FOCUS ON TRANSCATHETER HEART VALVE INTERVENTION

STATE-OF-THE-ART REVIEW

Expanding Indications of Transcatheter Heart Valve Interventions

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CME Objective for This Article:
At the end of this activity the reader should be able to: 1) appraise the rapid development of transcatheter aortic valve replacement as a treatment option in high-risk patients, in particular those who have previously undergone open-heart surgery; 2) compare the clinical outcomes of transcatheter aortic valve replacement in specific anatomical situations (bicuspid aortic valve, pure aortic regurgitation) with the results of the conventional procedure designed for the treatment of the stenotic tricuspid aortic valve; and 3) explain the technical aspects, potentials and limitations of the implantation of transcatheter aortic valve replacement devices in the mitral, tricuspid and pulmonary position.

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Expanding Indications of Transcatheter Heart Valve Interventions

ABSTRACT

Transcatheter aortic valve replacement (TAVR) has been established as a less invasive alternative to open-heart surgery in inoperable or high-risk patients presenting with symptomatic severe aortic valve stenosis. The feasibility and efficacy of valve-in-valve implantation in degenerated surgical aortic bioprostheses have also been described and can currently be considered a valuable treatment option in patients deemed unsuitable for repeat cardiac surgery. However, the clinical use of TAVR devices is not limited to the treatment of the tricuspid stenotic aortic valve. Several additional indications including treatment of the bicuspid stenotic aortic valve, aortic regurgitation, and valve-in-valve or valve-in-ring implantation in the mitral or tricuspid position as well as treatment of pure mitral, tricuspid, or pulmonary regurgitation have been described. The purpose of the present review is to summarize the available evidence concerning the emerging off-label use of TAVR devices in current clinical practice. Case examples have been selected to highlight the main procedural steps of each particular intervention. (J Am Coll Cardiol Intv 2015;8:1777–96) © 2015 by the American College of Cardiology Foundation.

During the past 10 years, transcatheter aortic valve replacement (TAVR) has emerged as a valuable minimally invasive treatment option for patients with symptomatic severe aortic stenosis. TAVR with the SAPIEN valve (Edwards Lifesciences, Irvine, California) was shown to be superior to medical treatment in the PARTNER (Placement of Aortic Transcatheter Valve) B trial, which found a profound and long-lasting reduction in mortality through 5 years of follow-up in patients deemed inoperable (93.6% vs. 71.8%; p < 0.0001) (1). Comparable results were obtained in extreme risk patients treated with the Medtronic CoreValve (MCV) (Medtronic, Minneapolis, Minnesota) transcatheter heart valve (2). In patients with severe aortic stenosis at high surgical risk included in the PARTNER 1A cohort, TAVR using the balloon-expandable SAPIEN prosthesis showed similar safety and efficacy compared with surgical aortic valve replacement during long-term follow-up (67.8% vs. 62.4% overall mortality; p = 0.76) (3). Along the same line, TAVR using the self-expanding CoreValve prosthesis in patients at increased surgical risk was associated with lower mortality compared with surgical aortic valve replacement at 2 years (22.2% vs. 28.6%; p = 0.04) (4).

On the basis of these data, TAVR is recommended as the therapy of choice for inoperable patients with symptomatic severe aortic stenosis with a life expectancy longer than 1 year (Class IB) and an alternative to surgical aortic valve replacement in patients considered at increased surgical risk (Class IIaB) in both U.S. and European guidelines.

Due to the ease of implantation and favorable outcomes in observational studies, transcatheter valve-in-valve (VIV) implantation has been rapidly embraced for the treatment of degenerated surgical aortic bioprostheses to avoid redo surgery in the elderly population. Results from the International VIV Data Registry reported high procedural success rates (93.1%) and low periprocedural mortality at 30 days (7.6%) while providing favorable hemodynamic outcomes (5).

Several other valuable indications have emerged during the past several years including treatment of aortic regurgitation (AR), VIV or valve-in-ring (VIR) implantation of transcatheter heart valves in surgical prostheses in the mitral or tricuspid position, as well as treatment of native valve mitral, tricuspid, or pulmonary regurgitation and stenosis. The purpose of this review is to summarize the available evidence concerning the expanding indications of TAVR devices. Review of the published data and detailed case descriptions are presented for the following indications:

1. TAVR for the treatment of pure aortic valve regurgitation
2. TAVR in native bicuspid aortic valves (BAVs)
3. TAVR for the treatment of transcatheter aortic valve degeneration
4. Transcatheter valve implantation in the mitral position
5. Transcatheter valve implantation in the tricuspid position
6. Treatment of pulmonary valve disease using transcatheter heart valves
TAVR FOR THE TREATMENT OF PURE AORTIC VALVE REGURGITATION

Pure AR is far less frequent than symptomatic aortic stenosis, affecting ~13% of patients with isolated, native left-sided valvular heart disease (6). Due to concerns of insufficient anchoring of conventional transcatheter heart valves within the noncalcified aortic annulus, surgical valve replacement remains the treatment of choice in operable patients. However, the implantation of conventional transcatheter heart valves not specifically designed for the treatment of the regurgitant aortic valves has been described in patients considered at prohibitive risk for open-heart surgery on a compassionate use basis (7,8). Due to the self-expanding frame with additional anchoring by means of abutment also against the ascending aorta, the self-expanding MCV has been used in the majority of cases. There is a single report describing the use of the transapical Medtronic Engager bioprosthesis (9) and another with the Edwards SAPIEN XT valve (ESV) in a patient with AR in the presence of a left ventricular assist device (10). Adequate deployment of transcatheter heart valves in an annulus with absent or minimal calcification remains challenging due to the absence of fluoroscopic landmarks, the need for oversizing, and the frequently concomitant dilation of the aortic root and/or the ascending aorta. Due to these technical and anatomical issues, valve deployment is less predictable and may be complicated by supra-annular (11) (Figure 1) or ventricular dislocation of the prosthesis, the latter possibly occurring up to several hours after implantation (12). To overcome these technical concerns, some groups advocate the use of 2 pigtail catheters for improved annular delineation (1 catheter placed in the noncoronary cusp, and the other placed in the left coronary cusp). Alternatively, transesophageal echocardiographic visualization may offer additional guidance, but requires general anesthesia. The use of rapid pacing, generally avoided during the implantation of self-expanding valves, can be useful in limiting the regurgitant volume as well as unintended valve motion.

Compared with TAVR for the treatment of native aortic valve stenosis, transcatheter treatment of pure AR is associated with a lower device success rate (74.4%), a higher rate of moderate to severe AR (21%), and an increased all-cause mortality (21.4%) at 12 months as reported in the largest multicenter study to date including 43 patients treated with the MCV for pure AR (13). Recently, another registry reported comparable results in 26 patients undergoing TAVR with the MCV (Table 1) (14). Of note, the need for permanent pacemaker implantation appears lower in this specific patient population compared with conventional TAVR patients despite the overwhelming use of self-expanding devices. This might be related at least in part to the absence of calcific aortic valve disease involving the surrounding structures, in particular, the atioventricular conduction system.

Several newer generation nondedicated self-expanding transcatheter prostheses have been investigated for the treatment of pure AR. In a small case series, the ACURATE TA device (Symetis SA, Ecublens, Switzerland) showed promising results in 8 patients followed for 1 year (15). Although there are only limited clinical data to date, the Lotus Valve System (Boston Scientific, Marlborough, Massachusetts) also has the potential to be successfully used in patients with pure AR (16) or regurgitant bioprosthetic valves (17) due to its partially self-expanding, repositionable design and the adaptive sealing skirt (Figure 2).

Substantial effort has been put into the development of dedicated devices enabling capture of aortic valve leaflets thanks to specific clips to minimize the risk of valve embolization and paravalvular leaks. The transapical, self-expanding JenaValve (JenaValve Technology, Munich, Germany) received CE mark of approval for the treatment of patients with pure AR in 2013 (18). Mid-term results after 6 months of follow-up in 31 patients (19) and after 1 year in 10 patients (20) showed sustained symptomatic improvement and good hemodynamic performance of the bioprosthesis with more than mild AR in only 1 patient (successfully treated with VIV implantation of an ESV after 3 months of follow-up). A similar system, the J-Valve (JC Medical, Inc., Redwood City, California), currently undergoes a first-in-human investigation in China. The recently published 90-day follow-up results showed favorable procedural outcomes with only minor AR in 90% of the patients. In 1 patient, conversion to surgical valve replacement was required due to device embolization into the ascending aorta (21).

The Helio transcatheter aortic docking device (Edwards Lifesciences) is another system designed to enable annular fixation of a standard balloon-expandable SAPIEN XT transcatheter heart valve in patients with a minimally calcified aortic annulus. The initial version with a combined transapical-transfemoral approach (22) has recently evolved into a fully transfemoral system that was successfully implanted in a patient with severe AR in 2013 (23).
TAVR IN BAV

BAV is the most frequent congenital heart defect with a prevalence of 0.5% to 2.0%, mostly affecting males (24,25). In as many as 50% of the cases, the valvular anatomic changes coexist with dilation of the aortic root and/or the ascending aorta (26). Approximately 20% of the patients 80 years of age and older have evidence of bicuspid anatomy (either congenital or due to fusion of severely degenerated leaflets) as observed during surgical aortic valve replacement (27). In clinical practice, a relatively small proportion of patients (~5%) evaluated for TAVR presents with bicuspid anatomy. TAVR in BAV remains challenging due to following anatomic and procedural factors:

1. Difficult valve positioning and anchoring due to the large anatomy of the ascending aorta and the elliptical shape of the aortic annulus
2. Incomplete valve frame apposition due to more severe, often eccentric, valve calcifications (28,29) frequently requiring post-dilation and associated

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**FIGURE 1** Examples of 2 Patients Undergoing Transfemoral TAVR for Treatment of Pure AR Using the MCV

In the first patient with severe central aortic regurgitation (A), implantation of a 26-mm Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) at proper height (B) resulted in almost complete abolition of the regurgitant jet (C), arrow indicates trivial residual AR. In the second patient (D), slight migration of a 29-mm MCV toward the ascending aorta after release (E) (white arrow indicates the bottom of the bioprosthesis frame; red line shows the aortic annulus plane) led to mild residual AR (arrow) originating from the noncoronary cusp visualized by transesophageal echocardiography (F). AR = aortic regurgitation; MCV = Medtronic CoreValve; TAVR = transaortic valve replacement.
with impaired hemodynamic outcomes (increased transvalvular gradient or paravalvular leak) (Figure 3).

 Increased risk of damage to the diseased aortic root and the ascending aorta during valvuloplasty, valve implantation, or the post-interventional course (30).

 Numerous case reports have described the feasibility of implanting both self-expanding and balloon-expandable transcatheter heart valve devices in patients with BAV using transfemoral or transapical access (31–34). To date, 8 distinct registries with a total of 381 patients reported on the outcomes of TAVR in BAV (Table 2). Five registries compared the performance of TAVR in BAV with that of TAVR in patients with tricuspid aortic valve anatomy and observed no significant differences in terms of device success and cardiovascular mortality at 1 year (28,35–39). However, in most studies, bicuspid anatomy was associated with a higher rate of moderate to severe paravalvular leaks, in particular if valve sizing was solely on the basis of echocardiography (40). This observation underscores the benefit of pre-procedural computed tomography of the aortic root, particularly in patients with unconventional anatomy. Despite frequent incomplete valve deployment, only 1 study reported a significant increase in the transvalvular aortic valve gradient compared with TAVR prostheses implanted in tricuspid anatomy (11.0 ± 2.6 vs. 8.2 ± 2.8; P = 0.04) (28).

 In summary, TAVR may be considered a treatment alternative in selected patients with bicuspid

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*Only case series included. †According to Valve Academic Research Consortium. ‡CoreValve, Medtronic, Minneapolis, Minnesota. §JenaValve, JenaValve Technology, Munich, Germany. ¶Symetis ACURATE, Ecublens, Switzerland.

AR = aortic regurgitation; ES = EuroSCORE; MCV = Medtronic CoreValve; NR = not reported; PPM = permanent pacemaker; STS = Society of Thoracic Surgeons; TA = transapical; TF = transfemoral; THV = transcatheter heart valve.
anatomy. Incomplete valve deployment, particularly when using self-expandable bioprostheses, may result in asymmetry of the frame favoring the occurrence of an associated paravalvular leak (41) and accelerating valve deterioration (42). Durability needs to be addressed by collecting long-term data.

TAVR FOR THE TREATMENT OF TRANSCATHETER AORTIC VALVE DEGENERATION

Implantation of a second transcatheter heart valve either “in series” (i.e., 2 functioning valves) or in a TAVR device (i.e., only 1 functioning prosthesis) has been initially described as a bail-out strategy for the treatment of device embolization (43) as well as for immediate or delayed treatment of hemodynamically significant paravalvular leak due to either device malposition (44) or, infrequently, acute leaflet dysfunction (45).

More recently, implantation of a second transcatheter heart valve for the treatment of bioprosthetic heart valve degeneration resulting in stenosis or transvalvular AR several months to years after a successful TAVR procedure has been proposed (46-52). For this purpose, self-expandable devices (CoreValve and Symetis ACURATE TA) have been mainly used. In 1 case, a second ESV was implanted via the transapical route 3 years after the first intervention (51).
Although several modes of transcatheter heart valve deterioration have been identified, including valve endocarditis, late embolization, and valve thrombosis, only structural degeneration is amenable to treatment by percutaneous implantation of a second transcatheter heart valve (52) (Figure 4). In nationwide registries reporting on long-term clinical outcomes after TAVR (up to 6 years), the incidence of structural valve failure appears rather low, ranging between 1.4% and 4.1% (54–56). Furthermore, in both PARTNER randomized trials, no valve degeneration has been observed during follow-up as long as 5 years in 2>500 TAVR recipients (1,3).

The mechanisms leading to transcatheter bioprosthesis deterioration are only incompletely understood. In surgical valves, calcification due to mechanical stress, glutaraldehyde fixation, immunological reactions, and generalized atherosclerosis have been identified as precipitating factors (57). Although similar mechanisms may act in transcatheter heart valve failure, specific pathophysiological factors including valve stent underexpansion or interaction with the calcified leaflets of the native aortic valve may also play an important role (42). Once TAVR-in-transcatheter aortic valve has been performed, the post-interventional gradient may represent a source of concern, in particular in patients with small anatomy and restenotic valve. Thus, data assessing the durability and long-term evolution of the transvalvular gradient after TAVR-in-transcatheter aortic valve need to be collected.

### TRANSCATHETER VALVE IMPLANTATION IN THE MITRAL POSITION

**MITRAL VIV IMPLANTATION.** Reoperation after mitral valve intervention is associated with increased perioperative mortality and morbidity exceeding 15% in patients 75 years of age and older (58). Since proof of principle in 2007 (59) and the first description in a human by Cheung et al. (60) in 2009, transcatheter VIV implantation in the mitral position has emerged as an alternative to redo open-heart surgery in selected high-risk patients. In numerous case reports and series, favorable clinical outcomes and hemodynamic results have been reported (Table 3) using either the transapical or, less frequently, the transfemoral-transseptal (61) or the transjugular-transseptal (62) approach. The available experience suggests an impressive reduction of the mitral transvalvular gradient or regurgitation severity in most of the treated patients. However, different types of procedural complications have been encountered including prosthesis dysfunction (63), acute (64) or late valve migration (65), valve thrombosis (66,67) as well as incomplete apposition resulting in paravalvular leakage and hemolysis (68). To avoid these adverse events, several considerations are of particular importance for the planning of mitral VIV interventions. First, the design of the degenerated bioprosthesis and its fluoroscopic appearance need to be well understood. Both play a crucial role when determining the implantation height of the transcatheter heart valve within the surgical bioprosthesis.
In the absence of radiopaque markers, the procedure has to be carefully guided by transesophageal echocardiography. Implantation of the transcatheter heart valve too low in the left ventricular cavity may result in left ventricular outflow tract (LVOT) obstruction, whereas deployment of the bioprosthesis too high may unnecessarily increase the amount of potentially thrombogenic material in the left atrium. Second, the true internal diameter of the surgical valve needs to be precisely assessed by transesophageal echocardiography and/or multislice computed tomography (MSCT). Due to the presence of the leaflets mounted inside the valve, the true internal diameter is typically 1 to 2 mm smaller compared with the stent diameter reported by the manufacturer. In the presence of calcific material or pannus, the true internal diameter can even be smaller, allowing implantation of a 29-mm ESV in a 31-mm bioprosthesis or, after careful evaluation, in a 33-mm surgical valve. The vast majority of the mitral VIV interventions have been performed using the balloon-expandable Edwards SAPIEN XT valves via the transapical route as they enable reliable alignment of the transcatheter heart valve in the surgical bioprosthesis in most of the cases. Because of the maneuverability of its delivery catheter, the transfemoral-transseptal route can also be alternatively used with the same device. Rapid pacing is helpful for stabilization of the implantation plane.

In a limited number of patients, the Medtronic Melody valve has been successfully implanted via the transfemoral-transseptal route. For this particular intervention, both the transapical and percutaneous transapical approaches are required to create a wire...
### TABLE 3 Summary of the Published Data Regarding Mitral VIV and VIR Procedures*

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<td>9</td>
<td>5 ± 2¶</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>ESV 1 TA</td>
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<td>ESV/TF</td>
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<td>8 ± 3¶</td>
<td>9</td>
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<td>0</td>
<td>9†</td>
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<td>9</td>
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</tbody>
</table>

*Only case series included. †Including second valve implantation or surgical access site revision. §SAPIEN valve, Edwards Lifesciences, Irvine, California. §Melody valve, Medtronic, Minneapolis, Minnesota. ‡Percutaneous closure of transseptal puncture site. ¶Mean gradient includes the VIV and VIR patients published in the same series. *Thrombosis observed after 8 weeks and 3 months in 2 patients on acetylsalicylic acid therapy only. **Thrombosis observed after 11 days and 17 months in 2 patients on acetylsalicylic acid and clopidogrel therapy only, respectively. ††Including 3 emergent procedures performed in very high risk patients (mean STS = 32%). ††Conversion to open heart surgery at 6 months due to heart failure and pulmonary hypertension.

TJ = transjugular; SVR = surgical valve replacement; MR = mitral regurgitation; VIV = valve in valve; VIR = valve in ring; other abbreviations as in Tables 1 and 2.
rail between the right femoral vein and the left ventricular apex (72,73). However, some of the limitations of using the Melody valve in this setting are the relatively small size with a maximal overexpanded diameter of 24 mm and the length of the covered valve stent increasing the risk of LVOT obstruction.

In 2015, the first successful implantation of a retrievable valve system, the Direct Flow Medical valve (25 mm) (Direct Flow Medical Inc., Santa Rosa, California), has been performed via the transapical approach for treatment of a regurgitant surgical valve (Carpentier-Edwards 29 mm)(74). Repositionable devices may play an important role for transcatheter mitral valve interventions as they allow for valve exchange in case of a sizing issue and retrieval in case of LVOT obstruction.

Overall, hemodynamic assessment after the intervention showed significant reduction (but not normalization) of the transmitral gradient in all case series. One study including VIV and VIR procedures also reported a significant increase in cardiac output (from 3.9 ± 1.0 l/min to 4.6 ± 1.5 l/min) and in valve area (from 1.6 ± 0.5 cm² to 2.2 ± 0.5 cm²) as well as a decrease in left atrial pressure (from 24.3 ± 9.5 mm Hg to 15.9 ± 4.4 mm Hg) and v-wave (from 44.1 ± 17.1 mm Hg to 22.2 ± 7.6 mm Hg) (75).

Similar to the experience with surgical patients, antithrombotic therapy plays a crucial role in preventing valve thrombosis, which occurs more frequently in the mitral position (66). However, there is no consensus regarding the optimal antithrombotic regimen. The current practice is to administer oral anticoagulation along with single antiplatelet therapy for at least 6 months in all patients who have been treated with a transcatheter heart valve in the mitral position. In patients in sinus rhythm, dual antiplatelet therapy for 6 months can be considered. In 2 independent studies, the use of single antiplatelet

(A) Twelve years after surgical mitral valve replacement using a 33-mm Medtronic Mosaic bioprosthesis, severe mitral valve regurgitation due to valve degeneration was diagnosed in this 88-year-old man. A 29-mm Edwards SAPIEN XT valve was implanted via the transapical approach (true inner diameter of the surgical valve, 28 mm). (B) The 3 white arrows show the eyelets on the stent post tips corresponding to the top of the ventricular part of the surgical valve. For proper implantation, the outflow part of the Edwards SAPIEN XT valve needs to be aligned with the radiopaque markers. Three-dimensional transesophageal echocardiography confirmed the correct position and function of the transcatheter valve with a limited amount of material in the left atrium (C) and trivial regurgitant jet (D, arrow).
therapy (either with aspirin or clopidogrel) was found to be insufficient in preventing late valve thrombosis (66,76).

MITRAL VIR IMPLANTATION. The mitral VIR procedure was first described in ovine models in 2009 using the 23-mm ESV implanted in a 26-mm Edwards Physio semirigid complete rings (77). In 2011, a 72-year-old patient underwent implantation of a balloon-expandable 26-mm ESV in a 28-mm Edwards Physio ring for the treatment of ischemic mitral regurgitation 8 years after surgical repair (78). The ESV was successfully delivered via the transapical route, achieving good acute hemodynamic results. So far, most of the published VIR implantations have been performed using the ESV via the transapical route. However, some groups have reported the transfemoral-transseptal approach as a technically more complex, but less invasive alternative (61). Less is known about mid- and long-term outcomes of mitral VIR procedures. Case reports and small series established the intervention’s safety and feasibility as well as the good hemodynamic results (Table 3). However, due to the D-shape of the annuloplasty rings, paravalvular leaks were frequently observed and may be associated with significant hemolysis.

From a technical point of view, mitral VIR procedures are more complex than VIV procedures for several reasons. As demonstrated by in vitro testing, the initially elliptical annuloplasty ring has to become circular during device implantation to accommodate the transcatheter heart valve and ensure sufficient sealing. Accordingly, valve deployment can only be performed in selected deformable complete and rigid semilunar annuloplasty devices (Online Table 1). In contrast, complete rigid rings are associated with an increased risk of stent deformation, impairing leaflet geometry with the possible appearance of transvalvular regurgitation. Moreover, the ring circularization during deployment also has relevant implications with regard to valve sizing. Rather than the labeled device diameter as specified by manufacturer, ring perimeter and area, which remain constant after circularization, are used for valve sizing.

**FIGURE 6** Transapical Mitral Valve-in-Ring Implantation

(A) In an 83-year-old female patient, severe mitral regurgitation recurred 3 years after mitral valve reconstruction using a semirigid 30-mm Edwards Physio II ring. After 3-dimensional ring reconstruction by multislice computed tomography, a perimeter of 74.1 mm was measured, corresponding to a 26-mm Edwards SAPIEN XT valve (B), which was implanted via a transapical access performed in the fifth intercostal space (C). Angiography and echocardiography showed an optimal hemodynamic result with only trivial regurgitation (D to F) and complete circularization of the semirigid ring (E).
selection. Both can be assessed by multislice computed tomography (MSCT) reconstructions, as shown in Figure 6B. The final diameter \( D \) of the anuloplasty ring can also be estimated using the following formula:

\[
D = 2 \times \sqrt[2]{A \div \pi}
\]

where \( A \) corresponds to the labeled ring area as stated by manufacturer. In addition, anatomic aspects regarding the native anterior mitral leaflet deserve consideration. First, along with its displacement toward the LVOT during prosthesis deployment, LVOT obstruction may occur. Second, in the situation of extensive overlap of the ventricular portion of the prosthetic valve through the native leaflets, the closing forces exerted over the leaflets may be insufficient. This may cause significant transvalvular regurgitation of the bioprosthesis secondary to leaflet dysfunction. Consequently, procedural success is critically dependent on both assessment of LVOT dimensions and careful placement of the transcatheter heart valve, aiming to position the bioprosthesis secondary to leaflet dysfunction.

The implantation of a second-generation, repositionable device, the Direct Flow Medical valve, in a radiolucent semirigid ring has also been described for this indication (81). The same advantages apply as previously described for the mitral VIV implantation. Due to the small size of the device, fixation by 2 sutures fixed to the apex has been proposed to prevent valve embolization (80).

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**Mitral Valve-in-Native Ring Implantation.** As a variant of mitral VIV implantation, deployment of transcatheter heart valves into severely calcified native mitral valve annulus via either the transfemoral-transseptal (83), the transapical (84), or the transatrial (85) approach have been reported in individual patients. The procedure was first described in 2012 by our group (85). For sizing purposes, MSCT and/or balloon inflation have been used. In most of the patients, the procedural results were satisfactory from a clinical as well as a hemodynamic point of view. In the case of on-pump transatrial access, some groups advocate the placement of additional sutures to ensure stable anchorage (Figure 7). In one patient who had this step omitted, valve dislocation and paravalvular leakage requiring surgical revision occurred. Finally, the bioprosthesis could be successfully secured by suturing to an atrial cuff (76). This highlights the importance of atrial anchorage for stabilization of transcatheter heart valves deployed in the mitral position and certainly has implications for the design of a dedicated mitral prosthesis.

**Transcatheter Valve Implantation in the Tricuspid Position.**

**Tricuspid VIV Implantation.** Tricuspid valve disease, in particular, tricuspid regurgitation (TR), is an uncommon condition and has received less attention in transcatheter heart valve therapy to date. However, severe TR is associated with a 3-fold increased all-cause mortality rate and a 4- to 5-fold increased risk of cardiac events during long-term follow-up (86). Cardiac surgery for correction of TR is associated with high perioperative mortality of up to 10% (87). Importantly, a relevant proportion of patients requiring tricuspid valve replacement have already undergone open-heart surgery. In particular, this is the case for young Ebstein patients requiring multiple valve replacements because of somatic growth or bioprosthesis degeneration (88). In these specific populations, transcatheter valve implantation may emerge as a valuable bridging option before repeat valve surgery (especially for young women of childbearing age). Transcatheter treatment of degenerated tricuspid bioprostheses was first explored using the Melody valve (89). The first tricuspid VIV intervention using a 26-mm ESV in a Medtronic Mosaic 27-mm bioprosthesis was performed in 2010 using a surgical approach off-pump via a right transatrial access (90). One year later, a fully percutaneous procedure via the transjugal route was described by Van Garsse et al. (91) a 23-mm ESV valve. Using the Edwards RetroFlex delivery system, a 26-mm ESV could be successfully implanted after pre-stenting in a 27-mm Edwards Perimount bioprosthesis via the transfemoral route the same year (92). During the
In selected patients presenting with severely calcified mitral valve annulus not amenable to decalcification (A, B arrows delineate the calcified native mitral valve annulus), on pump transatrial implantation of a transcatheter heart valve emerged as a possible alternative. After pre-dilation, a 26-mm Edwards SAPIEN XT valve was implanted via a transatrial approach using the Edwards Ascendra delivery catheter (C, D) in this 61-year-old male patient with severe mitral stenosis (mean gradient, 17 mm Hg; mitral valve area, 0.9 cm²). To avoid migration, the valve was sutured to the mitral annulus (E). Echocardiographic assessment showed mild residual mitral regurgitation. The post-operative course was uneventful.

In Table 4, the summary of the published data concerning the tricuspid VIV procedure is provided. The table includes the first author, year of publication, number of patients, device/access, mean log ES I, mean gradient post-procedure, residual tricuspid regurgitation, conversion to SVR, second intervention, valve thrombosis, 30-day mortality, and 12-month mortality.

*Only case series included. †including second valve implantation or surgical access site revision. ‡Melody valve, Medtronic, Minneapolis, Minnesota. §Implantation into a dysfunctional right atrial-right ventricular conduit in 5 patients. kSAPIEN valve, Edwards Lifesciences, Irvine, California. ¶Valve thrombosis due to heparin-induced thrombocytopenia. #Follow-up data at 12 months available for 9 patients, 0 deaths.

Mean gradient post = mean post-procedural gradient or mean gradient after the procedure; TR = tricuspid regurgitation; other abbreviations as in Tables 1 to 3.
following years, several case reports and 4 case series confirmed the safety and feasibility of this intervention using either the Melody valve or the ESV (Table 4). Only 1 case of valve thrombosis involving a Melody valve has been reported so far and was shown to be related to heparin-induced thrombocytopenia.

Several technical issues need to be considered when planning a tricuspid VIV implantation. First, the most appropriate access route needs to be determined. The less invasive transjugular and transfemoral approaches may be preferred to avoid thoracotomy in patients presenting with relevant comorbidities, in particular, chronic pulmonary disease. Although the transjugular access offers the most direct route to the tricuspid plane, catheter maneuverability enables transfemoral implantation in most patients. In either case, an extra stiff wire is positioned in the pulmonary artery, ensuring sufficient stabilization and traveling of the transcatheter heart valve through the right atrium into the ventricle (Figure 8C). Second, the valve type and size must be appropriately selected. For this purpose, conventional valve assessment using multimodal imaging (Figures 8A and 8B) as well as balloon sizing have been used. Due to greater availability and larger sizes, the ESV is the preferred system for this indication. However, the shorter frame compared with the Melody valve may impair coaxial alignment and render the bioprosthesis more prone to dislocation. To overcome this limitation, pre-stenting of the surgical valve (e.g., Cheatham-Platinum stent) has been proposed in particular in bioprostheses exceeding a labeled diameter of 30 mm. Pre-stenting was also recently described as a lead protection strategy in a patient with an implantable cardioverter defibrillator, which usually represents a contraindication to a VIV intervention in the tricuspid position. The defibrillator function could be preserved without changes in lead impedance after 1 year during the follow-up period. Although not mandatory, rapid pacing during the procedure can be obtained by placement of a transarterial temporary pacing lead in either the left ventricle or the sinus coronary. Alternatively, right ventricular guidewire pacing can be attempted. Pooled hemodynamic data from case reports demonstrated acceptable valve performance with a mean transvalvular gradient of 3.8 ± 2.0 mm Hg and moderate regurgitation in only 1 patient (of 71 cases reported). Cardiac magnetic resonance imaging performed in 5 patients showed an inconsistent hemodynamic response. The right ventricular end-diastolic volume decreased in 2 patients, increased in 1 patient, and remained unchanged in 2 patients.

Online Table 2 summarizes the surgical bioprostheses amenable to VIV intervention according to the published data. As also observed in a small proportion of patients with a surgical valve, early bioprosthesis degeneration was described in 3 patients treated by implantation of a Melody valve in the tricuspid position and in 1 patient with a 23-mm ESV. The cause of early degeneration may be associated with the particular hemodynamic environment, but the exact reason is still unknown.

TRICUSPID VIR IMPLANTATION. In contrast to mitral VIR, the experience with tricuspid VIR implantation is limited. To date, 4 case reports and 1 case series including 3 patients have been published. In 1 patient, the intervention included the simultaneous VIR implantation of 2 ESVs in mitral and tricuspid positions successfully performed via a transatrial off-pump approach. Another report described the treatment of a severe tricuspid stenosis after implantation of a mitral valve homograft with a 34-mm Edwards Physio ring. After pre-dilation and pre-stenting with an Intrastent LD Max (Covidien, Mansfield, Massachusetts), a 26-mm ESV could be implanted with a good final hemodynamic result (3-mm Hg mean gradient and trivial regurgitation). In 1 patient, the procedure was combined with the immediate implantation of an Amplatzer vascular plug for correction of residual paravalvular leak between the Melody valve and the ring. Finally, the recent case series by Bouleti et al. reported 1-year outcomes in 3 patients who had a 26-mm ESV successfully implanted in 2 30-mm and one 32-mm Carpentier-Edwards Classic rings, respectively. At 1 year, all patients were alive with a mean transvalvular gradient <5 mm Hg. However, 1 patient treated for severe TR still had moderate to severe TR due to incomplete apposition of the newly implanted device.

In contrast to the most frequently used mitral annuloplasty rings, the devices designed for tricuspid reconstruction are rigid, oval, and incomplete to prevent damage to the cardiac conduction system. This particularity complicates the selection of a suitable transcatheter heart valve. For appropriate decision making, balloon sizing should be performed before the final selection of the bioprosthesis. After implantation, only limited circularization and incomplete sealing of the ESV into the annuloplasty ring with subsequent relevant paravalvular regurgitation has been observed in some cases and may need to be addressed.
According to this early experience in a limited number of patients, tricuspid VIR implantation using the contemporary devices seems more prone to the appearance of associated paravalvular leakage and requires careful evaluation. In the future, the use of repositionable or dedicated devices may increase safety and predictability of the intervention.

CAVAL VALVE IMPLANTATION FOR THE TREATMENT OF TRICUSPID REGURGITATION

Alternative approaches aiming to reduce regurgitation into the inferior vena cava and possibly the superior vena cava have been recently proposed (102,103). In 2011, implantation of a dedicated valved stent in the inferior vena cava resulted in reduction of symptoms. In another first-in-human study, deployment of a 29-mm ESV in the inferior vena cava in 2 patients and in both the superior vena cava and the inferior vena cava in 1 patient was carried out from the right femoral vein. Due to caval enlargement, pre-stenting with 2 self-expanding stents was required to downsize the inferior vena cava to a diameter allowing secure implantation of a 29-mm ESV. The intervention, eventually leading to ventricularization of the right atrium, was followed by clinical improvement in all patients. However, several limitations prevent the widespread availability of this technique. First, caval diameter may exceed 30 mm in a large proportion of patients presenting with relevant TR. Second, it does not resolve impaired cardiac output associated with TR and does not prevent further deterioration of right ventricular function. Additionally, the high costs of the treatment need to be balanced against the net clinical benefit. Considering these points, the technique should be offered to patients presenting with intractable heart failure on a compassionate use basis.
TRANSCATHETER VALVE IMPLANTATION IN THE PULMONARY POSITION

Percutaneous pulmonary valve implantation was first performed using the Medtronic Melody valve. The intervention was described in 2000 in a 12-year-old boy with degeneration of a prosthetic conduit (104). In the meantime, good short- and long-term hemodynamic and functional results have been observed (105,106). In addition, favorable outcomes after Melody-in-Melody implantation for the treatment of device failure has also been demonstrated (107). However, as is the case for the indications previously described, the use of the Melody valve is limited by its small size and the risk of stent fracture. For these reasons, transcatheter heart valves initially designed to be delivered in the aortic position have been explored on a compassionate use basis. In 2006, a 23-mm Edwards-Cribier valve was successfully implanted in a previously stented 24-mm homograft in a 16-year old girl having undergone a Ross operation at 14 years of age (108). Subsequently, the valve was successfully evaluated for treatment of pulmonary stenosis or regurgitation in patients with or without degenerated valved conduit (Table 5) and received CE approval for percutaneous pulmonary valve implantation in 2010. Only 1 study compared the Melody valve with the ESV and found, except for a slightly increased transvalvular gradient in the ESV group, similar short- and midterm outcomes (109). In single cases, VIV delivery of the ESV in the pulmonary position, either in a previously implanted Melody valve or in a surgical bioprosthesis, has been shown to be feasible (106,110). As an alternative access, a surgical subxiphoid approach through the right ventricle has been proposed (111).

As encountered with the Melody valve, coronary compression may also occur using the ESV (112). Abnormal coronary anatomy emerged as the principal risk factor (113). Preinterventional MSCT used for careful analysis of the coronary anatomy combined with selective coronary angiography during simultaneous balloon inflation in the right ventricular outflow tract prevents this complication in the majority of the patients. According to a recent systematic review, valve endocarditis after percutaneous pulmonary valve implantation seems to be more frequent than in the aortic position and may exceed the corresponding risk for surgical patients (2.2% vs. 1.3%). These findings warrant further investigations to identify situations at risk and predictors of disease (114).

CONCLUSIONS

At this early stage, the expanded use of TAVR devices in alternative valvular positions or for other indications than initially intended appears feasible and safe. In the light of the published experience, the following points deserve consideration:

1. Treatment of pure AR with conventional devices is associated with rather low device success rate (~75%) and the need of a second valve in 20% of the patients. These results support the ongoing development of dedicated systems.
2. TAVR in bicuspid anatomy is feasible, but associated with a higher incidence of paravalvular leaks.
3. TAVR-TAV emerges as a valuable option for treatment of valvular degeneration.
4. Transcatheter mitral VIV or VIR interventions are characterized by overall good efficacy in reducing mitral regurgitation or treating mitral stenosis and low rates of complications. However, careful evaluation of the prosthesis/ring type and size using multimodality imaging is necessary. Appropriate antithrombotic therapy is crucial to avoid valve thrombosis.
5. Although rarely performed, tricuspid VIV procedures may emerge as an attractive treatment option. In contrast, tricuspid VIR implantation

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**TABLE 5** Short-Term Results After Implantation of an ESV* in the Pulmonary Position†

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<th>Device</th>
<th>Mean Gradient</th>
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<th>Valve/Stent Embolization, %</th>
<th>Conversion to SVR, %</th>
<th>Second Valve, %</th>
<th>30-Day Mortality, %</th>
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*SAPIEN valve, Edwards Lifesciences, Irvine, California. †Only case series included.

PR — pulmonary regurgitation; other abbreviations as in Table 2.
performed with the currently available devices are limited by the design of tricuspid rings.

6. Caval valve(s) implantation has been shown to be feasible and will compete with dedicated devices designed for the treatment of the native tricuspid valve.

7. Due to broader experience, the implantation of the Melody valve is still preferred for percutaneous pulmonary valve implantation. For particular indications, especially patients with large anatomy, the ESV represents an useful alternative.

Importantly, the innovative approaches summarized in this review mainly concern patients having previously undergone open-heart surgery. As such, they may emerge as valuable treatment options for patients otherwise treated medically or exposed to the increased risk of repeat valve surgery. The growing experience with the off-label use of TAVR devices may be of crucial importance for the future development of transcatheter techniques specifically designed to treat tricuspid and mitral valve disease.

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Intervention 2015;10:1336-1350


KEY WORDS bicuspid, mitral, TAVR, tricuspid, valve-in-ring, valve-in-valve

APPENDIX For supplemental tables, please see the online version of this article.

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