Summary

Patients with aortic stenosis and low left ventricular ejection fraction (LVEF) would benefit from transcatheter aortic valve replacement. However, the safety and efficacy of transcatheter aortic valve replacement in patients with aortic regurgitation and left ventricular dysfunction remains unknown.

We defined LVEF < 50% as left ventricular dysfunction. A total of 27 symptomatic patients with aortic regurgitation and ejection fraction < 50% underwent transcatheter aortic valve replacement using the J-Valve™ system (JieCheng Medical Technology Co, Ltd, Suzhou, China) in Zhongshan Hospital, Fudan University, from May 2014 to June 2019. Procedural and postoperative clinical outcomes were analyzed according to Valve Academic Research Consortium-2 (VARC-2) criteria.

All patients (eight females; 70.6 ± 7.1 years) were considered to be at least intermediate surgical risk and/or severe comorbidity precluding for surgical aortic valve replacement (logistic European System for Cardiac Operative Risk Evaluation, 16.8 ± 9.5%, range 4.6% to 37.9%) by a multidisciplinary heart team. Transapical implantations were successful in 26(96.3%) patients. All-cause mortality was 3.7% in the latest follow-up (25-590 days, median 369 days). Significant improvements in LVEF, left ventricular end-diastolic, and systolic dimensions were observed after procedure (from 40.3 ± 6.7% to 50.8 ± 10.5%, \( P < 0.001 \); from 65.1 ± 8.9 mm to 56.0 ± 9.6 mm, \( P = 0.002 \); from 52.2 ± 9.8 mm to 35.9 ± 13.4 mm, \( P < 0.001 \), respectively). No patient had aortic stenosis and paravalvular leak more than moderate and heart function improvement was obtained in the majority of patients at 1-year follow-up.

Transcatheter aortic valve replacement using the J-Valve™ system is a reasonable alternative for patients with aortic regurgitation and left ventricular dysfunction regarding promising short-term outcomes.

Key words: Aortic insufficiency, Self-expanding valve, LV function

Left ventricular dysfunction (LVD) is associated with an increased risk of poor periprocedural outcome in patients with severe aortic regurgitation (AR) undergoing surgical aortic valve replacement (SAVR).1,2 Previous studies have shown that transcatheter aortic valve replacement (TAVR) had revolutionized the treatment for patients with severe aortic stenosis (AS), who were ineligible or at high risk for SAVR.3,4 However, TAVR for treating predominant AR has not been admitted by Food and Drug Administration regarding compromising results yet. Since 2014, a novel TAVR system, the J-Valve™ (JieCheng Medical Technology Co, Ltd, Suzhou, China), has recently demonstrated excellent mid-term outcomes in the treatment of patients with predominant AR.5 Although several studies have demonstrated that the benefits of TAVR are also preserved among patients with AS and LVD, 6 little is known regarding the outcomes of TAVR in patients with predominant AR with LVD. This study aims to assess the potential benefit of TAVR in patients with AR and impaired ventricular function.

Methods

Population: On the basis of the 2014 American College of Cardiology/American Heart Association Guideline for the Management of Patients with Valvular Heart Disease, we defined left ventricular ejection fraction (LVEF) of < 50% as LVD in this study.6 We conducted a retrospective
analysis of all consecutive patients with LVD who underwent transapical TAVR with J-Valve™ for the treatment of severe AR with LVD from May 2014 through June 2019 in Zhongshan Hospital, Fudan University. Indications for TAVR were based on the relevant guidelines. All patients were at least intermediate surgical risk and/or had severe comorbidity precluding SAVR evaluated by a multidisciplinary heart team. The patients were followed and assessed with echocardiography before discharge and at 12 months after the procedure. The study protocol was approved by the Zhongshan Hospital ethics committee. All patients or their legal representatives were fully informed regarding the procedure and signed the written consent.

All patients underwent transthoracic echocardiography at baseline and follow-ups. The severity of paravalvular leakage and AR were assessed by an echocardiographer using semiquantitative parameters according to relevant guidelines. Left ventricular diameters, pulmonary artery systolic pressure, and LVEF were measured according to the current guideline. J-Valve™ system comprises a porcine bioprosthesis and a transapical delivery catheter. The bioprosthesis is supported by a self-expanding nitinol structure. (Figure 1) A set of 3 “U”-shaped nitinol hoops were designed around the valve as locators that can sit in three aortic sinuses individually to facilitate accurate positioning and fix the native valve. A loose connection between the locators and the frame differs from the JenaValve system and the Engager system (Medtronic, Minneapolis, Minnesota, USA).

Study outcomes: Study outcomes were evaluated at discharge and at 1 year after implantation according to the updated standardized endpoints defined by the VARC-2. The primary endpoint was all-cause mortality. Secondary endpoints included changes in LVEF and left ventricular (LV) size from baseline to 1-year follow-up, bleeding, stroke, kidney injury, valve dysfunction, and composite endpoints of early safety (before discharge) and clinical efficacy (1-year follow up).

Statistical analysis: Normally distributed continuous variables are presented as mean ± standard deviation. Non-normally distributed variables are presented as median and range, and categorical variables are presented as raw counts and percentages. Changes in LVEF, left ventricular end-systolic dimension (LVESD), and left ventricular end-diastolic dimension (LVEDD) from baseline to 1-year follow-up were compared using paired t test. All analyses were conducted using SPSS version 20.0 (IBM, Armonk, New York, USA).

Results

Baseline characteristics: A total of 27 symptomatic patients (eight female; mean age, 70.6 ± 7.1 years) with AR and LVD underwent TAVR between March 2014 and June 2019 in Zhongshan Hospital, Fudan University. The mean LVEF is 40.3 ± 6.7% (range from 27% to 49%). Three patients had congenital bicuspid aortic valves. The mean Logistic EuroScore was 16.8% ± 9.5%. A detailed description of the cohort characteristics is listed in Table I.

Procedural details and in-hospital outcomes: A detailed description of the J-Valve™ system and a protocol of the device implantation have been previously provided. Valve position and hemodynamics were assessed instantly after device implantation by both transesophageal echocardiography and angiography. The implantations of the J-Valve™ prosthesis were successful in all patients without cardiopulmonary bypass. There was no intra-aortic regurgitation or stenosis of the implanted valves immediately after the procedure in any of these cases. Additionally, we found that no coronary obstructions or annular ruptures occurred. Only one patient had moderate paravalvular leakage (PVL) and died of low cardiac output 25 days after the operation. One patient needed transfusion for pre-procedural anemia rather than major or life-threatening bleeding. One patient required surgery due to apical bleeding. Three patients developed acute kidney injury (stage 1), and the renal function recovered before discharge. One patient developed a complete atrioventricular block 9 months after the procedure. No patient experienced myocardial infarction, neurologic complications, or any vascular complications during 1-year follow-up. No patient required a valve-related reintervention during follow-up. The percentage of patients with New York Heart Association (NYHA) functional class III or IV decreased from 92.6% to 3.7% at 1 year after surgery. (Figure 2)

Echocardiography assessments: Echocardiographic examinations were performed at baseline and 1-year post-treatment. Figure 3 illustrates the changes in LVEF, LVESD, and LVEDD at baseline and follow-up. LVEF
significant improvement occurred in patients with LVD (from \(40.3\% \pm 6.7\%\) at baseline to \(50.8\% \pm 10.5\%\) at 1-year follow-up, \(P < 0.001\)). Additionally, the cohort had a significant decrease in LVEDD (from \(65.1 \pm 8.9\) mm at baseline to \(56.0 \pm 9.6\) mm at 1-year follow-up, \(P = 0.002\)) and LVESD (from \(52.2 \pm 9.8\) mm at baseline to \(35.9 \pm 13.4\) mm at 1-year follow-up, \(P < 0.001\)).

### Discussion

Although several previous studies had implicated that reduced LVEF was not associated with increased short- and long-term mortality after TAVR for severe AS, the experience of TAVR for AR in patients with LVD remains limited. To our best knowledge, the present study is the largest cohort about TAVR for this specific population.

The major findings of this study can be summarized as follows: 1) TAVR using the J-Valve™ system in patients with AR and LVD is technically feasible and safe via the transapical route. The periprocedural mortality rate was only 3.7%, which was much lower than that estimated by conventional surgical risk scores. 2) Symptom relief was demonstrated in the majority of the patients at 1-year follow-up (frequency of NYHA \(\geq III\) from 92.6% at baseline to 3.7% at 1-year follow-up, \(P < 0.001\)). 3) Patients with LVD would get significant improvement in LV geometry after TAVR and LV geometry would also be significantly improved.

A population-based study in China reported the local prevalence of symptomatic aortic regurgitation as approximately 1.24% in individuals over 60 years old. The characteristic progression of chronic AR has been well described, and the outcomes of patients with AR and LVD are poor. Patients with chronic AR may be asymptomatic for long periods of time, during which eccentric ventricular hypertrophy progressively develops in response to a combination of increased LV preload and afterload. Once deceleration has been established, the appearance of symptoms or evidence of LV impairment is strongly associated with clinical events, which may occur in rapid succession. Additionally, the long asymptomatic time period of AR suggests that older patients may have a lower LVEF at diagnosis, further increasing the

**Table I. Baseline Clinical Parameters**

| Variable                              | LVD, n = 27 |
|---------------------------------------|-------------|
| Age, mean ± SD (years)                | 70.6 ± 7.1  |
| Female, n (%)                         | 8 (29.6)    |
| Body mass index, mean ± SD (kg/m²)    | 22.2 ± 2.3  |
| NYHA class ≥ III, n (%)               | 25 (92.6)   |
| Logistic EuroScore, mean ± SD (%)     | 16.8 ± 9.5  |
| Logistic EuroScore, range             | 4.6 to 37.9 |
| Hypertension, n (%)                   | 14 (51.9)   |
| Diabetes mellitus, n (%)              | 2 (7.4)     |
| Peripheral vascular disease, n (%)    | 3 (11.1)    |
| Cerebrovascular disease or stroke, n (%) | 6 (22.2)   |
| Atrial fibrillation, n (%)            | 6 (22.2)    |
| Chronic lung disease, n (%)           | 8 (29.6)    |
| Serum creatinine > 200 μmol/L, n (%)  | 4 (14.8)    |
| Anemia, n (%)                         | 11 (37.3)   |
| Coronary artery disease, n (%)        | 6 (22.2)    |
| Previous cardiac surgery, n (%)       | 3 (11.1)    |

**Etiology**

- Degenerative, n (%) 20 (74.1)
- Bicuspid aortic valve, n (%) 3 (11.1)
- Inflammatory aortitis, n (%) 4 (14.8)
- Aortic stenosis > mild 0
- Aortic regurgitation grade, n (%)
  - Moderate 0
  - Severe 27 (100)
- MR moderate or greater, n (%) 7 (25.9)
- PASP, mean ± SD (mmHg) 42.4 ± 12.8
- LVEF, mean ± SD (%) 40.3 ± 6.7
- LVEF < 40%, n (%) 9 (33.3%)
- LVEDD, mean ± SD (mm) 65.1 ± 8.9
- LVESD, mean ± SD (mm) 52.2 ± 9.8

**Table II. Procedural Details and In-Hospital Outcomes**

| Details or outcomes                              | LVD, n = 27 |
|--------------------------------------------------|-------------|
| Aortic annulus diameter                          |             |
| MDCT perimeter-derived, mean ± SD (mm)           | 26.1 ± 2.5  |
| THV size, n (%)                                  |             |
| 25 mm                                            | 3 (11.1)    |
| 27 mm                                            | 13 (48.1)   |
| 29 mm                                            | 11 (40.7)   |
| “Oversize” strategy based on MDCT perimeter-derived, mean ± SD (%) | 2.3 ± 6.7 |
| Contrast agent, mean ± SD (mL)                   | 70.8 ± 21.1 |
| Device success, n (%)                            | 26 (96.3)   |
| Balloon dilation, n (%)                           | 0           |
| Conversion to open-heart surgery, n (%)          | 0           |
| Cardiopulmonary bypass, n (%)                    | 0           |
| Prosthesis malposition, n (%)                    | 0           |
| Aortic valve deployment, n (%)                   | 0           |
| Coronary obstruction, n (%)                      | 0           |
| All-cause mortality, n (%)                       | 1 (3.7)     |
| Cardiac mortality, n (%)                         | 1 (3.7)     |
| Myocardial infarction, n (%)                     | 0           |
| Annulus rupture, n (%)                           | 0           |
| Acute kidney injury, n (%)                       | 0           |
| Stage 1                                          | 3 (11.1)    |
| Stage 2 or 3                                     | 0           |
| Bleeding requiring surgery, n (%)                | 1 (3.7)     |
| Transfusion, n (%)                               | 1 (3.7)     |
| New permanent pacemaker, n (%)                   | 0           |
| Post-operation TEE outcomes                     |             |
| Mean aortic valve gradient, mean ± SD (mmHg)     | 5.2 ± 3.4   |
| Paravalvular regurgitation, n (%)                |             |
| None or trace                                    | 23 (85.2)   |
| Mild                                             | 3 (11.1)    |
| Moderate                                         | 1 (3.7)     |
| Severe                                           | 0           |
| Transvalvular aortic regurgitation, n (%)        |             |
| None or trace                                    | 27 (100%)   |
| ≥ Mild                                           | 0           |

LVD indicates left ventricular dysfunction; MDCT, multidetector computed tomography; THV, transcatheter heart valve; and TEE, transesophageal echocardiography.
surgical risk in the elders.

Recent guidelines have not recommended TAVR for surgical risk in the elders.

Table III. One-Year Outcomes

| Outcomes at 1 year | LVD, n = 27 |
|--------------------|-------------|
| All-cause mortality, n (%) | 1 (3.7) |
| Cardiac mortality, n (%) | 1 (3.7) |
| Myocardial infarction, n (%) | 0 |
| Stroke, n (%) | 0 |
| Bleeding complications, n (%) | 0 |
| Vascular complications, n (%) | 0 |
| New permanent pacemaker, n (%) | 1 (3.7) |
| Re-intervention, n (%) | 0 |
| Valve thrombosis, n (%) | 0 |
| NYHA class ≥ III, n (%) | 1 (3.7) |

Echocardiographic variable

| Mean aortic valve gradient, mean ± SD (mmHg) | 8.4 ± 2.9 |
| Paravalvular regurgitation, n (%) |  |
| None or trace | 23 (88.5) |
| Mild | 3 (11.5) |
| Moderate | 0 |
| Severe | 0 |
| Transvalvular aortic regurgitation, n (%) |  |
| None or trace | 26 |
| ≥ Mild | 0 |
| MR moderate or greater, n (%) | 1 (3.7) |
| LVEF < 40%, n (%) | 2 (7.7) |
| LVEF, mean ± SD (%) | 50.8 ± 10.5 |
| LVEDD, mean ± SD (mm) | 56.0 ± 9.6 |
| LVESD, mean ± SD (mm) | 35.9 ± 13.4 |

LVD indicates left ventricular dysfunction; NYHA, New York Heart Association; MR, mitral regurgitation; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic dimension; and LVESD, left ventricular end-systolic dimension.

the treatment of pure AR.11 Presently, the mainstream TAVR devices are originally designed for AS relying on oversized and radial forces of the prosthesis to anchor to the calcific aortic valve. Nonetheless, these technologies for isolated AR remain challenging because of dilated aortic annulus and lack of calcification. The Jena valve™ prosthesis (Jena valve Technology, Inc., Munich, Germany) is the first transcatheter valve designed for the treatment of pure AR by using supporting arms that can help locate and fix the prosthesis at the appropriate level in the aortic annulus.27 This smart design plays an important role in the treatment of AR. The J-Valve™ device separates locators from the prosthetic structure using wires to connect them so that its arms can be fully expanded during positioning, which differs from the Jena valve™ prosthesis. Consequently, the 1-year multicenter outcomes of TAVR for AR with the J-Valve™ devices showed extremely low mortality (4.7%) and morbidity.10 Additionally, a new transfemoral delivery system, Trilogy™ (Jenavalve Technology, Inc., Munich, Germany), has earned CE approval for the treatment of AS and pure AR in May 2021. Thus, TAVR using specific devices will also revolutionize the treatment of patients with isolated AR in the near future.

Presently, there are relatively few applications of TAVR for pure AR. We have conducted the exploring treatment for patients with AR and LVD, showing good short-term results. In our study, only one patient with end-stage cardiac dysfunction whose pre-operative LVEF was 27%, died of congestive heart failure 25 days after surgery. The patient had an enlarged annulus (29 mm) and bicuspid aortic valve, leading to moderate PVL after implantation and subsequent heart failure. Additionally, the majority of patients (25 of 26) had significant relief in symptoms of exertional dyspnea and improvement in exer-
exercise intolerance. But one patient who had been diagnosed with severe AR and LVD for 11 years before procedure was still in NYHA class III at 1-year follow-up. The patient had preprocedural LVEF of 27% and large LV size (LVESD 74 mm and LVEDD 81 mm) and a history of recurrent rehospitalization due to chronic heart failure. Long-term AR and LVD contribute to irreversible cardiac remodeling (LVESD 71 and LVEDD 79 mm at 1-year follow-up), leading to less benefit from TAVR in that patient. Generally, the short-term outcomes of this high-risk cohort were acceptable, which might imply that a low LVEF may not be a contraindication of TAVR for AR. Nonetheless, the optimal timing of TAVR for such patients remains unknown and requires further study.

Similar to SAVR,29 patients with LVD had significant improvement in LVEF and LV geometry at 1-year follow-up after TAVR. Furthermore, six of seven patients had amelioration of mitral regurgitation from moderate or greater to mild or trace owing to reduction in LV size after implantation. However, it was notable that not all patients with LVD were afforded improved postoperative LVEF. One patient had an obvious decrease in LVEF (from 43% at baseline to 27% 1 year after). The patient had a large LV size (LVEDD 69 mm and LVESD 54 mm at baseline) but without a history of myocardial infarction and dilated cardiomyopathy. The bioprosthesis performance is good without PVL, and the mean transvalvular gradient is 10 mmHg. The patient had a complete right bundle branch block before TAVR and developed a left anterior fascicular block after the procedure. Nevertheless, the patient failed to implant a permanent pacemaker. Moreover, it would be reasonable that the arrhythmia caused the worsening of LVEF.

With developments in palliative treatment and surgical techniques, the clinical consensus has shifted from the viewpoint that patients with low LVEF who underwent SAVR would have worse outcomes to the perspective that patients with low LVEF can be operated on with very low morbidity and mortality and similar postoperative outcomes and survival as patients with normal LV function.29) Consistent with this notion, our study reports that a less invasive surgery, TAVR, can be performed in patients with LVD as a reasonable alternative. Additionally, this finding both supports and extends the results of previous studies, which have shown the benefits of both TAVR and SAVR in patients with severe AR. To confirm our findings and to uncover more effective parameters to predict the clinical outcome of these patients, further studies are still necessary.

Limitations: This study had several limitations. Besides the inherent bias of retrospective studies, our study had a small sample size for short-term follow-up, as it only included a total of 27 patients and followed for approximately 1 year. The small sample size of our study limited the stratification of LVD, as only a few patients were evaluated by dobutamine stress echocardiography. Thus, future studies will require larger sample sizes to facilitate more granular stratification of LV dysfunction (e.g., severe, mild to moderate, and normal).

Disclosure

Conflicts of interest: The authors have declared no competing interests.

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