Pushing the limits—further evolutions of transcatheter valve procedures in the mitral position, including valve-in-valve, valve-in-ring, and valve-in-native-ring

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Objective: Transcatheter heart valve (THV) procedures are constantly evolving. We report our experience with valve-in-valve, valve-in-ring, and direct-view valve-in-native-ring implantation in the mitral position.

Methods: Fourteen patients undergoing THV implantation in the mitral position were included. Clinical and postoperative data, including echocardiography and further follow-up, were analyzed.

Results: Ten valve-in-valve and 2 valve-in-ring procedures were successfully performed using the transapical access route. For the third valve-in-ring procedure we used an antegrade left-atrial access via right anterolateral minithoracotomy. In 1 patient surgical mitral valve replacement was planned. Intraoperatively, the annulus appeared severely calcified and regular implantation of a bioprosthesis was not possible. As a last resort, a 29-mm Sapien XT valve (Edwards Lifesciences Inc, Irvine, Calif) was implanted under direct view. The initial result was satisfactory, but on the first postoperative day relevant paravalvular regurgitation occurred. Subsequently, the valve was fixed to an atrial cuff by 1 running suture. In this series 27-, 29-, and 31-mm bioprostheses and 28- and 30-mm annuloplasty rings were treated with 26- or 29-mm Sapien XT valves. Postoperative echocardiography on day 10 and after 6 weeks revealed good prosthesis function in all cases. In 2 valve-in-valve patients who solely received anticoagulation therapy with acetylsalicylic acid, signs of beginning valve thrombosis occurred after 8 weeks and 3 months, respectively. During further course, valve function was normalized using warfarin therapy.

Conclusions: Our results demonstrate feasibility of valve-in-valve and valve-in-ring THV procedures in the mitral position. Permanent anticoagulation therapy with warfarin seems to be necessary to prevent valve dysfunction. THV implantation in a calcified native mitral ring for bailout seems not to be reproducible and thus cannot be recommended. (*J Thorac Cardiovasc Surg* 2014;147:210-9)

The development of transcatheter heart valve (THV) procedures has induced profound changes in the treatment of valvular heart disease during the past decade.¹⁻⁴ The promising results of transcatheter aortic valve implantation (TAVI) procedures for symptomatic aortic valve stenosis in selected high-risk patients led to stepwise expansion of their possible fields of application.¹ Beside its originally designated application, the TAVI concept was successfully expanded to use in patients with history of previous cardiac surgery and for the treatment of degenerated aortic or mitral valve bioprostheses.^{2,3,5} Several studies

have described promising results of the valve-in-valve concept for deteriorated bioprostheses.^{1-3,6} Since Cheung and colleagues⁷ first demonstrated feasibility of mitral valve-in-valve implantation in a human in 2009, further studies have likewise praised the transapical approach to allow direct and coaxial access to the mitral valve.^{1,2} Those developments allowed the treatment of degenerated bioprostheses by THV procedures to become an elegant and viable alternative.^{1,5} But what about failed valve repairs in high-risk patients?

Despite excellent results reported for mitral valve repair, the late recurrence of mitral regurgitation is described in up to 30% of patients with ischemic mitral regurgitation.⁸⁻¹⁰ This course may boost the number of high-risk patients requiring reoperation for failed repair in the near future. Kempfert and colleagues⁸ additionally mentioned an association of reoperative mitral valve replacement in this high-risk subgroup with an increased risk for mortality up to 30%. The expansion of the valve-in-valve concept toward implantation of a THV into an annuloplasty ring could be a solution for this high-risk subgroup. Kempfert and colleagues⁸ demonstrated feasibility by successful implantation of a 23-mm Sapien bioprosthesis (Edwards

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Abbreviations and Acronyms

EuroSCORE	= European System for Cardiac Operative Risk
STS	= Society of Thoracic Surgeons
TAVI	= transcatheter aortic valve implantation
THV	= transcatheter heart valve

Lifesciences Inc, Irvine, Calif) into a 26-mm Physio annuloplasty ring (Edwards Lifesciences Inc, Irvine, Calif) in a sheep model in 2009. The first in-man implantation of a THV into a mitral annuloplasty ring was described by de Weger and colleagues in 2010.¹¹ An additional 2 cases have been reported since then. First, Hammerstingl and colleagues¹² described in 2013 implantation of transfemoral 26-mm Sapien XT bioprosthesis (Edwards Lifesciences Inc, Irvine, Calif) into a failed 30-mm Seguin annuloplasty ring (St Jude Medical, Saint Paul, Minn). Second, Mazzitelli and colleagues¹³ reported in the same year simultaneous antegrade valve-in-ring implantation for both a failed mitral and tricuspid annuloplasty ring. The implantation of a transcatheter valve into a native valve ring other than the aortic valve has not yet been described. Our series reports 10 successful valve-in-valve procedures in the mitral position, 3 successful mitral valve-in-ring implantations, and 1 successful direct-view implantation of a THV in a severely calcified mitral valve annulus.

PATIENTS AND METHODS**Patients and Study Design**

Since November 2008 a total of 550 patients have been treated with catheter-based valve implantations at our institution. We included 14 patients out of those undergoing a THV procedure in the mitral position. Ten out of these presented with failing mitral valve bioprostheses and a further 3 with failed mitral valve repair. One patient presented with severe mitral valve stenosis and was primarily considered for conventional surgical mitral valve replacement.

The general decision to perform TAVI was made by an interdisciplinary heart team consisting of cardiologists and cardiac surgeons. For risk estimation the European System for Cardiac Operative Risk (EuroSCORE) and EuroSCORE II as well as Society of Thoracic Surgeons (STS) score were used. Criteria for considering the TAVI approach were older than age 75 years and at high surgical risk as predicted by the applied scoring systems or at least presence of contraindications for conventional surgery like porcelain aorta. The final individual risk assessment ultimately relied on the clinical judgment of the heart team. Each of the reported cases in our study was an individual, single-case decision. All patients were at prohibitive surgical risk and presented in poor clinical condition with relevant comorbidities and general severe frailty.

Mean patient age was 75 ± 5 years. The patients were predominantly women ($n = 8$; 61.5%). Calculated STS score and EuroSCORE predicted high surgical risk. Mean logistic EuroSCORE for mortality was calculated with $54.70\% \pm 19.51\%$ and STS score averaged $11.59\% \pm 3.10\%$.

Pre-, intra-, and postoperative data were prospectively collected. Follow-up included direct interview of patients during ambulant reassessment at our institution. The follow-up was complete, ranging from 34 to

220 days with an average of 104 ± 69 days. The complete follow-up conformed a total of 34.4 patient-months.

The study was reviewed and approved by the institutional review board at Medical Faculty "Carl Gustav Carus" at Technical University of Dresden, Dresden, Germany (EK No. 53022010). Written informed consent regarding the off-label use of the Sapien valve was obtained from patients.

Statistical Analysis

Statistical analysis was performed with JMP 9.0 software (SAS Institute Inc, Cary, NC).^{2,3} Numeric variables are expressed as means $\pm$ standard error of mean or median with interquartile range due to the limited number of cases.^{2,3} If applicable, means were compared by the Student *t* test.^{2,3}

Setting, Access Routes, and Implantation Technique

THV procedures were performed in a specially equipped hybrid operating room by an interdisciplinary heart team consisting of cardiac surgeons, cardiologists, and cardiac anesthesiologists. For all procedures the reverse-crimped Sapien XT porcine valve was used, 26-mm THVs were delivered using the 24F-Ascendra-II delivery system (Edwards Lifesciences, Irvine, Calif) and 29-mm THVs were delivered using the 33F-Ascendra delivery system (Edwards Lifesciences, Irvine, Calif). Prior balloon valvuloplasty of the degenerated bioprosthesis or failing repair was not performed. As previously reported, stepwise fluoroscopy was performed throughout the procedure without use of a contrast agent.^{2,3} Subsequently, prosthesis function was evaluated by transesophageal echocardiography.^{2,3}

The following access route was used, as previously reported: standard transapical approach by left-antrolateral minithoracotomy.^{2,3} This access route was applied in all 10 patients receiving valve-in-valve implantations and 2 out of 3 patients receiving valve-in-ring TAVI. Valve-in-valve procedures were performed as previously reported²: right-antrolateral minithoracotomy using a left atrial access in 1 patient receiving valve-in-ring TAVI. Finally, median sternotomy was applied in 1 patient undergoing planned on-pump mitral valve replacement. The surgery was primarily performed using trans-septal access. Subsequent to failed surgical mitral valve replacement the THV was implanted under direct view.

Sizing of the THV

Sizing of the valve depended on the type of prior and actual surgery.

Valve-in-valve procedures. As shown in Figure 1, in patients with prior mitral valve replacement 26- and 29-mm Sapien THVs were used. Before implantation, the diameter of the degenerated bioprosthesis—ranging from 27 to 31 mm—was determined by transesophageal echocardiography. Besides the echocardiographically determined internal diameter, the internal diameter of the bioprosthesis provided by the manufacturer was used as the key parameter for valve sizing. As proposed, a 26-mm THV was used for diameters ranging from 21.5 to 24.5 mm and a 29-mm THV for diameters exceeding 24.5 mm. As previously reported, we occasionally observed a discrepancy between the internal diameter provided by the manufacturer and the measured diameter.^{2,3} Calcification or pannus formation were most likely supposed to be causative for the observed discrepancies. In those cases we relied on the manufacturer's information and tended to use the larger THV.

Valve-in-ring procedures. Previously in-human implantation ex-vivo trials were performed using different annuloplasty rings and THVs (see Figure 2). In our series solely 29-mm Sapien XT bioprostheses were used for valve-in-ring procedures. The patients experiencing failed mitral valve repair presented with Physio annuloplasty rings with sizes 28 and 30 mm. For determination of the estimated internal diameter of the circularized annuloplasty ring after the implantation procedures, the internal ring area—as provided by the manufacturer—was used. We assumed that the extent of the circularized annuloplasty ring is defined and would not

FIGURE 1. Mitral valve-in-valve procedure. The radiopaque markers of the degenerated bioprosthesis clearly indicate the landing zone and thus easy and orthograde positioning of the transcatheter heart valve. A, Positioning of the valve before inflation of the balloon. B and C, Gradual inflation of the balloon. D, Final result.

be changed by the THV implantation. This further means that the absolute ring area must stay the same after THV implantation. Based on these considerations we calculated the estimated internal diameter emanating from the known ring area using the formula: $\text{Area} = \pi \times (\text{diameter} \times \frac{1}{2})^2$, converted to $\text{diameter} = 2 \times \sqrt{(\text{area}/\pi)}$. [Figure 3](#) demonstrates sizing considerations.

Valve-in-native-ring procedure. As shown in [Figure 4](#), in this single case the severely calcified mitral annulus could not be passed by a 23-mm measurement device. For safety reasons the THV was oversized and a 29-mm Sapien XT bioprosthesis was chosen. The THV was implanted under direct view.

RESULTS

Clinical Baseline Characteristics

Patients selected for transcatheter valve-in-valve or valve-in-ring procedures were characterized by a high incidence of comorbidities and their high surgical risk. Preoperatively performed coronary angiography revealed presence of coronary artery disease in 8 patients. In 4 patients, coronary artery disease had previously been treated several weeks before by percutaneous coronary

intervention by means of a staged-hybrid approach. One patient presented with still-running bypasses after coronary artery bypass grafting and the remaining 3 patients had no hemodynamically relevant stenosis. Because the mitral valve was the leading pathology in all patients who were once considered unsuitable for conventional surgery due to their prohibitive surgical risk, TAVI was considered as a compromise solution, with a clear understanding that concomitant tricuspid disease must remain unaddressed. Preoperative clinical baseline characteristics of the TAVI candidates are summarized in [Table 1](#). One additional 61-year old woman who was initially planned for conventional mitral valve replacement presented with a severely calcified mitral valve causing high-grade stenosis accompanied by severe pulmonary hypertension (right ventricular end-systolic pressure 100 mm Hg). This patient also had history of alcohol abuse, toxic hepatic cirrhosis, and recurrent gastrointestinal bleeding. Preoperatively, active endocarditis was ruled out by echocardiography and lab findings in all patients.

FIGURE 2. Mitral valve-in-ring procedure. A centered position of the transcatheter heart valve with equal proportions in the left ventricle and in the atrium is advocated to prevent outflow tract obstruction, paravalvular leakage, or valve embolization.

Preoperative Echocardiographic Findings

Two patients presented with a high-grade stenosis of the mitral bioprostheses with a remaining orifice area of 0.25 and 1.1 cm². All remaining 8 valve-in-valve patients had a failing mitral bioprosthesis resulting in severe mitral regurgitation. Mechanisms of failure were leaflet prolapse (n = 6) and leaflet perforation (n = 2). Valve-in-ring patients all presented with a failed repair resulting in a severe regurgitation. The valve-in-native ring patients presented with high-grade mitral valve stenosis with a mean transvalvular pressure gradient rising to 17 mm Hg. Left ventricular ejection fraction averaged $44.5\% \pm 17.4\%$, ranging from 15% to 65%. All patients presented with a concomitant moderate (n = 7) or severe tricuspid regurgitation (n = 6) and significant pulmonary hypertension exceeding 60 mm Hg.

Procedural Data

All TAVI procedures were primarily successful without any procedural complications. Intraoperative echocardiography

revealed good prosthesis function without relevant para- or transvalvular regurgitation. Mean procedure time of TAVI was 51.1 ± 7.4 minutes. A standard transapical access route was used in all valve-in-valve (n = 10) and in 2 valve-in-ring procedures. Because of hostile chest configuration, the remaining valve-in-ring procedure was performed using an antegrade left-atrial access by right-anterolateral minithoracotomy.

A 26-mm Sapien XT bioprosthesis was implanted in failing Hancock II (Medtronic, Minneapolis, Minn) 27-mm valves (n = 1) and 29-mm valves (n = 3), and Sapien XT porcine 27-mm bioprostheses (n = 1). For Hancock 31-mm (n = 1), Hancock II 31-mm (n = 2), Perimount 29-mm (Edwards Lifesciences, Irvine, Calif) (n = 1), and Shelhigh 31-mm bioprostheses (Shelhigh Inc, Union, NJ) (n = 1), a 29-mm Sapien XT THV was used. The valve-in-ring patients presented with failing Physio annuloplasty rings with sizes 28 mm (n = 1) and 30 mm (n = 2). In all valve-in-ring procedures a 29-mm Sapien XT THV was implanted.

FIGURE 3. Sizing considerations for valve-in-ring procedures.

One patient was scheduled for conventional mitral valve replacement by median sternotomy. During the procedure, the mitral valve presented as being severely calcified with extensive calcifications infiltrating the ventricular muscle. The remaining orifice area could not be passed with a 23-mm measurement device and pledged valve sutures could not be placed because of the extensive calcifications. For bailout, direct-view implantation of a 29-mm Sapien XT bioprosthesis was performed. This patient was transmitted to our intensive care unit under intra-aortic balloon pump and catecholamine support. On postoperative day 1 transesophageal echocardiography demonstrated progressive paravalvular regurgitation. For those reasons a second-look procedure was performed. During this procedure, the scaffold of the Sapien valve was fixed to an atrial cuff using 1 running 3-0 polypropylene suture (Figure 4). Weaning from extracorporeal circulation was problem-free and echocardiography revealed good prosthesis function with only mild remaining paravalvular regurgitation and a peak/mean transvalvular pressure gradient of 7/2 mm Hg.

Postoperative Data

Postoperative course was mainly uneventful. Our main clinical endpoints are summarized according the Valve Academic Research Consortium-2 criteria in Table 2. No immediate procedural mortality within the first 72 hours was observed. During primary hospital stay a total of 2 patients died (15.4%). One patient from the valve-in-valve group died from pneumonia on day 34 and 1 valve-in-native-ring patient died after prolonged intensive care unit stay from massive upper gastrointestinal bleeding on day 41.

Seven patients (53.8%) experienced postoperative renal injury according Acute Kidney Injury criteria, but only 1 patient needed hemofiltration. During primary hospital stay and further follow-up neither myocardial infarction nor stroke, bleeding, or access-site complications were observed. One patient from the valve-in-valve-group needed permanent pacemaker implantation due to bradycardic atrial fibrillation. In summary, the hospital course and further follow-up was uneventful in all TAVI patients.

On the contrary, the valve-in-native-ring patient experienced a prolonged intensive care unit stay with high-dose catecholamine and intra-aortic balloon pump support as well as long-time ventilation and disturbed wound healing, finally dying from gastrointestinal bleeding.

FIGURE 4. Postoperative aspect after the second look procedure. The transcatheter heart valve is implanted in the native calcified mitral annulus and secured with a running 3-0 polypropylene suture to an atrial cuff.

TABLE 1. Clinical baseline characteristics (only transcatheter aortic valve implantation candidates [n = 13])

Characteristic	Result
Age, y	75.0 ± 5.0
Men	6 (46.2)
European System for Cardiac Operative Risk Evaluation (%)	54.70 ± 19.51
Society of Thoracic Surgeons score (%)	11.59 ± 3.10
Body mass index	24.6 ± 4.6
New York Heart Association functional class III	13 (100.0)
Left ventricular ejection fraction (%)	44.5 ± 17.4
Pulmonary hypertension >60 mm Hg	13 (100.0)
Atrial fibrillation	6 (46.2)
Permanent pacemaker	4 (30.8)
Arterial hypertension	12 (92.3)
Type 2 diabetes mellitus	8 (61.5)
Dietary	2 (25.0)
Oral	2 (25.0)
Insulin	4 (50.0)
Chronic renal failure	8 (61.5)
Preoperative creatinine, $\mu\text{mol/L}$	107 ± 46
Coronary artery disease	8 (61.5)
Chronic obstructive pulmonary disease	3 (23.1)
Extracardiac arteriopathy	4 (30.8)
History of stroke	3 (23.1)
History of previous cardiac surgery	
Isolated mitral valve replacement	9 (69.2)
Isolated mitral valve repair	2 (15.4)
Combined coronary artery bypass graft, mitral or tricuspid valve repair	1 (7.7)
Combined mitral or aortic valve replacement	1 (7.7)
Time interval to previous surgery, y	8.1 ± 3.1

Values are presented as mean ± standard deviation or n (%).

Nonetheless, the latest postoperative echocardiography demonstrated good hemodynamics and good prosthesis function in all 14 patients. Most patients (9 out of 10) from the valve-in-valve group showed no valvular regurgitation with only 1 patient having trace transvalvular regurgitation. Likewise, the valve-in-ring patients only showed trace regurgitation in 2 patients and mild transvalvular regurgitation in 1 patient. Measured transvalvular pressure gradients significantly decreased in all patients and revealed excellent prosthesis function (Table 2). In 2 valve-in-valve patients who received anticoagulation therapy solely with 100 mg acetylsalicylic acid per day, signs of beginning valve thrombosis occurred after 8 weeks and 3 months, respectively. They presented with increasing transvalvular pressure gradients and thickened valve leaflets. Endocarditis was ruled out by lab testing. The findings were interpreted as beginning valve thrombosis. For those reasons oral anticoagulation therapy with warfarin with a target international normalized ratio of 2.5 was initiated. During further course, the previously described echocardiographic findings were completely regressive and transvalvular pressure gradients decreased.

TABLE 2. Clinical endpoints according to Valve Academic Research Consortium-2 criteria* in all patients (n = 14)

Endpoint	Result
Procedural success (valve-in-valve/valve-in-ring)	13 (100.0)
Mean procedure time (valve-in-valve/valve-in-ring), min	51.1 ± 7.4
Immediate procedural mortality (<72 h after the procedure)	0
Procedural mortality (primary hospital stay)	2 (15.4)
Pneumonia on day 34	1
Fatal upper gastrointestinal bleeding on day 41	1
Mortality during further follow-up	0
Myocardial infarction	0
Bleeding complications	0
Vascular access site and access-related complications	0
Acute kidney injury classification	7 (53.8)
Renal failure (continuous veno-venous hemofiltration)	1
Stroke and transient ischemic attack	0
Conduction disturbances and arrhythmias	2 (15.4)
New onset atrial fibrillation	1
Permanent pacemaker implantation (bradycardic atrial fibrillation)	1
Other transcatheter aortic valve implantation-related complications	1
Rethoracotomy	1 (7.7)
Second-look for reanchoring the direct-view implanted transcatheter heart valve	1
Hospital stay, d	13.2 ± 11.3
Follow-up time, d	104 ± 69
Echocardiographic results for valve-in-valve-procedures	
No valvular regurgitation	9 (90.0)
Trace transvalvular regurgitation	1 (10.0)
Peak pressure gradient, mm Hg	15.3 ± 5.5
Mean pressure gradient, mm Hg	6.2 ± 2.6
Echocardiographic results for valve-in-ring-procedures	
Trace transvalvular regurgitation	2 (66.7)
Mild transvalvular regurgitation	1 (33.3)
Peak pressure gradient, mm Hg	13.5 ± 0.7
Mean pressure gradient, mm Hg	6.0 ± 1.4
Echocardiographic result for valve-in-native-ring-procedure (final result)	
Mild paravalvular regurgitation	1
Transvalvular pressure gradient $\text{dP}_{\text{max/mean}}$, mm Hg	7/2

Values are presented as mean ± standard deviation, n (%), or n. *From Kappetein AP, Head SJ, Gnreux P, Piazza N, van Mieghem NM, Blackstone EH, 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.

DISCUSSION

The development and implementation of transcatheter heart valve procedures has induced profound changes in the treatment of valvular heart disease.¹⁻³ At the same time, in conventional cardiac surgery a trend toward more frequent use of biologic substitutes instead of mechanical heart valves can be observed, potentially leading to an increasing number of patients presenting with deteriorated bioprosthesis in the near future.¹⁴ Additionally, mitral valve repair has been demonstrated to be superior for patients

with mitral regurgitation in general and ischemic mitral regurgitation in particular.⁸ Nonetheless, there is a high rate of ischemic mitral regurgitation recurrence after valve repair.⁸ Increasing life expectancy and those described developments will raise the absolute number of patients with degenerated bioprostheses or failed mitral valve repair needing repeat mitral valve surgery in the near future. However, redo procedures, especially in elderly and high-risk patients, are still affected by increased perioperative risk up to 20%.^{1,15-17}

Our success in highest-risk patients and encouraging results of TAVI in general progressively expand the potential scopes of application to now include patients with previous cardiac surgery and failed bioprostheses or mitral valve repair in particular.^{1-3,5,8,13}

Our study included 3 different entities of further evolutions in THV procedures: valve-in-valve, valve-in-ring, and valve-in-native-ring, which have to be discussed separately.

Transcatheter Mitral Valve-in-Valve Implantation

The first description of the valve-in-valve concept for failed aortic bioprosthesis by Walther and colleagues in 2007¹⁸ heralded a new era of catheter-based valve therapies. Since then multiple studies have demonstrated the safety and feasibility of aortic valve-in-valve therapies.¹ In 2008 Kempfert and colleagues¹⁹ adapted the aortic valve-in-valve concept for mitral bioprostheses in a sheep model and not that much later, in 2009, Cheung and colleagues⁷ first performed a mitral valve-in-valve procedure in a human. Since that time, valve-in-valve procedures have progressively advanced to being considered a viable and elegant alternative in selected highest-risk patients.^{1,20} A main concern is the exact determination of the internal diameter of the degenerated bioprosthesis.¹ Because of nonstandardized methodologies for labeling valve sizes, the labeled sizes usually do not reflect the real internal diameter.¹ The internal diameter needs to be carefully determined by echocardiography and set in relation to the internal diameter given by the manufacturer.^{1,2} In our series we observed a significant discrepancy between these.² This discrepancy might be caused by calcification or pannus formation of the biologic substitute.^{1,2} It has to be assumed that the expansion of the transcatheter valve is mainly impeded by the sewing ring and calcifications additionally might ease during valve expansion. Thus it seems to be justified to rely on the internal diameter of the biologic substitute given by the manufacturer.^{1,2} For secure anchoring, a moderate oversizing of the transcatheter valve exactly matching or exceeding the internal diameter of the degenerated bioprosthesis is advocated by most groups.^{1,2,14,21} It has to be kept in mind that excessive oversizing might impair leaflet opening and thus promote early valve degeneration, whereas significant underexpansion might venture paravalvular leakage or valve migration.¹

FIGURE 5. Mitral valve-in-valve procedure in a patient with history of previous aortic and mitral valve replacement. The projection of both bioprostheses over each other made the procedure more demanding. In the end the presence of aortic bioprosthesis was not a drawback.

In line with other series, our experience with transcatheter mitral valve-in-valve implantations did not reveal any procedural problem.^{2,14,21} The transapical approach allowed a direct and coaxial access to the mitral valve.² Herein, the degenerated bioprosthesis and its radiolucent markers allowed exact and easy-to-perform orthograde positioning of the transcatheter valve.² In particular, patients with history of previous aortic and mitral valve replacement has to be mentioned. After initial concerns that the aortic bioprosthesis might impair placement of the THV in the mitral position or even could get damaged, the procedure fortunately was uncomplicated. Projection of the valves over each other during angiography made THV positioning a little more demanding (Figure 5). In the end, the presence of aortic bioprosthesis was no drawback and the procedure was as convenient to perform as the other valve-in-valve procedures. In contrast to TAVI procedures in general or valve-in-valve procedures for failed aortic bioprostheses, mitral-valve-in-valve TAVI needs no administration of contrast agent.² In line with other series, all patients in our study demonstrated excellent postprocedural echocardiographic results and experienced a significant reduction of preoperative mitral regurgitation to grade 0 or 1.^{2,14,21} The observed short procedure times reflect the straightforward character of the procedure. Such short procedure times are less consuming for the patient and the operating surgeon, as well.² Additionally, the risk of trauma to cardiac structures or patent bypass grafts is minimized in comparison to complex conventional redo procedures. An interesting

observation was the fact that 2 patients for whom anticoagulation was solely achieved with acetylsalicylic acid therapy developed beginning valve thrombosis within several weeks after the procedure. Maybe there exist low-flow areas between the stent-scaffold of the THV and the struts of the bioprosthesis that promote thrombosis. The modification of the anticoagulation regimen to permanent warfarin therapy led to a complete regression of the beginning valve thrombosis. These observations suggest that sole therapy with acetylsalicylic acid is not sufficient in cases of mitral valve-in-valve THV. Summing up, the simplicity of positioning the valve, guided by radiolucent markers of the degenerated bioprosthesis, and the direct and coaxial access as provided by the transapical approach, make valve-in-valve TAVI for degenerated mitral bioprostheses as convenient to perform as a penalty kick without goal keeper. Permanent warfarin therapy should routinely be initiated.

Transcatheter Mitral Valve-in-Ring Procedures

Far less is known about valve-in-ring procedures. The initial idea was developed by Kempfert and colleagues,⁸ who reported in 2009 successful mitral valve-in-ring TAVI using an antegrade transatrial approach. For those purposes, they unexceptionally used 26-mm Physio annuloplasty rings and 23-mm Sapien transcatheter valves.⁸ The procedure itself was successful in all sheep and provided acceptable hemodynamic results, ranging from no paravalvular leakage ($n = 1$) to mild ($n = 5$) and moderate leakage ($n = 1$).⁸ Not that much later, in 2011, de Weger and colleagues¹¹ reported the first successful valve-in-ring TAVI in a human using a transapical approach. They described successful implantation of a 26-mm Sapien transcatheter valve in a 28-mm Physio annuloplasty ring in a 72-year old man with history of prior combined mitral valve repair and coronary artery bypass graft 8 years ago.¹¹ Double mitral and tricuspid valve-in-ring implantation was recently reported by Mazzitelli and colleagues in 2013.¹² Using a transatrial antegrade approach, Mazzitelli and colleagues¹³ described implantation of a 26-mm Sapien bioprosthesis in both a 28-mm Physio mitral ring and 26-mm Classic (Edwards Lifesciences, Irvine, Calif) tricuspid ring during 1 procedure. PredischARGE echocardiography showed good prosthesis function.¹² The most recently reported case was published by Hammerstingl and colleagues in early 2013.¹³ They described transfemoral implantation of a 26-mm Sapien XT transcatheter valve in a 30-mm Seguin annuloplasty ring.¹³ The procedure was uneventful and postoperative echocardiography revealed an excellent hemodynamic result.¹³

Until today, there existed besides the reported animal model only 3 case reports.^{8,11-13} Our series summarizes 3 consecutive cases of mitral valve-in-ring TAVI procedures at our institution. Two of the procedures were performed using the transapical approach, which has meanwhile become

a convenient standard access route. In line with the above-mentioned advantages of transapical access for mitral valve-in-valve procedures, valve-in-ring TAVI likewise benefits from the direct and coaxial access as provided by transapical access route. In the remaining patient with a so-called hostile chest we opted for an antegrade left-atrial access using a right-anterolateral minithoracotomy. This approach was quite challenging because it did not provide a coaxial access to the mitral annulus. The length of the delivery device and the angle of the mitral axis made it difficult to align the THV in an orthograde position. Finally, the procedure was—despite technically challenging aspects, as the 95-minute procedure time reflects—uneventful and the hemodynamic result was excellent. In contrast, the transapical valve-in-ring procedure lasted only about 55 minutes in both cases.

Sizing of the valve and determination of the inner diameter is essential in valve-in-ring procedures. Exact determination of the final internal diameter of the annuloplasty ring might be the most challenging aspect of the procedure. In contrast to valve-in-valve procedures, echocardiography and computed tomography are useless for measurements in this context. The shape of an annuloplasty ring and its dimensions before implantation are completely contrary to the shape and dimensions of the circularized annuloplasty ring after THV implantation. In line with other study groups we first proofed different combinations of annuloplasty ring and THV before implantation in an ex-vivo model,¹³ but additionally calculated the estimated postimplantation internal diameter. For approximation of the internal diameter we used the ring area as provided by the manufacturer. Assuming that the ring area and the circumference must stay constant even after THV implantation, it is possible to calculate the estimated diameter of the circularized annuloplasty ring using the circle formula ($\text{Area} = \pi \times (\text{diameter} \times \frac{1}{2})^2$). The internal diameter so created provides a sufficient lead for sizing the THV. Unfortunately, annuloplasty rings are semirigid and implantation of a THV will not be able to totally reshape and circularize the ring—as demonstrated by our ex-vivo trials. Especially in the area of the commissures, a small gap remained between ring and THV. Surprisingly, these gaps seem to be meaningless in in-vivo implantations. It has to be assumed that surrounding valvular tissue or pannus formation seals these gaps. We observed no paravalvular leakages at those gap areas. All valve-in-ring procedures of our series provided excellent hemodynamic results and good prosthesis function. In our series, we successfully used 29-mm Sapien XT valves for 28-mm and 30-mm Physio annuloplasty rings.

Accordingly, for valve-in-valve procedures, the radiopaque markers of the annuloplasty ring clearly indicate the landing zone and the procedure usually can be performed without administration of contrast agent.¹¹

During the procedure we advocate placement of stiff wire in the upper pulmonary vein, which provides a favorable angle to the mitral valve. Finally, it has to be mentioned that exact positioning of the THV is of utmost importance. We advocate a centered position of the THV in the mitral annulus with equal proportions within the left atrium and the ventricle (Figure 2). This is in line with de Weger and colleagues.¹¹ Positioning of the THV more toward the ventricle might cause outflow tract obstruction by the THV itself or the displaced anterior mitral leaflet. On the contrary, positioning more toward the left atrium might promote paravalvular leakage or even valve embolization during systole. Summing up, valve-in-ring procedures are feasible, providing excellent hemodynamic results, but are burdened with some technically challenging aspects like sizing and imponderables like durability. As of today, including our series, only 6 cases are published worldwide. Thus, much more data is needed to provide a final statement on this developing but promising technique.

Mitral Valve-in-Native-Ring Procedure

A comparable procedure has not been reported until today. In our patient presenting with a severe mitral valve stenosis a surgical valve replacement was planned. Intraoperatively the mitral annulus presented severely calcified with extensive calcifications deeply infiltrating the ventricular muscle. Valve sutures could not be placed and the annulus could not be passed with a 23-mm measurement device. For those reasons we decided for direct-view implantation of a 29-mm Sapien XT valve into the native mitral annulus. Due to its severe calcification, the native annulus initially allowed somewhat secure anchoring of the valve. On first postoperative day we had to perform a second-look procedure because of incipient valve dislocation and paravalvular leakage. During this procedure, the THV stent was fixed by a running 3-0 polypropylene suture to an atrial cuff (Figure 4). Afterward, echocardiography revealed constantly good prosthesis function without paravalvular leakage. The patient died after prolonged intensive care unit stay on postoperative day 41 from massive upper gastrointestinal bleeding. Nonetheless, this case demonstrated that valve-in-native ring procedures are not really feasible. In this absolute bailout situation it worked once, but can surely not be recommended. With the presently available devices, valve-in-native-ring procedure seems not to be reproducibly possible.

Study Limitations

Our study was mainly limited by the number of patients studied. Our main focus was on technical aspects and to demonstrate feasibility of the described procedures. The final value of the procedures cannot be determined until much more data are available. Additionally, it has to be kept in mind that despite the euphoria concerning

catheter-based heart valve procedures, conventional surgery still remains the gold standard and provides excellent results. The reported techniques, which are stringent off-label use of THVs, are geared toward individually selected patients at prohibitive surgical risk, which always must remain an individual assessment.

CONCLUSIONS

For mitral valve-in-valve or valve-in-ring procedures for access, the transapical approach and the antegrade left-atrial approach are feasible. The transapical approach, which provides direct and coaxial access, is far more convenient and easy to perform. Valve-in-valve procedures have nearly advanced to being standard procedure in selected highest-risk patients with prohibitive surgical risk. Valve-in-ring procedures are feasible, but much more data are needed to provide a final statement. Both techniques can be seen as complementary surgical techniques for tailor-made and patient-oriented surgery in the near future. Finally, valve-in-native ring procedure seems to be possible in defined anatomic requirements in an ultima ratio bailout situation, but cannot generally be recommended.

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