Transapical Transcatheter Valve-in-Valve Implantation for Failed Mitral Valve Bioprosthesis

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ABSTRACT: **Background:** The rate of mitral bioprosthesis implantation in clinical practice is increasing. Transcatheter valve-in-valve implantation has been described for high risk patients requiring redo valve surgery.

Objectives: To report our experience with transapical valve-in-valve implantation for failed mitral bioprosthesis.

Methods: Since 2010, 10 patients have undergone transapical valve-in-valve implantation for failed bioprosthesis in our center. Aortic valve-in-valve implantation was performed in one of them and mitral valve-in-valve implantation in nine. Mean age was 82 ± 4 years and 6 were female (67%). Mean time from original mitral valve (MV) replacement to valve-in-valve procedure was 10.5 ± 3.7 years. Follow-up was completed by all patients with a mean duration of 13 ± 12 months.

Results: Preoperatively, all patients presented with significant mitral regurgitation, two with mitral stenosis due to structural valve failure. All nine patients underwent successful transapical valve-in-valve implantation with an Edwards Sapien™ balloon expandable valve. There was no in-hospital mortality. Mean and median hospital duration was 15 ± 18 and 7 days respectively. Valve implantation was successful in all patients and there were no major complications, except for major femoral access bleeding in one patient. At last follow-up, all patients were alive and in NYHA functional class I or II. Echocardiography follow-up demonstrated that mitral regurgitation was absent or trivial in seven patients and mild in two. At follow-up, peak and mean gradients changed from 26 ± 4 and 8 ± 2 at baseline to 16.7 ± 3 and 7.3 ± 1.5, respectively.

Conclusions: Transcatheter transapical mitral valve-in-valve implantation for failed bioprosthesis is feasible in selected high risk patients. Our early experience with this strategy is encouraging. Larger randomized trials with long-term clinical and echocardiographic follow-up are recommended.

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KEY WORDS: transcatheter aortic valve implantation (TAVI), valve in valve, transapical valve implantation, mitral bioprosthesis, minimally invasive surgery

Since 2002, when Cribier et al. [1] described the first successful transcatheter aortic valve implantation (TAVI), the treatment of valvular heart disease has undergone significant evolution. Refinements in TAVI techniques and technology with promising early and mid-term results have raised interest to utilize this procedure in more complex situations [2-5].

Over the last two decades the clinical use of bioprosthetic valves in the treatment of valvular heart disease has been growing steadily, even in younger patients [6]. This has led to a substantial increase in the number of patients requiring redo mitral valve surgery as a result of degenerated bioprosthesis. The high morbidity and mortality associated with reoperative valve surgery, especially in older patients with co-morbidities, are well recognized and tend to be even more significant regarding mitral valve surgery [7-9]. Less invasive procedures, such as the transcatheter technique, might be the solution for some of these high risk patients.

Although there are currently several devices for transcatheter heart valves for the aortic valve, there is no designated device for the mitral valve, which has a much more complex anatomy and structure. However, in 2008, Kempfert and fellow-researchers [10] demonstrated the successful implantation of a mitral valve in valve in a sheep model, and in 2009 Cheung et al. [11] performed a transcatheter mitral valve-in-valve implantation (TAMVI) for a degenerated bioprosthesis in a human subject using the transapical approach. Since then, while various reports have described small case series of successfully performed TAMVI, there is still insufficient information concerning safety, feasibility and a definitive clinical course throughout follow-up.

We report a series of nine patients with a deteriorated mitral valve bioprosthesis who underwent TAMVI, and describe our experiences with this novel technique.

PATIENTS AND METHODS

Since January 2010, 70 patients have been treated with transapical transcatheter valve implantation at our medical center. Ten patients within this cohort presented with a deteriorated valve bioprosthesis in the aortic or mitral position. Of them, nine underwent mitral valve-in-valve implantation. All of them had undergone previous mitral valve replacement with biological

valve prostheses and were symptomatic with advanced heart failure: New York Heart Association (NYHA) functional class III or IV. Patients were assessed by a multidisciplinary heart team of cardiac surgeons and cardiologists and were deemed unsuitable for reoperative mitral valve surgery because of excessive risk.

PROCEDURES

All procedures were performed by a multidisciplinary heart team comprising cardiac surgeons, cardiologists and cardiac anesthesiologists in a specially equipped hybrid operating room. In all cases we used the transapical approach and implanted an Edwards Sapien™ transcatheter porcine heart valve (Edwards Lifesciences, Irvine, CA, USA). Internal diameter data were obtained from the valve manufacturer's official publication, and confirmation of size was performed by transesophageal echocardiography (TEE) and electrocardiography (ECG) gated computed tomography (CT) scan.

All patients underwent general anesthesia with single-lumen intubation. The transapical approach was performed with left anterolateral mini-thoracotomy at the fifth or sixth intercostal space. After placement of ventricular pacing wires, two circular Teflon-pledgetted sutures were placed to secure the apex at the end of the procedure. After puncture of the apex, a 0.35 J-tipped wire was inserted followed by the introduction of a 6F catheter across the mitral bioprosthesis. Subsequently, an Amplatz extra-stiff wire was exchanged and passed into the left atrium. The 6F catheter was then withdrawn and the delivery system was inserted over the wire The reversely crimped Sapien™ valve was placed in the mitral position under rapid ventricular pacing of 160–200 beats/min during deployment to prevent excessive motion. None of the procedures required balloon valvuloplasty.

Valve implantations and confirmation of the precise final positioning before deployment were aided by 2D and 3D transesophageal echocardiographic analysis and fluoroscopy [Figure 1]. Echocardiographic analysis was used to confirm valve-in-valve stability and paravalvular leakage, as well as assess hemodynamics [Figure 1].

STATISTICAL ANALYSIS

Statistical analysis was performed with JMP 9.0 Software (SAS Institute Corp, Cary, NC, USA). Numeric variables are expressed as mean with standard deviation of the mean or median with interquartile range (IQR) owing to the limited number of cases.

RESULTS

BASELINE CHARACTERISTICS

All patients were symptomatic with NYHA functional class III or IV heart failure. Mean age was 82 ± 4 years and six patients were female. Baseline demographics of all patients are presented in Table 1. All patients were considered high risk for conventional redo mitral valve replacement due to advanced age, comorbidities or frailty. Mortality risks were calculated using the European System for Cardiac Operative Risk I and II and the Society of Thoracic Surgeons score 25.5 ± 9.1% (15.14–41.39%), 11 ± 8% (4–28.3%) and 12 ± 4% (5.6–19.3%) respectively.

PREOPERATIVE ECHOCARDIOGRAPHIC FINDINGS

A variety of mitral bioprostheses were treated at a median of 10.5 years (5–15 years) post-mitral valve replacement. Bioprosthesis failure was due to mitral regurgitation in six, stenosis in two, and one patient who had combined regurgitation and stenosis. For the two patients with severe stenosis, average peak and mean transvalvular pressure gradients reached 31.5 mmHg and 8.5 mmHg, respectively. Table 2 summarizes data prior to the implanted bioprosthesis and the actual implanted transcatheter valve.

PROCEDURAL OUTCOMES

Device success was 100% according to the Valve Academic Research Consortium-2 (VARC-2) definitions [12]. There was no intra-procedural mortality and no procedure-associated complications were recorded. Mean procedure time averaged 137.5 ± 22.83 minutes. Intraoperative TEE revealed good prosthesis placing and function. The transmitral valve gradients decreased from 26 ± 4 and 8 ± 2 mmHg (peak and

Figure 1. Echocardiogram and angiogram during the procedure. Mitral valve-in-valve implantation of an Edwards Sapien™ valve into degenerated bioprosthesis valve. **[A]** Echocardiographic and **[B]** angiographic imaging of the Sapien™ valve within the degenerative mitral bioprosthesis prior to inflation. **[C & D]** echocardiographic and angiographic imaging after valve deployment

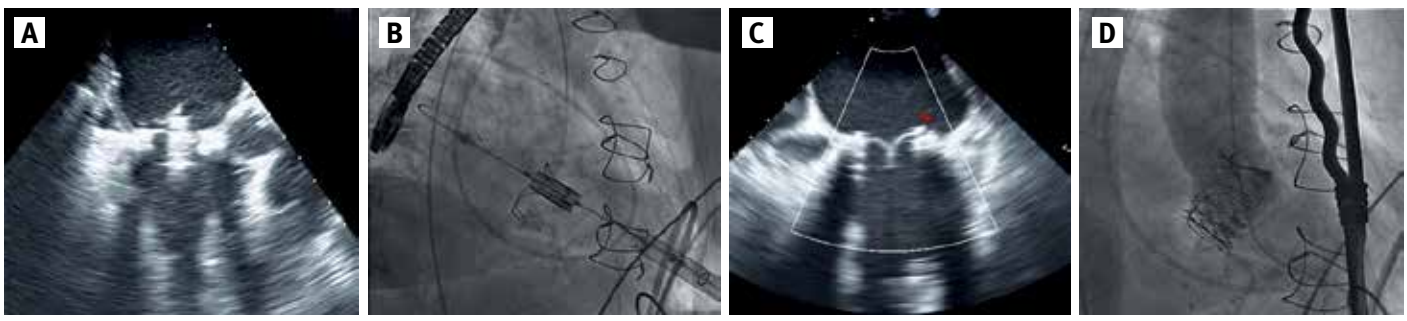

Table 1. Patient characteristics

	Patients (n=9)
Gender (Male)	3 (33%)
Age (years)	82 ± 4
Hypertension	6 (86%)
Hypercholesterolemia	7 (100%)
Diabetes	4 (44%)
Peripheral occlusive disease	0
Chronic obstructive lung disease	2 (22%)
Chronic renal failure (GFR ‹ 60 ml/min)	2 (22%)
Coronary heart disease	4 (44%)
Previous stroke	3 (33%)
Permanent atrial fibrillation	3 (42%)
Previous coronary artery bypass graft surgery	4 (44%)
NYHA Functional Class III/IV	9 (100%)
EuroScore I mortality risk	25.5 ± 9.1%
EuroScore II mortality risk	11 ± 8.6%
STS mortality risk	12 ± 4%

All values are expressed as mean ± SD or n (%)

GFR = glomerular filtration rate, EuroScore = European System for Cardiac Operative Risk Evaluation, NYHA = New York Heart Association, STS = Society of Thoracic Surgeons

mean) to 17 ± 6 and 8 ± 3 mmHg, respectively ($P < 0.05$). Two patients (# 1 and 7) presented with elevated postoperative peak transvalvular pressure gradients (29/14 and 22/10 mmHg, respectively). In none of the cases was hemodynamic compromise encountered, and support with cardiopulmonary bypass or conversion to a sternotomy was not necessary. There were no cases of valve embolization or inappropriate valve positioning, and none of the patients had any mitral regurgitation at the end of the procedure. Data regarding prior implanted prostheses and actual implanted transcatheter valves are presented in Table 2.

IN-HOSPITAL COURSE

The postoperative course was uneventful in eight of the nine patients. One patient (# 7) experienced major postoperative retroperitoneal bleeding from the iliac artery due to leakage from the closing device. The patient underwent covered stent implantation to control the bleeding. Her situation was later complicated by acute lung injury and she required prolonged ventilation. A tracheostomy was performed and she was discharged from hospital after she had been decannulated.

There was no in-hospital or 30 day mortality. No apical hemorrhaging was encountered, and no reoperation for bleeding or tamponade was required. The median stay in the intensive care unit was 2 days (IQR 2–42 days). With the exception of patient # 7, neither postoperative coagulopathy nor major bleeding was observed. All patients had stable hemodynamics, and no patient required mechanical circulatory support (i.e., intraaortic balloon pump). All patients (excluding # 7) were weaned from ventilation after 25 ± 23 hours. No patient experienced respiratory failure later that required reintubation. The median length of stay was 7 days (IQR 4–58 days). Acute kidney injury of stage 2 or higher, according to VARC-2 criteria, was not documented. None of the patients suffered stroke, and none experienced major atrioventricular conduction disturbances that required permanent pacemaker insertion. Wound healing was uneventful in all patients except for patient # 6 who suffered from superficial wound infection at the thoracotomy incision line. All patients were discharged on dual antiplatelet therapy (aspirin 100 mg and clopidogrel 75 mg daily) for 6 months. Table 3 summarizes the postoperative data.

Table 2. Preoperative data and echo and peri-operative echo results

	Prior implanted bioprosthesis				Implanted bioprosthesis	Peri-operative echo results	
Patient #	Years after MVR	Size (mm)	Failure	Peak/mean pressure gradient (mm Hg)	Sapien™ size	Peak/mean pressure gradient (mm Hg)	MR grade
1	15	27	Regurgitation	25/6	26	29/14	Trivial
2	11	27	Regurgitation	24/9	29	17/5	Trivial
3	10	27	Regurgitation	25/7	26	12/7	Trivial
4	12	29	Regurgitation	24/7	29	15/6	Trivial
5	5	27	Regurgitation	24/8	26	15/9	Trivial
6	14	29	Regurgitation	22/8	26	12/6	Trivial
7	8	27	Stenosis	28/12	26	22/10	Trivial
8	13	29	Stenosis	35/5	26	14/5	Trivial
9	6	27	Regurgitation + stenosis	28/12	26	20/6	Trivial

Table 3. Early results and follow-up data

	Patients (n=9)
Mortality	0
Stroke	0
Pacemaker	0
Ventilation time (hours)*	25 ± 22
ICU time (median) (days)	2
Hospital stay (median) (days)	7
Follow-up time (months)	13 ± 12
Late mortality	0
Sub-acute endocarditis	0
Thromboembolisem	0
Major bleeding	1(11%)
MV peak/mean gradient	17 ± 3/7 ± 1.5
MR ≤ mild	9 (100%)

*Excluding patient # 7
ICU = intensive cardiac unit, MV = mitral valve, MR = mitral regurgitation

FOLLOW-UP DATA

Follow-up was completed by 100% of the patients, with a mean clinical follow-up time of 13 ± 12 months (IQR 2–36 months). No patient died during this period. At the most recent follow-up all patients were in NYHA functional class I or II. The mean echocardiographic follow-up time was 13 ± 11 months (IRQ 1–36 months). The echo results demonstrated good valvular function in all patients, and no structural valve deterioration was detected. The peak and mean transvalvular pressure gradients decreased to 16 ± 3 and 7 ± 1.5 mmHg, peak and mean respectively. Before the intervention left ventricular ejection fraction was 61 ± 5%, and after the valve implantation 54 ± 9%. No anticoagulation-dependent complications were recorded.

DISCUSSION

During the last decade transcatheter therapy for aortic stenosis in high risk patients has provided a significant platform for the advancement of catheter-based treatment of several structural valve diseases. Since 2007, several studies have demonstrated the feasibility of the valve-in-valve concept for deteriorated aortic bioprostheses. Although the transatrial approach to the mitral valve proved to be difficult, conversion to the transapical approach was adopted in 2008 by Kempfert et al. [10] initially in a sheep model, followed in 2009 by Cheung et al. [11] who performed an implantation in humans. Since then only a few reports have focused on this new and promising approach [13-15], with a few case reports of the percutaneous transjugular transseptal route [16] which is used for emergency cases only. Therefore, evidence regarding technical aspects as well as clinical and long-term outcome is still of particular interest.

TECHNICAL ASPECTS OF TAMVI

In accord with previous series reported by Cheung and team (11 patients) [11], Seiffert and co-authors (6 patients) [6] and Wilbring et al. (7 patients) [15], we did not experience any procedural issues with TAMVI. The procedural success rate was 100% in all reported cases [13-15]. We did not encounter major apical bleeding, nor did the authors of the above mentioned series, except for Seiffert et al. [6] who reported major apical bleeding in two of their six patients. As the mitral valve is typically oriented toward the apex, the transapical approach allows a direct and co-axial access to the mitral valve. In our study, fluoroscopy and TEE were used to position the valve stent within the mitral prosthesis. Fluoroscopy is most useful in cases where the prosthesis incorporates a radiopaque sewing ring, which indicates the landing zone for the new valve. If there are only minimal radiolucent markers within the prosthesis, guidance of the valve can be successfully carried out by TEE. Actually, unlike routine TAVI or valve-in-valve procedures for degenerated aortic bioprostheses, the administration of a contrast agent is not necessary for TAMVI. All patients experienced a reduction of mitral regurgitation to grade 0 or I after implantation of the Sapien™ valve, accompanied by excellent prosthesis function and significantly reduced transvalvular pressure gradients. Nevertheless, the transvalvular pressure gradients were high immediately after the procedure in patients 1 and 7, but were reduced later on, as seen in the echocardiographic follow-up examinations. Our results are comparable with those observed by other groups [13-15].

In our series we used 26 and 29 mm valves. Other series reported labeled sizes from 23 to 29 mm. The key variable for sizing the Edwards Sapien™ valve was the internal diameter given by the manufacturer. TEE and CT were used to confirm the internal diameter of the degenerated bioprosthesis as well as provide further insights on bioprosthesis features (e.g., thrombi, vegetation, calcifications). The internal diameter measured and that given by the manufacturer can differ significantly, presumably because of calcification or pannus formation of the tissue leaflets. If there was a significant difference between the manufacturer's specifications and the one we measured, justifying a larger prosthesis, then we tended to choose the larger Sapien™ valve.

POSTOPERATIVE COURSE AND CLINICAL OUTCOME

In our study the postoperative course was substantially uneventful. Two procedure-associated complications were observed. Patient # 6 suffered from wound infection in the thoracotomy incision line; in patient 7 major bleeding from the femoral access necessitated blood products and respiratory failure occurred later which led to prolonged ventilation

requiring a tracheostomy. Bearing in mind the patients' ages and morbidities, most of them had a quick postoperative recovery, in accord with other reports [13-15].

There was no hospital mortality in our series. The in-hospital mortality rate in the series of Cheung et al. [13], Seiffert et al. [14] and Wilbring et al. [15] was 4.3% (1/23), 16.7% (1/6) and 14.3% (1/7) respectively. Taking into account the limitations of a mid-term follow-up period (13 ± 12 months) as in the present series, no patient died during follow-up. Cheung and team [13] provided a median follow-up of 753 days and a survival rate of 90.6%. In the present study and comparable series, all surviving patients experienced a significant improvement in NYHA functional class during follow-up [13-15].

CONCLUSIONS

Our series is small and represents our early experience with transcatheter transapical mitral valve-in-valve implantation. Still, our study demonstrates that transcatheter transapical mitral valve-in-valve implantation for failed bioprosthesis is feasible in selected high risk patients. Clinical and hemodynamic outcomes were good at mid-term follow-up. The post-procedure gradients across the mitral valve were elevated and could impact patient functional class, long-term survival, and quality of life. Larger series, randomized trials and long-term clinical and echocardiographic follow-up are recommended. For now, we propose that for patients at high risk for reoperative mitral valve surgery, transapical mitral valve in valve should be considered an option.

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References

1. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcificaortic stenosis: first human case description. *Circulation* 2002; 106: 3006-8.
2. Cribier A, Eltchaninoff H, Tron C, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol* 2006; 47: 1214-23.
3. Webb JG, Pasupati S, Humphries K, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. *Circulation* 2007; 116: 755-63.
4. Webb JG, Altwegg L, Boone RH, et al. Transcatheter aortic valve implantation: impact on clinical and valve-related outcomes. *Circulation* 2009; 119: 3009-16.
5. Finkelstein A, Birati EY, Abramowitz A, et al. Transcatheter aortic valve implantation: a single-center experience of 300 cases. *IMAJ* 2013; 15 (10): 613-16
6. Seiffert M, Conradi L, Baldus S, et al. Transcatheter mitral valve-in-valve implantation in patients with degenerated bioprostheses. *J Am Coll Cardiol Cardiovasc Interv* 2012; 5: 341-9.
7. Jones JM, O'kane H, Gladstone DJ, et al. Repeat heart valve surgery: risk factors for operative mortality. *J Thorac Cardiovasc Surg* 2001; 122: 913-18.
8. Maganti M, Rao V, Armstrong S, Feindel CM, Scully HE, David TE. Redo valvular surgery in elderly patients. *Ann Thorac Surg* 2009; 87: 521-5.
9. Houser S, Salomon J, Carias N, Hashmi F, Lehmann T, Chawla S. Predictors of perioperative morbidity and mortality in repeat valve replacement: a seven-year experience. *Conn Med* 1993; 57: 715-20.
10. Kempfert J, Blumenstein JM, Borger MA, et al. Minimally invasive off-pump valve-in-a-valve implantation: the atrial transcatheter approach for re-operative mitral valve replacement. *Eur Heart J* 2008; 29: 2382-7.
11. Cheung A, Webb JG, Wong DR, et al. Transapical trans catheter mitral valve-in-valve implantation in a human. *Ann Thorac Surg* 2009; 87: e18-20.
12. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg* 2013; 145: 6-23.
13. Cheung A, Webb JG, Barbanti M, et al. 5-year experience with transcatheter transapical mitral valve-in-valve implantation for bioprosthetic valve dysfunction. *J Am Coll Cardiol* 2013; 61: 1759-66.
14. Seiffert M, Franzen O, Conradi L, et al. Series of transcatheter valve-in-valve implantations in high-risk patients with degenerated bioprostheses in aortic and mitral position. *Catheter Cardiovasc Interv* 2010; 76: 608-15.
15. Wilbring M, Alexiou K, Tugtekin SM, et al. Transapical transcatheter valve-in-valve implantation for deteriorated mitral valve bioprostheses. *Ann Thorac Surg* 2013; 95: 111-17.
16. Schaefer U, Frerker C, Busse C, Kuck K-H. Transjugular and transseptal treatment of a degenerated mitral valve prosthesis with a balloon-expandable biological valve. *Heart Lung Circ* 2012; 21: 836-40.