JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 5, NO. 5, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
DOI: 10.1016/j.jcin.2012.03.008

# Transcatheter Valve-In-Valve Implantation for Failed Balloon-Expandable Transcatheter Aortic Valves

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**Objectives** This study sought to evaluate outcomes after implantation of a second transcatheter heart valve (THV-in-THV) for acute THV failure.

**Background** Aortic regurgitation after transcatheter aortic valve replacement (TAVR) may be valvular due to prosthetic leaflet dysfunction or paravalvular due to poor annular sealing.

**Methods** Patients undergoing aortic balloon-expandable TAVR at 3 centers were prospectively evaluated at baseline, intraprocedurally, at hospital discharge, and annually.

**Results** Of 760 patients undergoing TAVR, 21 (2.8%) received a THV-in-THV implant due to acute, severe regurgitation. Aortic regurgitation was paravalvular in 18 patients and transvalvular in the remaining 3 patients. THV-in-THV implantation was technically successful in 19 patients (90%) and unsuccessful in 2 patients (10%), who subsequently underwent open heart surgery. Mortality at 30 days and 1 year was 14.3% and 24%, respectively. After successful THV-in-THV, mean aortic valve gradient fell from 37 ± 12 mm Hg to 13 ± 5 mm Hg ($p < 0.01$); aortic valve area increased from 0.64 ± 0.14 $cm^2$ to 1.55 ± 0.27 $cm^2$ ($p < 0.01$); and paravalvular aortic regurgitation was none in 4 patients, mild in 13 patients, and moderate in 2 patients. At 1-year follow-up, 1 patient had moderate and the others had mild or no paravalvular leaks. The mean transvalvular gradient was 15 ± 4 mm Hg, which was higher than in patients undergoing conventional TAVR (11 ± 4 mm Hg, $p = 0.02$).

**Conclusions** THV-in-THV implantation is feasible and results in satisfactory short- and mid-term outcomes. (J Am Coll Cardiol Intv 2012;5:571–7) © 2012 by the American College of Cardiology Foundation

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Manuscript received January 3, 2012; revised manuscript received March 14, 2012, accepted March 16, 2012.

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 5, NO. 5, 2012
MAY 2012:571–7

Malposition or malfunction of an aortic transcatheter heart valve (THV) can result in aortic regurgitation. Regurgitation may be through (transvalvular) or around (paravalvular) the newly implanted THV. If regurgitation is sufficiently severe, then congestive failure, hemodynamic instability, or cardiogenic shock may ensue (1–4). In this setting, implantation of a second valve (THV-in-THV) has been used to restore normal prosthetic leaflet function or extend the annular seal (5). We evaluated our experience with THV-in-THV implantation for acute THV failure.

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## Methods

**Study population.** Between January 2005 and March 2011, 760 patients (429 transfemoral, 331 transapical) underwent balloon-expandable transcatheter aortic valve replacement (TAVR) for treatment of severe aortic stenosis at 3 centers: St. Paul's Hospital, Vancouver; the Quebec Heart and Lung Institute, Quebec City; and the Cleveland Clinic, Cleveland. A total of 21 (2.8%) patients underwent aortic balloon-expandable THV-in-THV implantation for prosthesis malposition/malfunction. Patients undergoing THV-in-THV implantation were compared with patients undergoing conventional TAVR. Patients were evaluated before and after TAVR, at hospital discharge, and at 1 year. Baseline characteristics, procedural details, and clinical outcomes were prospectively entered into a dedicated database.

**Abbreviations and Acronyms**

CE = Cribier-Edwards valve

TAVR = transcatheter aortic valve replacement

THV = transcatheter heart valve

**Procedure.** The procedure has been described in detail previously (6–8). Femoral arterial access was the default transcatheter approach, with apical access used in the presence of small or diseased iliofemoral arteries. Balloon valvuloplasty was performed in a standard manner with a balloon slightly smaller than the diameter of the planned prosthesis. Rapid right ventricular pacing was used for balloon valvuloplasty and prosthesis implantation. To ensure sufficient annular seal, the prosthesis was positioned such that it extended to the tips of the calcified native valve while extending into the left ventricle below the angiographic basal hinge point of the native valve (9). The prosthesis used was initially the Cribier-Edwards (CE) valve, then the Sapien valve, and more recently the Sapien XT valve (all Edwards Lifesciences, Irvine, California). Two sizes were available. A 23-mm valve with an expanded frame height of 14.3 mm and a maximal fabric sealing cuff of 7.7, 10.1, and 9.9 mm for the CE, Sapien, and Sapien XT valves, respectively. The larger 26-mm valve has a frame height of 16.1 mm (CE and Sapien) and 17.2 mm (Sapien XT) and a maximal fabric sealing cuff of 8.6, 11.4, and 12.3 mm for the CE, Sapien, and Sapien XT valves, respectively (Fig. 1). A minority of patients underwent implantation of a 20- or 29-mm Sapien XT valve, which both became recently available.

In case of evident malpositioning of the first valve, no balloon dilation was attempted. Implantation of the second valve was done similar to the implantation of the first valve under rapid pacing. A second valve was implanted by the same operator about 25% to 35% of the stent frame height lower (initial implant too high) or higher (initial implant too low or transvalvular regurgitation) than the first valve. The goal was to position the second valve in a way that the sealing fabric of both valves overlapped and that the second valve ensured sealing with the native valve annulus. The same valve size was used for both valves because a 23-mm valve is too small to get a firm hold inside a 26-mm valve.

**Statistical analysis.** Statistical analysis was performed using IBM SPSS Statistics 18 (IBM Corporation, Somers, New York). If not indicated otherwise, data are presented as mean ± SD for continuous and as number and frequency for categorical variables. Continuous parametric variables were compared using unpaired and paired Student *t* tests. Categorical variables were compared using the chi-square test. Survival rates at 1 year were estimated and graphed using the Kaplan-Meier method. A 2-sided $p < 0.05$ was considered statistically significant.

## Results

A total of 760 patients underwent balloon-expandable TAVR. Aortic regurgitation after TAVR was less than or mild in 665 (87%) patients, moderate in 72 (10%) patients, and severe in 23 (3%) patients. THV-in-THV implantation was attempted in 21 patients (2.8%). One patient was converted to open heart surgery after embolization of the first valve into the left ventricle, and 1 patient whose intraprocedural transesophageal echocardiogram showed moderate aortic regurgitation was treated medically with a good outcome. Baseline and procedural characteristics of patients undergoing THV-in-THV were compared with those of patients undergoing conventional TAVR (Tables 1 and 2). There were significantly more transapical procedures in the THV-in-THV cohort (67% vs. 43%, $p = 0.03$). Otherwise, baseline and procedural characteristics did not differ.

In the THV-in-THV cohort, the initial valve implanted was the CE in 2 patients, Edwards Sapien in 17 patients, and Sapien XT in 2 patients. Aortic regurgitation after initial THV implantation was paravalvular in 18 patients. The implant was too high (aortic) in 8 patients and too low (ventricular) in 10 patients (Fig. 2). Regurgitation was transvalvular in 3 patients, all of whom received an Edwards Sapien valve (Fig. 3). Acute aortic regurgitation was associated with cardiogenic shock in 11 patients (52%), requiring cardiopulmonary support in 7 pa-

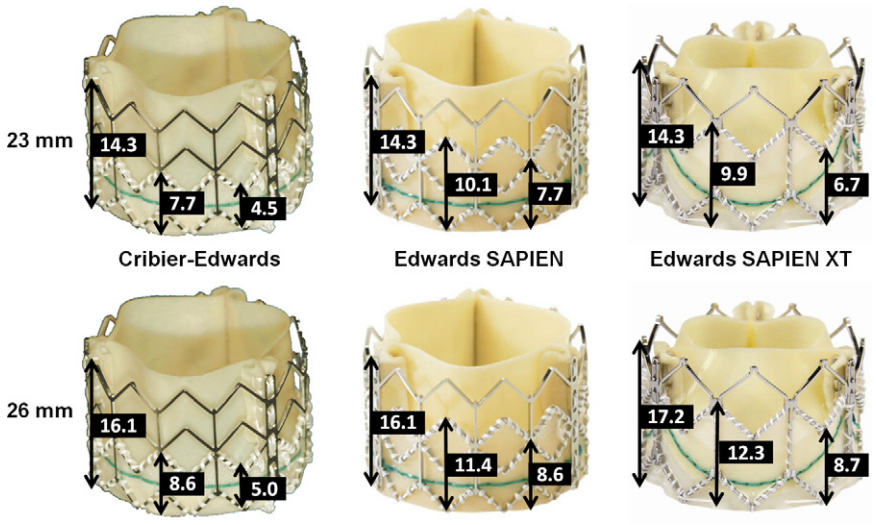


**Figure 1. Dimensions of the 3 Generations of the 23- and 26-mm Edwards Balloon-Expandable Valves**

Dimensions of the 3 generations of the 23- and 26-mm Edwards (Edwards Lifesciences, Irvine, California) balloon-expandable valves (frame height and maximal and minimal heights of the fabric skirt).

tients (33%) and cardiopulmonary resuscitation in 3 patients (14%).

**THV-in-THV implantation.** Implantation of the second THV was carried out at the time of the initial procedure in 17 patients (81%) and after a median of 5 (range 3 to 6) days in the remaining 4 patients (2 with transvalvular regurgitation and 2 with paravalvular regurgitation). In all cases, the diameter of the second THV was the same as the initial THV, and the same access route was used for both procedures.

THV-in-THV implantation was successful in 19 of 21 patients (90%) and unsuccessful in 2 patients (10%) (Table 3). Both unsuccessful procedures were transapical, associated with low implantation of the initial valve followed by embolization of both valves into the ventricle (immediately in 1 patient and at 2 days in a second patient), and subsequently required emergent open heart surgery. One patient died perioperatively, and the other survived with a

**Table 1. Baseline Characteristics**

| | THV-in-THV (n = 21) | Conventional TAVR (n = 739) | p Value |
|---|---|---|---|
| Age, yrs | 81 ± 7 | 81 ± 8 | 0.66 |
| Female | 10 (48%) | 359 (49%) | 0.92 |
| Coronary artery disease | 19 (91%) | 557 (76%) | 0.12 |
| Prior myocardial infarction | 10 (48%) | 294 (40%) | 0.48 |
| Prior CABG | 11 (52%) | 304 (41%) | 0.30 |
| Diabetes mellitus | 5 (24%) | 237 (32%) | 0.42 |
| Porcelain aorta | 6 (29%) | 127 (17%) | 0.19 |
| STS score, % | 8.6 ± 3.7 | 8.9 ± 5.2 | 0.78 |
| eGFR, ml/min | 51 ± 19 | 53 ± 24 | 0.60 |
| Prior stroke | 5 (24%) | 114 (16%) | 0.30 |
| COPD | 10 (48%) | 212 (29%) | 0.06 |
| Atrial fibrillation | 9 (43%) | 220 (30%) | 0.21 |
| Mean aortic gradient, mm Hg | 37 ± 12 | 43 ± 16 | 0.08 |
| Aortic valve area, $cm^2$ | 0.64 ± 0.13 | 0.63 ± 0.16 | 0.96 |
| Ejection fraction, % | 51 ± 13 | 53 ± 14 | 0.45 |

Values are mean ± SD or n (%).

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve.

**Table 2. Procedural Characteristics and 30-Day Outcomes**

| | THV-in-THV (n = 21) | Conventional TAVR (n = 739) | p Value |
|---|---|---|---|
| Implant diameter | | | 0.86 |
| 23 mm | 9 (43%) | 297 (41%) | |
| 26 mm | 12 (57%) | 404 (56%) | |
| 20 or 29 mm | 0 (0%) | 25 (3%) | |
| Access | | | 0.03 |
| Transfemoral | 7 (33%) | 422 (57%) | |
| Transapical | 14 (67%) | 317 (43%) | |
| Mean gradient, mm Hg | 13 ± 5* | 11 ± 5 | 0.23 |
| Aortic valve area, $cm^2$ | 1.55 ± 0.27* | 1.54 ± 0.38 | 0.94 |
| Ejection fraction, % | 53 ± 13* | 55 ± 13 | 0.56 |
| Permanent pacemaker | 2 (10%) | 41 (6%) | 0.44 |
| Coronary artery occlusion | 0 (0%) | 6 (1%) | 0.67 |
| Stroke | 1 (5%) | 16 (2%) | 0.43 |
| Mortality | 3 (14.3%) | 54 (7.3%) | 0.23 |

Values are n (%) or mean ± SD. *After successful THV-in-THV procedure (n = 19).

Abbreviations as in Table 2.

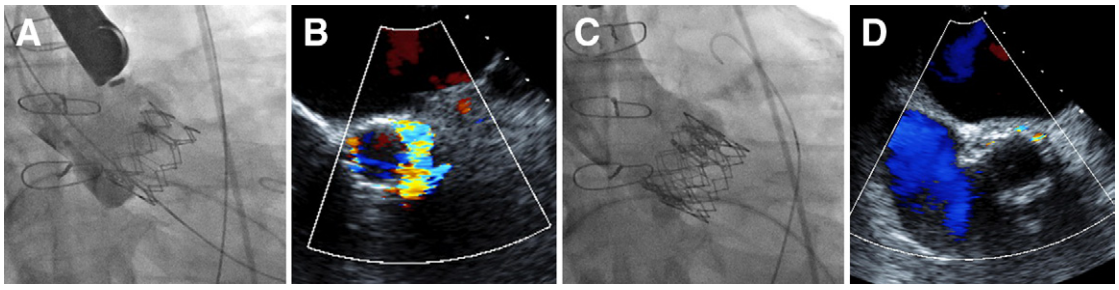


**Figure 2. Example of a THV-in-THV Procedure for Paravalvular Regurgitation**

In this 86-year-old patient, the annulus as measured by transesophageal echocardiography was 22 mm. A 26-mm Edwards Sapien XT valve was implanted **(A).** A low implantation resulted in severe paravalvular aortic regurgitation **(B).** A second 26-mm valve was subsequently implanted in a higher position thus extending the annular seal **(C)** and resulting in mild paravalvular leak **(D).** THV = transcatheter heart valve.

stroke and prolonged hospital stay. Two patients (10%) required implantation of a permanent pacemaker due to third-degree atrioventricular block. None of the patients undergoing THV-in-THV had a major vascular or bleeding complication.

**Survival.** Survival rates of patients undergoing THV-in-THV compared with patients undergoing conventional TAVR are shown in Figure 4. Mortality at 30 days was 14.3% (3 of 21 patients) in patients undergoing THV-in-THV implantation and 7.3% (54 of 739 patients) in patients undergoing conventional TAVR ($p = 0.23$). Cause of death in the THV-in-THV cohort was cardiogenic shock (1 patient who underwent surgical AVR), pneumonia ($n = 1$), and ischemic bowel after plaque embolization ($n = 1$). Survival rates at 1 year were 76% in patients undergoing THV-in-THV and 78% in patients undergoing conventional TAVR (log rank: $p = 0.37$). Causes of death beyond 30 days in patients undergoing successful THV-in-THV were heart failure (2 patients, at 32 and 731 days after the procedure) and pneumonia (2 patients, at 31 and 439 days after the procedure). At 1-year follow-up, all but 1 surviving patient undergoing THV-in-THV was in New York Heart Association functional class I or II.

**Post–THV-in-THV echocardiographic outcome.** Of the 19 patients undergoing successful THV-in-THV implants, none had transvalvular aortic regurgitation after the second TAVR. Paravalvular aortic regurgitation was none in 4 patients, mild in 13 patients, and moderate in 2 patients. Mean aortic valve gradient fell from 37 ± 12 mm Hg at baseline to 13 ± 5 mm Hg ($p < 0.01$) after implantation of the second valve. Aortic valve area improved from 0.64 ± 0.13 $cm^2$ at baseline to 1.55 ± 0.27 $cm^2$ ($p < 0.01$). Ejection fraction remained unchanged. When compared with patients undergoing conventional TAVR, there were no significant differences in gradient, aortic valve area, and ejection fraction (Table 2).

**One-year echocardiographic outcome.** At 1-year follow-up, 1 patient had a moderate paravalvular leak, and the other patients had no or mild paravalvular leaks. The mean gradient across the aortic valve was 15 ± 4 mm Hg ($p = 0.57$ compared with post-TAVR levels), which was significantly higher than in patients undergoing conventional

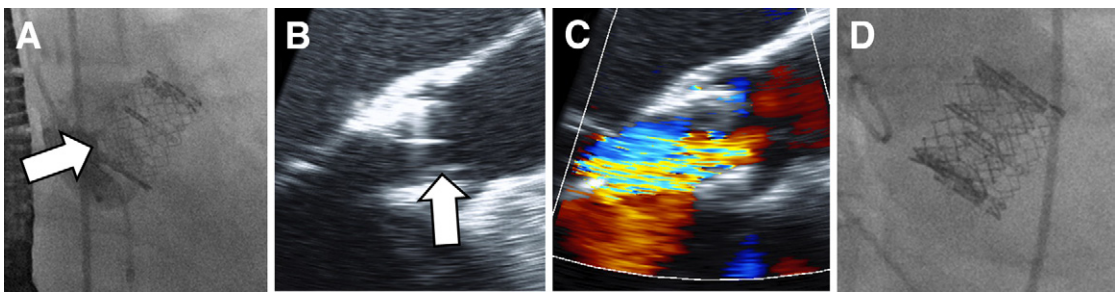


**Figure 3. Example for a THV-in-THV Procedure for Transvalvular Regurgitation**

This patient underwent transcatheter aortic valve replacement with a 26-mm Sapien valve. Angiography after the procedure showed severe aortic regurgitation, most likely caused by an overhanging native leaflet **(A, arrow)** leading to a "frozen leaflet" of the prosthesis **(B, arrow).** The patient had acute severe transvalvular aortic regurgitation **(C).** A Sapien XT valve was implanted in a slightly higher position with an excellent functional result **(D).** Abbreviation as in Figure 2.

**Table 3. Aortic Regurgitation, Valve Positions, and Outcome of Patients Undergoing THV-In-THV**

| Patient # | Position of First Valve | AR Location | AR Severity | Position of Second Valve | Outcome |
|---|---|---|---|---|---|
| 1 | Correct | Trans | Severe | Higher | Uncomplicated |
| 2 | Too low | Para | Severe | Higher | Uncomplicated |
| 3 | Too high | Para | Severe | Lower | Moderate paravalvular AR, heart failure, death |
| 4 | Too high | Para | Severe | Lower | Uncomplicated |
| 5 | Too high | Para | Severe | Lower | Uncomplicated |
| 6 | Too low | Para | Severe | Higher | Valves embolized, open heart surgery, stroke |
| 7 | Too low | Para | Severe | Higher | Uncomplicated |
| 8 | Too low | Para | Severe | Higher | Valves embolized, open heart surgery, death |
| 9 | Too high | Para | Severe | Lower | Uncomplicated |
| 10 | Too low | Para | Severe | Higher | Pacemaker implant |
| 11 | Too high | Para | Severe | Lower | Uncomplicated |
| 12 | Too high | Para | Severe | Lower | Death from pneumonia/sepsis |
| 13 | Too low | Para | Severe | Higher | Pacemaker implant, death from ischemic bowel |
| 14 | Correct | Trans | Severe | Higher | Uncomplicated |
| 15 | Too low | Para | Severe | Higher | Uncomplicated |
| 16 | Too low | Para | Severe | Higher | Uncomplicated |
| 17 | Too low | Para | Severe | Higher | Uncomplicated |
| 18 | Too low | Para | Severe | Higher | Uncomplicated |
| 19 | Correct | Trans | Severe | Higher | Uncomplicated |
| 20 | Too high | Para | Severe | Lower | Uncomplicated |
| 21 | Too high | Para | Severe | Lower | Uncomplicated |

AR = aortic regurgitation; para = paravalvular; THV = transcatheter heart valve; trans = transvalvular.

TAVR (11 ± 4 mm Hg, $p = 0.02$) (Fig. 5). Ejection fraction was 46 ± 12% ($p = 0.25$ compared with post-TAVR levels), which was significantly less than in patients undergoing conventional TAVR (58 ± 12%, $p < 0.01$).

## Discussion

The need to implant a second THV within a recently implanted, but severely regurgitant THV, was infrequent and represented only 2.8% of all TAVR procedures in this 760 patient multicenter experience. Similarly, in the PARTNER (Placement of Aortic Transcatheter Valves) trials, 1.7% and 1.4% of patients underwent repeat TAVR to treat clinically significant aortic regurgitation, respectively (10,11). Although infrequently required, THV-in-THV implantation was generally successful in restoring a good functional result. Initial procedural failure was converted into procedural success in 90% of attempts. Because about 50% of patients developed cardiogenic shock after malpositioning of the first valve, implantation of a second valve may be lifesaving. Although not statistically significant, the study suggests a higher mortality in the THV-in-THV group, despite similar Society of Thoracic Surgeons risk scores. Hopefully, the necessity for acute THV-in-THV implants will decrease, and the likelihood of THV-in-THV success when needed will increase, with experience.

**Paravalvular regurgitation.** Paravalvular leaks are common after TAVR with current technology. However, most leaks are mild, well-tolerated, and do not require intervention. Prior studies have reported paravalvular regurgitation grades ≥2 in 5% to 18% of patients and ≥3 in 0% to 5% of patients (7,8,10–17). Moderate or severe leaks were present in 11.8% and 12.2% as determined by echocardiographic core laboratory evaluation of the Sapien valve in the PARTNER trials, respectively (10,11).

Although the fabric sealing cuff of the first-generation CE valve was relatively short, the subsequent Edwards Sapien and Sapien XT valves featured longer sealing cuffs (Fig. 1), facilitating more reliable annular sealing. Nevertheless, severe leaks may still occur when an initial THV is implanted too aortic or too ventricular, resulting in ineffective sealing. Such cases may be effectively managed by implantation of a second overlapping THV, thereby extending the annular seal.

Paravalvular leaks may also be due to undersizing. In such patients, implantation of a second valve in higher or lower position is not indicated, and the options are more limited. The valve may be post-dilated with a slightly overfilled balloon used for the implantation or with a new balloon with a larger diameter.

**Transvalvular regurgitation.** Structural valve failure due to a "frozen leaflet" is extremely rare and was documented in only 3 cases in this experience for an incidence of <0.4%. Moderate or severe transvalvular aortic regurgitation was reported in 1.3% in the PARTNER trial (10). There have

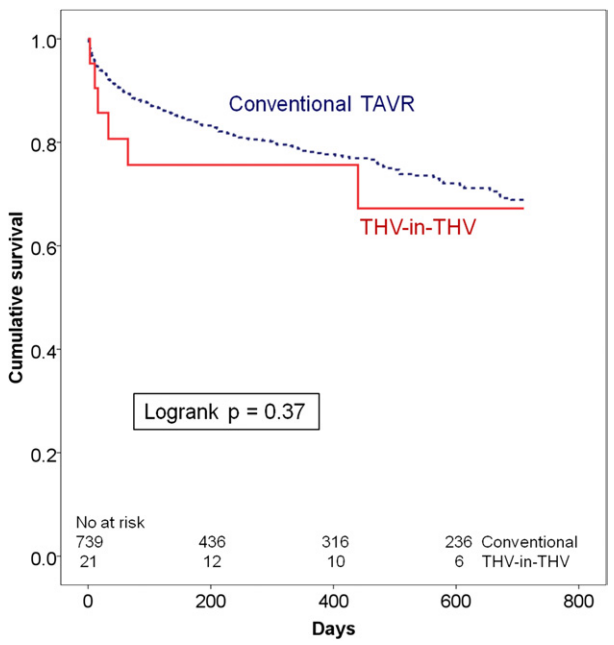


**Figure 4. Kaplan-Meier Curves for All-Cause Mortality**

Kaplan-Meier curves for all-cause mortality in patients undergoing THV-in-THV **(red line)** and patients undergoing conventional transcatheter aortic valve replacement (TAVR) **(dotted blue line).** THV = transcatheter heart valve.

been scattered, unpublished reports of immobile leaflets responding to catheter manipulation; however, documentation is limited, the mechanisms of leaflet dysfunction are speculative, and the durability of these interventions is uncertain. Importantly, in each of our 3 patients with an immobile leaflet, implantation of a second valve resulted in the durable return of normal valve function.

The CE and Sapien valves were designed such that their leaflets were fully open and apposed to the stent frame at rest. As with a native aortic valve, the initial force to close the leaflets of the prosthesis is created by backflow during diastole. When such a valve is implanted low in the aortic annulus, then surrounding annular tissue or an overhanging native leaflet may reduce this closing force, resulting in what appears to be a "frozen" or "stuck" leaflet. The newer-generation Sapien XT THV addressed this problem by incorporating tissue leaflets that open fully in response to systolic ejection, but are slightly closed at rest, theoretically allowing more reliable leaflet closing (Fig. 6). All the cases observed in this experience were with the earlier Sapien THV, whereas, to our knowledge, acute leaflet failure has not been observed with the current generation Sapien XT THV.

**Late outcome.** Survival of THV-in-THV and conventional TAVR at 30 days was 86% and 93%, respectively. Survival at 1 year was 76% and 78%, respectively. One patient had moderate paravalvular regurgitation 1 year after THV-in-THV, and the remaining patients had no or mild regurgitation. Mean transvalvular gradient did slightly increase and was 15 ± 4 mm Hg at 1-year follow-up, which was significantly higher than in patients undergoing conventional TAVR (11 ± 4 mm Hg). For comparison, mean gradients at 1-year follow-up were 13 and 10 mm Hg in the PARTNER studies (10,11). In a recent publication by our group, we noticed a small increase in gradients after conventional TAVR with the balloon-expandable valve resulting in a gradient of 12.1 mm Hg 3 years after the procedure

**Figure 5. Transvalvular Gradients in Patients Undergoing THV-in-THV and Conventional TAVR**

The transvalvular gradients in patients undergoing THV-in-THV **(red)** and conventional TAVR **(blue)** are shown. At 1-year follow-up, gradients were significantly higher after THV-in-THV. Abbreviations as in Figures 2 and 4.

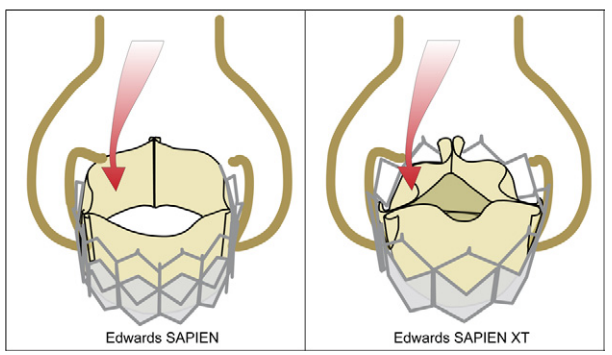


**Figure 6. Mechanism of Transvalvular Regurgitation**

As with a native aortic valve, the initial forces closing the leaflets of the prosthetic valve are the result of backflow during diastole **(arrows).** Where there is overlapping tissue, such as an overhanging native leaflet in the case of a relatively low implant, this may result in the appearance of a "frozen leaflet" and severe transvalvular regurgitation. This has been addressed in the newer-generation Sapien XT prosthesis where the leaflets are partially closed at rest and not apposed to the prosthetic frame.

(18). Longer follow-up will clarify if gradients continue to rise after THV-in-THV.

Recently, Ussia et al. (4) reported 24 of 663 (3.6%) patients undergoing THV-in-THV procedures with the self-expanding CoreValve (Medtronic Inc., Minneapolis, Minnesota) device. All patients had a paravalvular leak after too low (n = 18) or too high (n = 6) implantation of the initial THV. None of their patients died within 30 days, but 33% required a permanent pacemaker. At 12-month follow-up, mean gradient was 10.5 ± 5.2 mm Hg, which was not different from patients undergoing a conventional CoreValve procedure. Of note, the CoreValve already has a limited ability for repositioning in case of initial malpositioning.

**Study limitations.** THV-in-THV was performed based on the operator's decision without pre-specified criteria. Little is known about long-term durability of THV-in-THV implants, and information from in vitro models is not available. The possibility for stasis between the 2 implanted valves is a concern, and the risk of thrombosis and the optimal anticoagulation regimen are not known.

## Conclusions

This multicenter study shows that THV-in-THV implantation for failed balloon-expandable TAVR is feasible and results in satisfactory short- and mid-term outcomes. This may have important implications for patients who develop late failure of transcatheter valves.

**Acknowledgment**

The authors would like to thank Eldon Underhill for preparation of Figure 6.

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**Key Words:** aortic stenosis ■ aortic valve regurgitation ■ transcatheter aortic valve implantation ■ transcatheter aortic valve replacement.