St. Paul's Hospital, 1081 Burrard Street, Vancouver, British Columbia V6Z 1Y6, Canada. E-mail: webb@providencehealth.bc.ca.

PERSPECTIVES

WHAT IS KNOWN? Selection of an appropriately sized THV is a complex component of TAVR. Undersizing may result in PVR or instability, whereas oversizing may result in annular injury. The choice between a valve that is too small and one that is too large may be difficult when annular dimensions are uncertain due to suboptimal annular imaging or in patients at increased risk of annular injury or PVR.

WHAT IS NEW? We used a strategy of controlled underexpansion of potentially oversized balloon-expandable valves in patients with "borderline" annular dimensions at risk of annular injury. Post-dilation to achieve nominal expansion was required in 10.7%. The clinical outcomes in 47 patients were good with favorable hemodynamics, minimal PVR, and no apparent annular injury. Clinical, echocardiographic, and CT frame geometry remained durable at 1 year.

WHAT IS NEXT? Further studies are needed to evaluate the long-term durability of this strategy. In addition, the emergence of newer valves with better sealing properties might allow for implantation of smaller valves and a lesser role for a strategy of controlled underexpansion.

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