Transcatheter Heart Valves for Failing Bioprostheses

State-of-the-Art Review of Valve-in-Valve Implantation

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Transcatheter aortic valve implantation (TAVI) is emerging as an alternative to conventional surgical aortic valve replacement (AVR) in high-risk patients with severe symptomatic aortic stenosis (AS).[1,2] Since the first-in-man procedure in 2002,[3] TAVI has been rapidly adopted in Europe and Canada, and, to date, more than 30 000 procedures have been performed worldwide. TAVI early and medium-term results have been promising.[3–5] In the first prospective, multicenter, randomized, controlled clinical trial in the United States (PARTNER), safety and effectiveness of TAVI was evaluated in a stratified population of inoperable and high-risk patients with severe symptomatic AS.[6,7] Superiority of TAVI over medical therapy, including balloon aortic valvuloplasty, has been proven in inoperable patients in whom TAVI significantly improved survival and reduced cardiac symptoms.[6] Furthermore, in high-risk surgical cohorts, TAVI demonstrated noninferiority to gold-standard surgical AVR in which all-cause mortality was similar at 1 year.[7] However, in both inoperable and high-risk cohorts, TAVI was associated with higher incidence of major stroke and major vascular events.[6,7]

While TAVI experience within native AS rapidly progresses, TAVI offers an attractive option for patients with failing bioprostheses (valve-in-valve concept). Over time, bioprostheses have been preferentially used over mechanical valves for valve replacement because of favorable clinical results, patient age, and preference—outperforming mechanical valves in market share.[8] As life expectancy increases, degeneration of previously implanted bioprostheses will inevitably become more common, requiring reoperative valve replacement. Reoperation in patients with degenerated bioprostheses carries an operative mortality risk ranging from 1.5% to 23%, depending on patient age, sex, preoperative New York Heart Association (NYHA) class, left ventricular dysfunction, number of previous operations, urgency of operation, and technical difficulties caused by adhesions.[9] In high-risk surgical patients who are candidates for reoperative valve replacement, TAVI is particularly appealing to achieve adequate valvular function for symptom relief without prolonged recovery. Off-label valve-in-valve implantation has been performed in numerous case reports in Europe and Canada.[10–13] In this review, we examined available literature to provide an overview of valve-in-valve implantation using transcatheter heart valves (THVs), with an emphasis on aortic and mitral positions.

Transcatheter Valves

Two THVs are currently approved for clinical use in Europe: balloon-expandable Edwards valve (Cribier-Edwards, Edwards SAPIEN, and SAPIEN XT; Edwards Lifesciences, Irvine, CA) and self-expanding Medtronic CoreValve *ReValving* System (CoreValve *ReValving* Technology; Medtronic Inc, Minneapolis, MN). The Edwards SAPIEN valve consists of trileaflet pericardial bovine valve sutured to a stainless steel frame (or cobalt chromium in SAPIEN XT), deployed through either the transfemoral or transapical approach (Figure 1). SAPIEN is available in 2 sizes, 23-mm diameter designed to fit annulus sizes ranging from 18 to 22 mm, and 26-mm diameter for 21–25-mm annulus.[14,15] Recently, 20 mm and 29 mm SAPIEN XT have become commercially available in Europe for smaller and larger aortic annulus sizes.[15] The Medtronic CoreValve is constructed from 3 porcine pericardial leaflets mounted in a self-expandable nitinol stent (Figure 2). CoreValve is available in 2 sizes, 26-mm diameter, designed for 20–23-mm annulus, and 29-mm diameter for 23–27-mm annulus.[15] CoreValve can be deployed through the percutaneous transfemoral approach, or in severe peripheral vascular disease through the subclavian/transaxillary approach.[14] Both Sapien and CoreValve implantation have isolated reports of direct aortic access.[15]

Edwards SAPIEN and Medtronic CoreValve received Conformite′ Europe′enne (CE) Mark approval in 2007 and are commercially available in Europe. Both are available in Canada with special access procedures for high-risk and inoperable patients. In the United States, SAPIEN was investigated in the PARTNER (Placement of Aortic Transcatheter Valve) trial,[6,7] whose results are used to obtain Food

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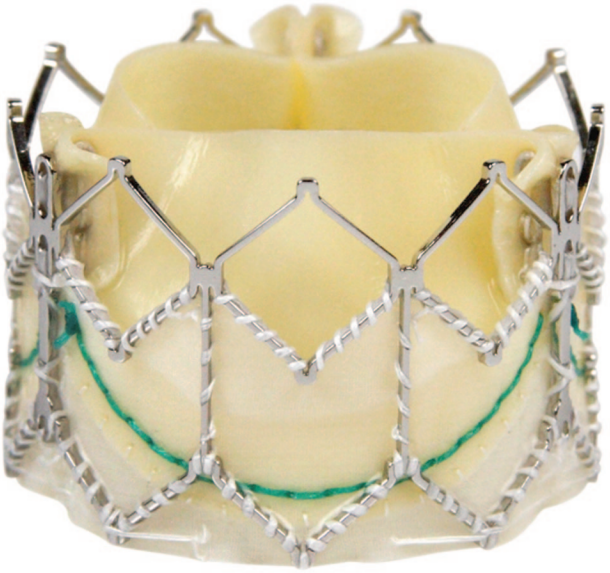

Figure 1. Edwards SAPIEN XT. Courtesy of Edwards Lifesciences.

and Drug Administration approval, slated for late 2011/early 2012. CoreValve began a multicenter, randomized, controlled clinical trial in the United States in 2010, comparing high-risk AVR with TAVI, whereas inoperable patients undergo TAVI because PARTNER demonstrated clear TAVI reduction in absolute mortality.[6] Both SAPIEN and CoreValve are not yet available commercially in the United States. At least 18 other THVs are in active development, with 7 having first-in-man results.[16]

Figure 2. Medtronic CoreValve System with AccuTrak Stability Layer. Copyright Medtronic, Inc. Reprinted with permission.

Valve-in-Valve Implantation

THV implantation represents an invaluable, minimally invasive alternative to surgical valve re-replacement in elderly high-risk patients with bioprosthetic structural valve deterioration. Valve-in-valve terminology was originally coined for THV implantation within a degenerated surgical bioprosthesis.[17] However, "valve-in-valve" more recently has also been used to refer to emergent THV implantation within another THV to fix a malfunctioning valve, correct malpositioning, or reduce paravalvular leakage.[18,19] Preclinical data regarding feasibility and hemodynamics of valve-in-valve implantation in degenerated bioprostheses are described in the online-only Data Supplement. To date, clinical implementation of valve-in-valve in degenerated bioprostheses (aortic, mitral, tricuspid) has been described in ≈134 patients worldwide, based on published reports. Compared with TAVI within native AS, in which >30 000 procedures have been performed, valve-in-valve implantation is gradually developing as viable off-label therapy for high-risk elderly patients with degenerated bioprostheses.

The largest valve-in-valve series reported thus far describes 24 patients with failed aortic (n=10), mitral (n=7), pulmonary (n=6), and tricuspid (n=1) bioprostheses from a Canadian multicenter experience.[13] Edwards THVs were implanted using the transapical or transfemoral approach for aortic and mitral bioprostheses, transvenous for pulmonary valves, and direct right atrial access for the tricuspid valve. Overall procedural success was 96%, and 30-day mortality was 4.2%, related mainly to an early learning curve. No pacemakers were required, and there was 1 stroke (4%). By bioprosthetic position, 30-day mortality was 0% for aortic, 14% for mitral, and 0% for pulmonary and tricuspid valves. Valve-in-valve implantation is discussed below for aortic and mitral bioprostheses and in the online-only Data Supplement for tricuspid valves.

Valve-in-Valve Implantation in Aortic Bioprostheses

The first-in-man valve-in-valve was implanted for severely regurgitant aortic bioprosthesis in an 80-year-old man with 35.6% preoperative logistic Euroscore, from 2 prior thoracic operations, pulmonary hypertension, coronary artery disease, and reduced ventricular function.[20] A 21F CoreValve was implanted through the transfemoral route within a 23-mm Mitroflow, using hemodynamic support from femoral-femoral cardiopulmonary bypass. He became asymptomatic, in NYHA class I, and at 1 year, excellent THV function was seen on echocardiography with 12 mm Hg mean gradient. Shortly after, a first-in-man valve-in-valve was implanted through the transapical approach, using the 23-mm SAPIEN in a severely stenotic 21-mm Perimount.[21] An 82-year-old woman became asymptomatic with good valvular function. Since these first reports, feasibility of valve-in-valve implantation has been described in various failed bioprostheses, using SAPIEN or CoreValve (online-only Data Supplement Table 1).

Worldwide clinical experience of valve-in-valve implantation in aortic position is listed in online-only Data Supplement Table 2. Indications for valve-in-valve implantation

included bioprosthetic stenosis, regurgitation, or both. Paraprosthetic regurgitation of degenerated bioprosthesis is not a good indication because the paravalvular leak around the bioprosthesis cannot be corrected from THV implantation within the bioprosthesis. Among published reports of valve-in-valve in aortic position, indications were distributed as 46% stenosis, 38% regurgitation, and 14% both. Overall, the transapical route has been preferred, with 69% transapical, 25% transfemoral, and 5% transaxillary/subclavian access for degenerated aortic bioprostheses. Recently, 1 case was reported of transaortic access for CoreValve within degenerated aortic Mitroflow.[22] Studies have not all clearly delineated exact bioprosthetic models; for example, Carpentier-Edwards aortic bioprosthesis may refer to porcine or pericardial valve and is commonly not specifically clarified. Valvular hemodynamics was not always clearly ascertained. No studies thus far report valve-in-valve implantation within 19-mm degenerated bioprostheses, which is important because currently available THVs would not be expected to be effective, based on experimental evidence (preclinical data in the online-only Data Supplement).[23,24] The first-in-man TAVI of 20-mm Sapien XT in the small annulus of native AS[25] may enable future treatment of select 19-mm bioprostheses, albeit with elevated gradients, based on experimental results.[26]

Recently, German Heart Center, Munich, reported the largest case series of TAVI within failing aortic bioprostheses.[10] Twenty patients, 14 with stented and 6 with stentless bioprostheses, were treated with SAPIEN transapically (n=17) and CoreValve transfemorally (n=3). Procedural success was 90%, with 1 failure from CoreValve migration to the ascending aorta twice in a patient with severely regurgitant homograft requiring surgical conversion and the other failure from "stone heart" after balloon aortic valvuloplasty resulting in intraprocedural death. Unlike other series, in-hospital mortality was 10% higher than mean Society of Thoracic Surgeons (STS) risk score for mortality of 7±4%, with 1 death as stated above and the other caused by left main coronary occlusion, which was successfully stented but still resulted in death. Mean transvalvular gradient after TAVI was 20.0±7.5 mm Hg. Paravalvular leakage was none to trivial, mild, and mild-moderate in 10, 6, and 2 patients, respectively. There was no stroke and no need for a pacemaker.

In contrast, 2 other German case series from Berlin[27] and Leipzig[11] of TAVI within degenerated aortic bioprostheses demonstrated better procedural success (100% in 14 and 11 patients, respectively) with no in-hospital mortality despite mean STS risk scores of 21.9±10.9% and 7.2±2.6%, respectively. In the Berlin series, perioperative recovery was uneventful in 13 patients; 1 patient required reoperation 3 months later because of endocarditis and 2 late deaths occurred at 3 and 4.5 months. All patients in the Leipzig series were alive and well after follow-up at a mean of 330±293 days. Both series exclusively performed the transapical approach with SAPIEN. Mean transvalvular gradient was reduced from 37.1±25.7 to 13.1±6.4 mm Hg (range, 5–29 mm Hg) in Berlin and from 40.2±13.2 to 11±4 mm Hg in the Leipzig series. Neither series had paravalvular leak, but in Leipzig, 2 patients (18%) had mild central regurgitation. Neither series was complicated by stroke or pacemaker implantation. These studies demonstrated clinical proof of concept of valve-in-valve strategy in select high-risk patients, with caveats of potential patient-prosthesis mismatch and unknown long-term results.

With respect to CoreValve, comparatively there are fewer clinical reports of valve-in-valve implantation.[12,28] The 2 largest series included 4 cases each; Khawaja's series used transfemoral access in 3 patients and transaxillary in 1, whereas Dvir's used 50% transfemoral and 50% transaxillary. In both series, valve-in-valve implantation in stenotic and regurgitant aortic bioprostheses was successful in 100%, with 0% in-hospital mortality. Peak transvalvular pressure gradient in Khawaja's series decreased from 50–120 mm Hg to 24–59 mm Hg on follow-up at 2–6 months. Mean gradient decreased from 43±9.3 mm Hg to 12.3±8.6 mm Hg in Dvir's series. No patients had strokes or required pacemakers in either series. A summary of available aortic valve-in-valve hemodynamics, based on valve type and size, is provided in the online-only Data Supplement.

Valve-in-Valve Implantation in Mitral Position

Experience with mitral bioprosthetic valve-in-valve implantation has been limited with ≈24 patients, in whom only SAPIEN has been implanted. THV implantation in the mitral bioprostheses was quite challenging, with 2 deaths initially in the multicenter Canadian experience. The first-in-man attempt was unsuccessful through the percutaneous transseptal approach with THV embolization into the left ventricle, emergent surgical conversion, and death.[13] Recently, the largest series of mitral valve-in-valve implantation was reported from Vancouver (n=11).[29] The first patient underwent open transatrial approach that failed, necessitating transapical conversion to obtain successful THV implantation with eventual death on day 45. Atrial approaches were abandoned and the transapical approach was adopted subsequently for successful valve-in-valve implantation. In-hospital mortality was 9% for patients with 16.1±5.8% mean STS risk. Mean THV gradients ranged from 3 to 9 mm Hg for mitral valve sizes 23–29 mm, and THV regurgitation was at most mild. A summary of available mitral valve-in-valve hemodynamics by valve type and size is presented in the online-only Data Supplement.

Discussion

Valve-in-valve implantation is emerging as an attractive new alternative to conventional reoperation for degenerated bioprostheses in high-risk elderly patients. The valve-in-valve concept has proven technically feasible in in vitro and in vivo animal experiments with acceptable hemodynamics in select THV/bioprosthesis combinations.[17,24] However, limited combinations of numerous available surgical bioprosthetic valve types, sizes, and configurations have been investigated with respect to 2 CE Mark approved THVs. Appropriate THV sizing recommendations for a given bioprosthesis requires comprehensive in vitro hemodynamic evaluation of all potential valve-in-valve configurations not currently available. As such, reported clinical experiences are the only surrogate to provide available evidence. Clinical experiences to date are

limited and consist primarily of small case reports with incomplete data on hemodynamics and valve types (online-only Data Supplement Tables 1–4). Nevertheless, the number of patients referred for valve-in-valve implantation is increasing as the result of TAVI availability in select centers and increasing awareness by referring physicians.[11] Clinical outcomes thus far suggest that valve-in-valve implantation may be an acceptable treatment in elderly high-risk surgical patients. The global success rate of valve-in-valve implantation in patients with degenerated aortic bioprostheses has been 96%, based on published cases. However, durability of THVs within bioprostheses is unknown, as is the durability of THVs in general. Recently, the first case of degenerated THV in native AS was reported of a severely stenotic, second-generation 26-mm CoreValve implanted 5.5 years earlier[30]—a time frame significantly shorter than expected for degeneration of surgical bioprostheses. A third-generation 26-mm CoreValve was implanted as valve-in-valve successfully. Therefore, longer-term follow-up of treated patients and increased experience with valve-in-valve implantation is required to determine the true role of this novel therapy for management of bioprosthetic degeneration. Future possibilities in valve-in-valve implantation are presented in the online-only Data Supplement.

Feasibility of valve-in-valve implantation using both Edwards SAPIEN and Medtronic CoreValve has been shown for failed aortic bioprostheses. However, only SAPIEN has been used for valve-in-valve implantation in mitral and tricuspid bioprostheses. Overall, SAPIEN exceeds CoreValve in total number of valve-in-valve implantations reported (online-only Data Supplement Table 1). For failed mitral and tricuspid bioprostheses, the lower profile height of SAPIEN THVs makes them better suited for valve-in-valve implantation than CoreValve, with its longer stent. However, CoreValve can be used successfully in degenerated bioprostheses in the aortic position. At this time, preclinical and clinical data are limited, and fair comparison between SAPIEN and CoreValve for valve-in-valve implantation in aortic bioprostheses cannot be made.

Valve-in-valve implantation has been feasible through either the percutaneous or minimal invasive approach. However, the transapical approach has been favored because of its direct access in both aortic and mitral positions. In general, SAPIEN may be implanted through the transapical (93%) or transfemoral (5%) approach for the aortic position, with transapical being the preferred route.[10] CoreValve does not have the transapical approach and thus may be implanted in the aortic position through the transfemoral (81%) or transaxillary (8%) approach. SAPIEN is primarily implanted in the mitral position through the transapical approach, given initial poor outcomes through other approaches.[29] Successful tricuspid valve-in-valve implantation has been performed through the right internal jugular vein or transfemoral venous approach.

TAVI within native AS is based on the principle of THV oversizing[1]; similarly, in stentless bioprostheses or homografts, THVs are usually oversized by 2–3 mm to achieve stability and minimize paravalvular leakage. Without THV oversizing or valve calcification, THV migration forces are greater into the left ventricle than distally, based on computational simulations,[31] though clinically THVs may migrate distally during deployment if not anchored in the annulus or may migrate into the left ventricle if positioned too far below the annulus.[13] Frictional force provided by oversizing and/or calcification of leaflets or the aortic wall is required to prevent THV migration in native valves as well as stentless valves or homografts. As such, for stentless valves or homografts, appropriate choice of THV size requires proper sizing of the annulus by transesophageal echocardiography (TEE) or computed tomography (CT), because stentless valves do not have a rigid ring. However, in stented bioprostheses, the rigid annulus of the sewing ring and stent posts can constrain an oversized THV to prevent full expansion of the stent.[24] Lack of THV expansion to nominal size may result in patient-prosthesis mismatch, with higher than desirable gradients for valve-in-valve implantation.

Selection of appropriate THV and THV size for valve-in-valve implantation should ideally be based on in vitro hemodynamic evaluation of valve-in-valve combinations. Valve-in-valve implantation within 19- and 21-mm Carpentier-Edwards Perimount using available 23-mm THV size may result in high pressure gradients, depending on inner bioprosthetic stent diameter.[23] Lack of THV stent expansion to nominal dimensions resulted in THV leaflet distortion. Based on in vitro hemodynamics, 23-mm THV within 19-mm Perimount bioprostheses would be contraindicated clinically, but 20-mm THV would yield potentially acceptable but elevated mean gradients >20 mm Hg.[26] However, 20-mm THV did not yield acceptable gradients in 19-mm Edwards porcine valves. Thus, first-in-man application of 20-mm Sapien XT in native AS[25] may potentially treat select smaller-sized bioprostheses.

With respect to 21-mm bioprostheses, current clinical literature demonstrates that valve-in-valve implantation can yield acceptable hemodynamics in some patients but can also result in mean gradients >20 mm Hg, suggesting incomplete relief of obstruction, which is concerning (online-only Data Supplement Table 1). For high-risk elderly patients, such elevated gradients may reflect the use of valve-in-valve implantation as a palliative procedure. On the other hand, significant patient-prosthesis mismatch may be detrimental. One such case in which a 23-mm SAPIEN was implanted within a 21-mm Hancock (inner diameter, 18.5 mm), unacceptably high transvalvular gradients (43 mm Hg) required reoperation at 1 year with surgical AVR.[32] In addition, THV oversizing can lead to THV leaflet distortion, which may affect long-term THV durability. Long-term follow-up is essential to determine the impact of THV-bioprosthesis mismatch on clinical outcome, left ventricular mass regression, and ejection fraction.

Because only limited in vitro data of select THV/bioprosthesis combinations are available regarding valve-in-valve hemodynamics, THV size selection should be matched on the basis of bioprosthetic inner diameter. However, stented bioprostheses of different models or from different companies have no consistent size labeling, and labeled valve size has no correlation with true bioprosthetic inner stent diameter. The inner diameter of surgical bioprostheses varies, based on

manufacturer, model, and size and is listed in online-only Data Supplement Table 5. Kempfert et al[11] have suggested general recommendations for selecting SAPIEN size for valve-in-valve implantation, based on aortic bioprosthesis inner diameters, but cannot be considered an extensive guideline. A complementary but essential approach is intraoperative sizing of bioprosthetic internal diameter by TEE and/or CT to guide the choice of THV size, because information regarding make and model of degenerated bioprosthesis from prior operative reports may not be available.

Principles of valve-in-valve implantation are similar to that of TAVI within native AS, but with key differences. One such difference is that TAVI in native valves is performed in stenosis, whereas valve-in-valve implantation has been performed for both stenosis and regurgitation. Unlike native AS, in which the calcified leaflets and annulus anchor THVs, the rigid sewing ring of stented bioprostheses anchors THVs in valve-in-valve implantation. Thus degenerated stented bioprostheses with regurgitation, stenosis, or mixed pathology are amenable to valve-in-valve implantation. No guidelines to date have suggested THV sizing for valve-in-valve implantation on the basis of degenerative pathology but rely on inner bioprosthetic stent diameter. Stentless valves and homografts that do not have rigid sewing rings have also undergone successful valve-in-valve implantation for both stenosis and regurgitation. These valves are known to degenerate by calcification, but what role THV oversizing versus valve calcification plays in anchoring THV is unknown, based on current reports.

As in TAVI in native AS, imaging modalities, TEE, and CT imaging are essential for determining anatomic suitability of valve-in-valve implantation. Bulky leaflet calcification and pannus in degenerated bioprostheses can be identified to avert procedural complications. Coronary angiograms or coronary CT scans are critical for both TAVI and valve-in-valve implantation in aortic bioprostheses to assess risks of coronary ostial obstruction. Two coronary occlusion cases have been described recently with valve-in-valve treatment of a degenerated 21-mm Mitroflow.[33] Unlike most bioprostheses, Sorin Mitroflow (Sorin, Vancouver, BC, Canada) and St Jude Trifecta (St Jude, St Paul, MN) have leaflets mounted outside the stent to maximize orifice area. During valve-in-valve implantation, these bioprosthetic leaflets, not being constrained within stent frame, may extend to aortic wall and potentially obstruct coronaries. Although successful valve-in-valve within the Mitroflow has been reported (online-only Data Supplement Table 1), these 2 coronary occlusion cases raise concern about THV implantation within these valves. Aortic root anatomy, coronary ostial position, and specifics of the bioprosthesis are important considerations for valve-in-valve implantation to avoid coronary obstruction. Particularly, the relationship of the bioprosthetic stent and leaflet height in relation to coronary orifices and size of sinotubular junction should be noted by CT scan before intervention.

Another key difference between valve-in-valve implantation and TAVI is the presence of radiopaque markers in most stented bioprostheses[11] (Figure 3). Carpentier-Edwards bioprostheses have a visible annular and strut frame. Medtronic Mosaic and Hancock valves have 3 small radiopaque rings at the top of struts, but in addition, the Hancock has a radiopaque sewing ring. The sewing ring of the Mitroflow is also radiopaque, but the St Jude bioprostheses have a faintly radiopaque annulus that requires high-resolution imaging. Overall, the ability to see stented bioprostheses fluoroscopically is a significant advantage by providing an ideal landmark to facilitate correct THV positioning. Stentless bioprostheses and homografts are similar to native aortic valves, in which leaflet calcification provides the landmark for positioning. However, when the failure mode is regurgitation, stentless valves may be more challenging than native valves because sufficient calcium may not be present to determine annulus location.

Valve-in-valve implantation differs from TAVI in optimizing THV positioning and delivery. For SAPIEN, coaxial alignment of THV within degenerated bioprosthesis is critical for success, which favors the transapical over the transfemoral approach. Positioning for valve-in-valve implantation requires THV overlap to extend below the bioprosthetic annulus (Figures 3 and 4).[13] Without sufficient overlap, struts of the bioprosthetic stents may be splayed during deployment with distal ejection of the THV. Such THV/bioprosthetic annulus overlap is advantageous for long-term stability and secure THV fixation. On the other hand, for CoreValve, the longer stent design with wider-diameter upper section designed as an ascending aortic landing zone allows stent fixation to prevent distal migration. Thus, the goal for CoreValve may be to implant THV as distal as feasible within the bioprosthesis to allow supra-annular position of THV leaflets, potentially improving hemodynamics of THVs constrained within inexpandable bioprosthetic ring.

Proper stent expansion is important for successful valve-in-valve implantation. Surgical stented bioprostheses are fundamentally different from THVs in design. Bioprostheses have highly consistent, reproducible leaflet kinematics because their valve leaflets are mounted within a rigid framework. In contrast, THV leaflet kinematics is determined by degree of THV expansion and symmetry and circularity of deployed THV. Optimal THV function requires expansion of the valve to its nominal dimensions.[23,34] Underexpanded THVs may function suboptimally, demonstrating increased transvalvular pressure gradients and impaired coaptation of leaflets.[24] Leaflet distortion increases stress on leaflets and may result in THV premature failure.[13] Long-term THV durability and failure mode is unknown. Underexpanded THVs may prematurely fail from leaflet tearing and/or calcification. Because THV oversizing is necessary to achieve appropriate valve anchoring and decrease paravalvular regurgitation, a balance must be achieved to reduce the adverse impact of THV oversizing on valvular hemodynamics and long-term durability.[23]

Patient-prosthesis mismatch may inevitably occur after valve-in-valve implantation in patients with small bioprostheses. The role of patient-prosthesis mismatch after standard AVR has been well described with respect to left ventricular mass regression, cardiac failure, and perioperative and long-term mortality.[35] Severe patient-prosthesis mismatch after TAVI has been reported to be significantly less than after surgical AVR.[36] However, after valve-in-valve within degen-

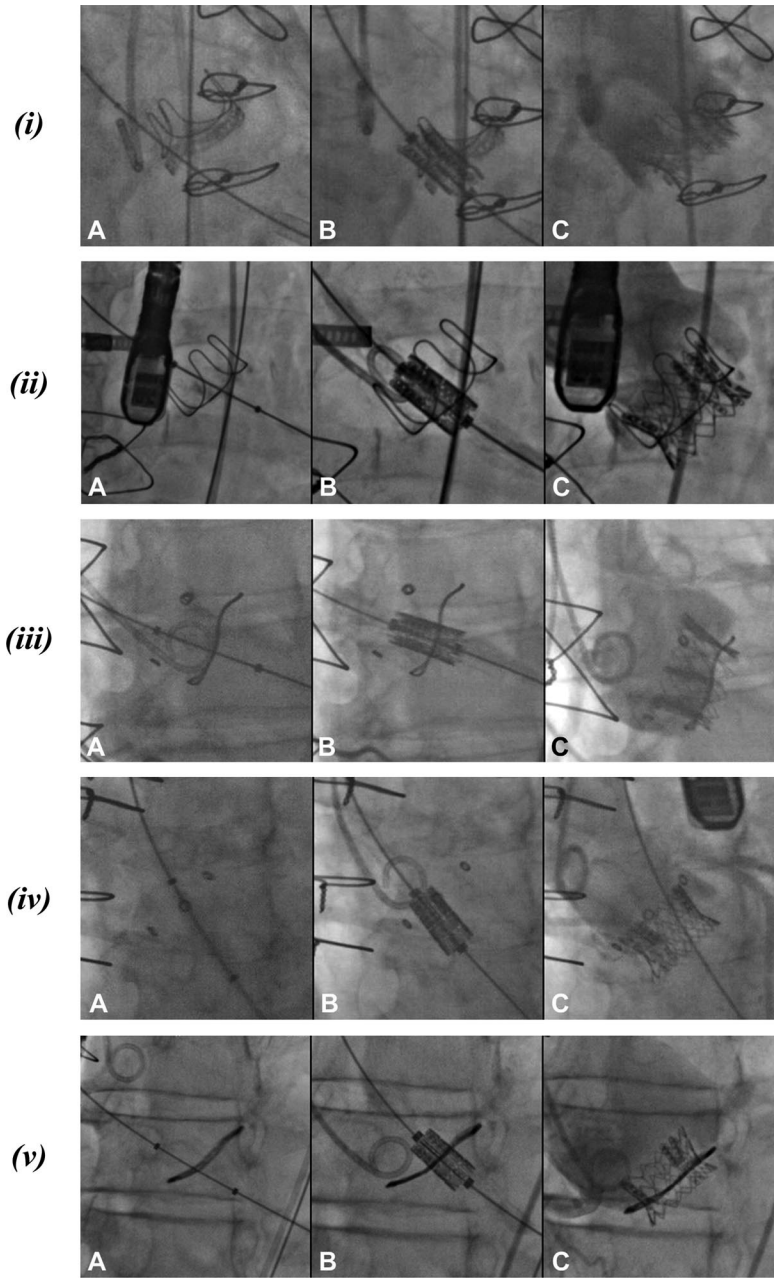

Figure 3. Valve-in-valve aortic: (i) 23-mm SAPIEN in 21-mm CE Perimount, (ii) 26-mm SAPIEN in 25-mm CE Porcine, (iii) 26-mm SAPIEN in 25-mm Hancock, (iv) 23-mm SAPIEN in 21-mm Mosaic, and (v) 23-mm SAPIEN in 23-mm Mitroflow. **A**, Orthogonal view before balloon valvuloplasty. **B**, Valve positioning. **C**, Final angiographic result. Reprinted with permission from Elsevier.[11]

erated bioprostheses, moderate or even severe patient-prosthesis mismatch may be expected. One potential solution to reduce patient-prosthesis mismatch is to use the supravalvular THV, in which the valve of the THV is situated above the bioprosthesis to maximize available orifice area[37] or, alternatively, to increase available THV sizes to match smaller bioprosthetic diameters.[26] Experimental evidence suggests that 20-mm THVs may improve patient-prosthetic mismatch in 19-mm Perimount[26] compared with 23-mm THV counterparts, but neither 20- nor 23-mm SAPIEN are precisely matched for 19- and 21-mm surgical bioprostheses. Based on current 23-mm THV technology, aortic enlarging procedures may be considered at the time of primary operation to implant larger bioprostheses if future valve-in-valve implantation with THVs is considered.

Permanent pacemaker implantation has been less frequent with valve-in-valve than TAVI. Pacemaker implantation after TAVI within native valves is significantly higher for CoreValve (20–38%) than SAPIEN (3–10%),[15] which may be because SAPIEN is shorter than CoreValve, and, with CoreValve, there is continued pressure on the septal conduction system.[15] Based on published valve-in-valve cases (online-only Data Supplement Table 2), none of 58 cases treated with SAPIEN developed heart blocks, and only 2 of 22 CoreValve-treated patients required a permanent pacemaker (9%). Lack of heart block with valve-in-valve implants may be due to the rigid bioprosthetic ring protecting the conduction system from THV compression, though the precise mechanism is unknown.

One nearly unavoidable phenomenon after TAVI in native AS is paravalvular leakage, occurring up to 70% of the time,

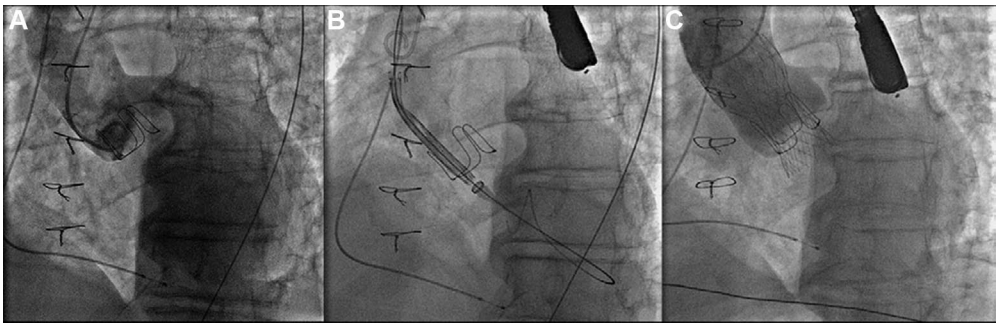

Figure 4. A, Aortography demonstrating aortic regurgitation of 23-mm CE bioprosthesis. **B**, Bioprosthetic target for 26-mm CoreValve. **C**, Aortography showing transcatheter heart valve final position within original device scaffold without regurgitation. Reprinted with permission from Elsevier.[12]

mostly mild but occasionally moderate in severity.[15] The German TAVI registry data suggested worse short-term outcome, with increased in-hospital mortality, in patients with at least moderate aortic regurgitation after TAVI.[38] In contrast, valve-in-valve implantation results in fewer paravalvular leaks due to the symmetrical sewing ring of surgical bioprostheses, which facilitates sealing.[11,13] However, for Carpentier-Edwards pericardial valves, SAPIEN did not sufficiently conform to the bioprosthetic annulus to prevent paravalvular leakage. A new SAPIEN cloth-THV has been tested experimentally to reduce paravalvular leakage with valve-in-valve implantation.[39]

Current THVs match and may exceed hemodynamic performance of surgically implanted bioprostheses, based on pressure gradient, effective orifice area, and blood flow velocity.[36,40] However, none of these standard criteria take into account paravalvular regurgitation. Transvalvular energy loss may become the new benchmark for comparing hemodynamic results among THVs and surgical valves because residual regurgitation is routinely found after TAVI but not AVR. Transvalvular energy loss may be more appropriate criteria to assess THV performance by determining valvular hemodynamics during the entire cardiac cycle.[41] Although mild to moderate aortic regurgitation post-TAVI may not have significant clinical impact in high-risk elderly patients, this degree of regurgitation may have considerable consequences in the long term if THVs are implanted in younger, healthier patients.

Conclusions

Valve-in-valve implantation is an attractive alternative to conventional reoperation for elderly high-risk surgical patients with bioprosthetic degeneration. THV within degenerated bioprostheses has demonstrated clinical proof-of-concept and is a promising therapy for patients of advanced age and comorbidities. Valve-in-valve implantation has shown less morbidity and mortality than predicted for reoperative valve replacement. However, clinical experience is still limited for this off-label indication. The ideal approach would be to evaluate patients individually in a multidisciplinary setting, where the procedure of choice should be selected on the basis of experience of the center, expertise of cardiologists and cardiac surgeons, and size and type of bioprosthesis. Long-term follow-up of treated patients and increasing clinical experience will be necessary to establish the true role of valve-in-valve implantation for bioprosthetic degeneration. Until outcomes are proven in large cohort studies or randomized trials, patients should be evaluated and treated on an individual basis. Long-term durability and outcome of valve-in-valve implants will be critical to expansion of this technology to lower risk subsets. The valve-in-valve concept may revolutionize treatment of bioprosthetic degeneration and shift the paradigm from mechanical to bioprosthetic valves in younger patients.

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Disclosures

None.

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