Transapical Implantation of a Second-Generation Transcatheter Heart Valve in Patients With Noncalcified Aortic Regurgitation

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Objectives This study sought to report on the feasibility and early results of transcatheter aortic valve implantation employing a second-generation device in a series of patients with pure aortic regurgitation.

Background Efficacy and safety of transcatheter aortic valve implantation in patients with calcified aortic stenosis and high surgical risk has been demonstrated. However, experience with implantation for severe noncalcified aortic regurgitation has been limited due to increased risk for valve dislocation or annular rupture.

Methods Five patients (mean age: 66.6 ± 7 years) underwent transapical implantation of a JenaValve (JenaValve Technology GmbH, Munich, Germany) transcatheter heart valve for moderate to severe, noncalcified aortic regurgitation. All patients were considered high risk for surgical aortic valve replacement after evaluation by an interdisciplinary heart team (logistic EuroSCORE [European System for Cardiac Operative Risk Evaluation] range 3.1% to 38.9%). Procedural and acute clinical outcomes were analyzed.

Results Implantation was successful in all cases without relevant remaining aortic regurgitation or signs of stenosis in any of the patients. No major device- or procedure-related adverse events occurred and all 5 patients were alive with improved exercise tolerance at 3-month follow-up.

Conclusions Noncalcified aortic regurgitation continues to be a challenging pathology for transcatheter aortic valve implantation due to the risk for insufficient anchoring of the valve stent within the aortic annulus. This report provides first evidence that the JenaValve prosthesis may be a reasonable option in these specific patients due to its unique stent design, clipping the native aortic valve leaflets, and offering promising early results. (J Am Coll Cardiol Intv 2013;6:590–7) © 2013 by the American College of Cardiology Foundation.
Efficacy and safety of transcatheter aortic valve implantation (TAVI) in patients with severe aortic stenosis and contraindications or high risk for conventional surgery have been demonstrated (1,2). However, off-label treatment of severe noncalcified aortic regurgitation using the self-expanding Medtronic CoreValve prosthesis (Medtronic, Minneapolis, Minnesota) or the balloon-expandable Edwards Sapien XT valve (Edwards Lifesiences, Irvine, California) has only been described infrequently (3–6). Although feasibility has been demonstrated, pure regurgitation poses a challenge on TAVI due to the absence of annular or leaflet calcifications required for secure anchoring of transcatheter heart valves (THV), increasing the risk of dislocation.

With the recent CE-mark (Conformité Européenne) approval of second-generation devices for TAVI, new stent designs and technologies have become available. The JenaValve prosthesis (JenaValve Technology GmbH, Munich, Germany) features a unique clip fixation mechanism of the native aortic valve leaflets that may offer secure anchorage of the THV even in the absence of calcifications (7). Therefore, this device may be an appropriate option, even in patients with noncalcified aortic regurgitation.

We report for the first time on the feasibility and early results of TAVI using the JenaValve THV in a series of patients with pure aortic regurgitation.

Methods

Patient population and diagnostic work-up. Between September 2007 and December 2012, 750 TAVI procedures have been performed at our institution, almost exclusively for severe symptomatic aortic stenosis. From May through September 2012, 5 patients were admitted; 4 presented with symptomatic noncalcified aortic regurgitation, and 1 patient with severe heart failure scheduled for implantation of a left ventricular assist device (LVAD) and concomitant moderate aortic regurgitation. All patients presented with severe comorbidities or previous operations, yielding an increased operative risk for surgical aortic valve replacement as determined by an interdisciplinary heart team (Table 1). In addition to routine work-up, pre-operative transesophageal echocardiography was performed to determine valve pathology and to assess ventricular function and dimensions. The aortic annulus diameter was measured in the short-axis view. Aortic regurgitation was assessed in the parasternal long-axis view and graded according to the Doppler vena contracta width (8,9). Additionally, the color Doppler jet width was indexed to the left ventricular outflow tract width, as obtained in the parasternal short-axis view (9,10). A contrast-enhanced multislice computed tomography with prospective electrocardiogram-gating was employed to assess aortic valve and root morphology (Fig. 1). Area- and perimeter-derived aortic annulus diameters, optimal C-arm angulation, and transapical access location were determined using the 3mensio valves software (3mensio Medical Imaging BV, Bilthoven, the Netherlands), as previously described (11).

Procedure. TAVI was performed in a specially equipped hybrid suite under general anesthesia by an interdisciplinary heart team of cardiac surgeons, interventional cardiologists, and anesthesiologists. Transapical access was gained in the usual fashion through a left lateral minithoracotomy and purse-string sutures were applied to the left ventricular apex. The delivery catheter was introduced and positioned over a stiff guidewire. The THV size was selected according to the annulus diameters gained from multislice computed tomography. Following the manufacturer’s recommendations, a 23-mm prosthesis was chosen for an aortic annulus of 21 to 22.9 mm, a 25-mm prosthesis for an aortic annulus of 23 to 24.9 mm, and a 27-mm prosthesis for an aortic annulus of 25 to 27 mm. Anatomically oriented implantation of the JenaValve prosthesis, a trileaflet porcine root tissue valve attached to a nitinol stent, was performed without the use of rapid ventricular pacing under fluoroscopic control (Fig. 2, Online Video 1), as previously described (12). Briefly, the delivery catheter with the loaded JenaValve prosthesis was advanced through the native valve into the ascending aorta and the positioning feelers were released and placed into the corresponding sinuses of the aortic root. After correct orientation had been verified in 2 different fluoroscopic angulations, the lower stent part was subsequently released, resulting in the clipping and attachment of the noncalcified aortic valve leaflets to the device and expansion of the stent. Subsequently, valve performance was assessed by transesophageal echocardiography and fluoroscopy. We refrained from balloon valvuloplasty of the native aortic valve before THV implantation except for 1 patient with secondary commissural fusion (Patient #2). In another patient, TAVI was followed by subsequent implantation of an LVAD (HVAD, HeartWare, Framingham, Massachusetts).

Data management and clinical follow-up. All relevant baseline, procedural, and follow-up data were prospectively collected. Clinical and echocardiographic examinations were performed prior to discharge, at 30 days, and at 3 months. Outcomes were analyzed in accordance with the updated standardized endpoints defined by the Valve Academic Research Consortium-2 consensus document (13).

Ethics. All patients were fully informed about the procedure and this off-label use of the THV, and they signed written consent forms.

Results

Baseline characteristics. Five patients (mean age: 66.6 ± 7 years, 80% men) presented with noncalcified aortic
regurgitation due to different etiologies. Four patients were highly symptomatic for severe aortic regurgitation (Fig. 3), and 1 patient was scheduled for LVAD-implantation for end-stage heart failure with concomitant moderate aortic regurgitation. This patient had an indication for aortic valve replacement (Fig. 4) because even moderate aortic regurgitation can result in malfunction of the LVAD. Due to a porcelain aorta, aortic cross clamping for surgical aortic valve

Table 1. Baseline Clinical Parameters

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Age, yrs</th>
<th>Sex</th>
<th>BMI, kg/m²</th>
<th>Log ES, %</th>
<th>STS-PROM, %</th>
<th>NYHA Class</th>
<th>Comorbidities</th>
<th>Creatinine, mg/dl</th>
<th>PAP, mm Hg</th>
<th>MR Grade</th>
<th>TR Grade</th>
<th>EF, %</th>
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<td>1</td>
<td>70</td>
<td>Male</td>
<td>25.8</td>
<td>11.0</td>
<td>1.8</td>
<td>3</td>
<td>Coronary artery disease, status after myocardial infarction and coronary artery bypass grafting, arterial hypertension</td>
<td>0.9</td>
<td>22</td>
<td>1</td>
<td>0</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>Male</td>
<td>20.2</td>
<td>11.4</td>
<td>6.3</td>
<td>4</td>
<td>Severe COPD requiring home oxygen therapy, coronary artery disease, atrial fibrillation, previous stroke, arterial hypertension</td>
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<td>60</td>
<td>2–3</td>
<td>2</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>72</td>
<td>Male</td>
<td>22.9</td>
<td>38.9</td>
<td>7.0*</td>
<td>4</td>
<td>Severe ischemic cardiomyopathy—scheduled for LVAD implantation, coronary artery disease with previous myocardial infarction, status after mitral valve repair and coronary artery bypass grafting, diabetes mellitus, atrial fibrillation, prior implantation of AICD, porcelain aorta</td>
<td>1.0</td>
<td>65</td>
<td>3</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>Female</td>
<td>39.0</td>
<td>3.1</td>
<td>3.0</td>
<td>3</td>
<td>History of adrenal carcinoma with subsequent unilateral nephrectomy and Cushing disease, pneumonia, and sepsis with respiratory failure, diabetes mellitus, arterial hypertension</td>
<td>1.1</td>
<td>48</td>
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<td>1</td>
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<tr>
<td>5</td>
<td>62</td>
<td>Male</td>
<td>24.4</td>
<td>33.9</td>
<td>3.5</td>
<td>4</td>
<td>NSTEMI with subsequent resuscitation, PCI, 2 months prior to procedure, prolonged ICU care with pneumonia and respiratory failure, coronary artery disease, rheumatoid arthritis, prior implantation of AICD, porcelain aorta</td>
<td>0.7</td>
<td>60</td>
<td>1–2</td>
<td>2</td>
<td>28</td>
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</table>

*STS-PROM calculated for isolated TAVI procedure due to nonavailability for combined TAVI and LVAD implantation.

AICD = automated internal cardioverter-defibrillator; BMI = body mass index; COPD = chronic obstructive pulmonary disease; EF = left ventricular ejection fraction; log ES = logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE); ICU = intensive care unit; LVAD = left ventricular assist device; MR = mitral regurgitation; NSTEMI = non-ST-segment elevation myocardial infarction; NYHA = New York Heart Association functional class; PAP = systolic pulmonary artery pressure; STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI = transcatheter aortic valve implantation; TR = tricuspid regurgitation.

Figure 1. Aortic Valve Morphology

Baseline computed tomography scan for assessment of aortic valve morphology and annular measurements. Multiplanar reconstruction in axial views at the Valsalva level (A, B, C) and corresponding coronal views (D, E, F) of Patient #1 (A, D), Patient #2 (B, E), and Patient #3 (C, F).
replacement was precluded, yielding a hybrid approach of transapical TAVI and LVAD implantation in this particular case (Patient #3). The remaining 4 patients underwent TAVI without additional procedures. All patients were evaluated by an interdisciplinary heart team and deemed eligible for a transcatheter approach due to comorbidities resulting in excessive operative risk, which was not necessarily reflected by the commonly used risk stratification tools (mean logistic EuroSCORE [European System for Cardiac Operative Risk Evaluation] range: 3.1% to 38.9%, STS-PROM [Society of Thoracic Surgeons Predicted Risk of Operative Mortality] range: 1.8% to 7%). Despite low risk scores, 1 patient (Patient #1) was deemed eligible for a transcatheter approach due to patent bypass grafts after coronary artery bypass surgery several years ago. Detailed patient characteristics are listed in Table 1; aortic valve specifications are listed in Table 2.

**Procedural outcomes and valve function.** TAVI using the JenaValve second-generation THV was performed successfully in all 5 patients without hemodynamic compromise or the need for extracorporeal circulation. A 27-mm device was chosen in 4 patients and a 23-mm device in 1 patient according to aortic annulus measurements by multislice computed tomography and transesophageal echocardiography (Table 2). Procedure times ranged from 55 to 90 min (Table 3). No post-dilation was necessary in any of the cases. Echocardiographic evaluation after TAVI ruled out relevant aortic regurgitation or signs of aortic stenosis in all patients (Figs. 3 and 4). Left ventricular end-diastolic diameters remained fairly unchanged at this early stage after implantation.

**Clinical outcomes and follow-up.** No major procedure- or device-related adverse events occurred during 3-month follow-up. According to the Valve Academic Research Consortium-2 document, 3 patients suffered from acute kidney injury stages 1 or 2. One patient with pre-existing pulmonary disease and home oxygen therapy suffered from severe pneumonia and subsequent sepsis after discharge that eventually resolved under antibiotic treatment. No new-onset conduction disturbances, yielding a permanent pacemaker implantation, or bleeding complications were
**Figure 3. Echocardiographic Valve Performance**

Echocardiographic evaluation depicting severe noncalcified central aortic regurgitation before transcatheter aortic valve implantation (A, B). Color Doppler confirms optimal function of the implanted 27-mm JenaValve transcatheter heart valve. No paravalvular leaks are detected (C, D) (Patient #2).

**Figure 4. TAVI and Concomitant LVAD Implantation**

Moderate central aortic regurgitation prior to implantation of a left ventricular assist device (LVAD) (A, B). In anticipation of worsening aortic regurgitation and hemodynamic compromise during LVAD support, a 27-mm JenaValve prosthesis was implanted transapically beforehand. Color Doppler confirms optimal function of the implanted transcatheter heart valve (C, D) (Patient #3). TAVI = transcatheter aortic valve implantation.
observed. Device success was achieved in all patients, whereas the combined 30-day safety endpoint was not met in any of the cases. All 5 patients were alive with improved exercise tolerance at 3 months (Table 3).

**Discussion**

According to recent guidelines (14), aortic valve surgery is recommended in patients with chronic severe aortic regurgitation and subsequent symptoms or impaired left ventricular function (Class IB indication). If patients are not considered surgical candidates, however, therapeutic options are scarce. Noncalcified or predominant aortic regurgitation has typically been considered a contraindication for TAVI (15) due to the risk of valve dislocation as a consequence of insufficient anchoring.

Few cases have been published describing the off-label use of currently available THV devices in patients with pure aortic regurgitation. Several groups used the Medtronic CoreValve prosthesis for implantation (3,5,6) because additional anchorage of the valve stent in the left ventricular outflow tract and ascending aorta may offer sufficient stability. Others have reported the implantation of an Edwards Sapien prosthesis employing substantial oversizing (4), accepting a significant hazard for annular rupture or incomplete valve expansion. Limitations are obvious to both approaches because either THV was designed for implantation into calcified aortic valves through radial expansion at the annular plane level.

In contrast, the JenaValve system relies on a feeler-guided positioning and a clip fixation mechanism of the native aortic valve leaflets, allowing for anatomically correct and secure implantation even in the absence of annular or leaflet

**Table 3. Procedural and Follow-Up Parameters**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Fluoroscopy Time, min</th>
<th>Contrast Medium, ml</th>
<th>BAV Adverse Events</th>
<th>NYHA Class</th>
<th>AR Grade</th>
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<td>1</td>
<td>60</td>
<td>4.4</td>
<td>200 None</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>85</td>
<td>5.7</td>
<td>149 Once Acute kidney injury stage 2,* severe pneumonia and sepsis requiring antibiotic therapy</td>
<td>3 Trace</td>
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<tr>
<td>3</td>
<td>55</td>
<td>7.1</td>
<td>140 None Acute kidney injury stage 1,* LVAD driveline infection requiring surgical revision</td>
<td>3 None</td>
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<td>5</td>
<td>60</td>
<td>5.2</td>
<td>202 None Pleural effusion requiring drainage</td>
<td>2 Trace</td>
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</tr>
</tbody>
</table>

*According to the Valve Academic Research Consortium-2 consensus document.

BAV = balloon aortic valvuloplasty; other abbreviations as in Tables 1 and 2.
calcifications (7). Therefore, this THV may be particularly suitable for patients with predominant or pure aortic regurgitation. Additionally, there is no need for oversizing, alleviating the risk of annular dilation or rupture after TAVI in patients with noncalcified aortic annuli. In the absence of calcifications, no balloon valvuloplasty of the native aortic valve is necessary before implantation. We performed pre-balloononing only in 1 patient who was noted to have partially fused left and noncoronary cusps. No rapid ventricular pacing is needed during valve deployment, allowing for beating-heart implantation, hence adding safety to the procedure especially in patients with hemodynamic compromise or depressed left ventricular function.

Early promising results with the JenaValve THV in patients with aortic stenosis have been published as part of the first-in-man (16) and CE-mark trials (12). Long-term data are currently being investigated within the JUPITER (Longterm Safety and Performance of the JenaValve; NCT01598844) study. As for all other valve types, patients with very inhomogeneous calcification patterns may not be ideal candidates for this THV and the stent design essentially precludes the JenaValve implantation in certain morphologies, such as bicuspid aortic valves. Additionally, dilated aortic roots with annuli exceeding a diameter of 27 mm should be avoided to prevent valve dislocation or suboptimal function. Dilation of the ascending aorta is not a contraindication for the JenaValve prosthesis because valve implantation does not require extensive manipulation in the ascending aorta. However, a dilated ascending aorta exceeding 5 cm in diameter should be considered as an indication for surgical replacement of the aorta, at least in patients with acceptable operative risk.

Beyond that, and for the first time, this report highlights the feasibility of implanting a JenaValve prosthesis in patients with noncalcified aortic regurgitation. Despite the small number of patients, hemodynamic and clinical outcomes were promising in this series without any major procedure- or device-related adverse events during early follow-up. The straightforward implantation technique and excellent acute results may establish aortic regurgitation as a new indication for this device. However, before recommending broad application for noncalcified aortic regurgitation (off-label use), longer-term follow-up and larger patient numbers should be awaited. Study limitations. Despite the obvious limitations of this study, certain factors may make patients with pure aortic regurgitation particularly suitable for transcatheter approaches: First, no relevant aortic regurgitation was observed in this patient series after implantation, most probably due to the absence of annular calcifications allowing for optimal valve stent expansion. The implications of location and severity of aortic valve calcium for paravalvular regurgitation were thoroughly investigated (17) and a negative impact on outcome is well known (18), underlining the importance of this issue. Second, in aortic stenosis, catheter manipulations of the calcified aortic valve and the diseased aorta seem to be associated with an increase in stroke risk (19). The absence of aortic leaflet calcifications in many cases of aortic regurgitation may therefore lower the risk for thromboembolic events during TAVI, especially in the absence of prior balloon aortic valvuloplasty and rapid ventricular pacing. Third, the low radial force of the JenaValve THV in combination with the absence of balloon aortic valvuloplasty or the necessity for post-dilation may lower the risk for conduction disturbances related to the procedure if compared with the outcomes of patients after TAVI for calcified aortic valve stenosis (12).

An increase in aortic regurgitation has been described in patients undergoing LVAD therapy with subsequent recurrence of heart failure symptoms (20). Hence, 1 patient underwent TAVI prior to scheduled LVAD implantation to treat the moderate aortic regurgitation and allow for optimal hemodynamic support, making this a promising hybrid procedure for select heart failure patients.

Conclusions

To the best of our knowledge, this is the first report on the feasibility of TAVI in patients with noncalcified aortic regurgitation using the second-generation JenaValve THV. Promising procedural and early results have been accomplished in this small patient series but larger patient numbers and longer-term follow-up have to be awaited before drawing final conclusions.

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REFERENCES


Key Words: aortic regurgitation • JenaValve • transapical aortic valve implantation • transcatheter aortic valve implantation.

APPENDIX

For the supplemental video and its legend, please see the online version of this paper.